CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 22, 2015
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	206317
Applicant	Rockwell Medical, Inc.
Date of Submission	March 24, 2014; received March 24, 2014
PDUFA Goal Date	January 24, 2015
Proprietary Name / Established (USAN) names	Triferic/ Ferric pyrophosphate citrate
Dosage forms / Strength	Solution for addition to bicarbonate concentrate/27.2 mg iron (III)/5 mL (5.44 mg of iron (III) per mL)
Proposed Indication(s)	Treatment of iron loss or iron deficiency to maintain hemoglobin and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels
Recommended:	Approval, for revised indication: • 'Triferic is indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).' And with agreed upon revisions to wording of the sponsor's proposed labeling.

1. Introduction

Triferic (ferric pyrophosphate citrate) is an iron replacement product developed by the sponsor for administration in hemodialysis fluid via transfer across the dialysis membrane to the blood to replenish iron loss in patients with chronic kidney disease who are hemodialysis-dependent.

In this initial NDA submission the sponsor is seeking approval of Triferic:

- For the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD), and
- To reduce the ESA and (b) (4) requirements in CKD 5HD patients.

The proposed dose is one ampule of Triferic (27.2 mg of iron) added to 2.5 gallons of bicarbonate concentrate to prepare hemodialysate with final concentration of Triferic iron (III) in the final hemodialysate of 2 micromoles/L. Triferic is administered at each hemodialysis session.

2. Background

Patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) have an ongoing need for replenishment of body iron due to loss of iron during dialysis and may develop anemia due to low body iron stores and impaired utilization of iron. In patients with HDD-CKD, oral iron is poorly absorbed. Consequently, in these patients iron deficit is typically treated with parenteral iron administration. In clinical practice, parenteral iron is used in conjunction with erythropoiesis agents (ESAs) to manage anemia in patients with HDD-CKD.

Parenteral iron products currently on the U.S. market include INFeD and Dexferrum (iron dextran), Ferrlecit (sodium ferric gluconate complex), Venofer (iron sucrose), Injectafer (ferric carboxymaltose) and Feraheme (ferumoxytol). All except Injectafer are approved for treatment of iron deficiency anemia in patients with HDD-CKD. A chief safety concern for all the injectable iron products is hypersensitivity/anaphylaxis reactions.

Triferic is not marketed anywhere in the world.

To support the proposed indication the sponsor has submitted 2 pivotal randomized, single-blind, placebo-controlled, parallel group studies of essentially identical design (SFP-4 and SFP-5), each of which also had an open-label extension following the randomized treatment period. The application also includes supporting Phase 2 and short-term safety studies and other studies. The sponsor proposes an additional indication statement for Triferic "to reduce the ESA and (b) (4) requirements in CKD 5HD patients" based on results of a Phase 2, randomized, placebo-controlled study (Study NIH-FP-01) provided in the application.

The detailed review and evaluation of clinical efficacy, safety and benefit/risk of this application has been performed by Dr. M. Lu (Clinical Review finalized 12/19/2104) and Statistical Review and Evaluation was conducted by L. Luo (12/24/2014).

3. CMC/Device

In this NDA the sponsor is seeking approval of Triferic (ferric pyrophosphate citrate) solution. The primary Chemistry, Manufacturing and Controls (CMC) Review of the application was conducted by Office of New Drug Quality Assessment I (ONDQA I) (CMC Reviews by W.M. Adams, digitally signed 12/17/2014 and 1/20/2015).

The proposed formulation is a solution concentrate for hemodialysis, having a strength/potency of 27.2 mg Fe (III)/5 mL (5.44 mg Fe(III)/mL. The non-proprietary name (USAN) is Ferric Pyrophosphate Citrate

The review showed the following as the primary and secondary structure of Triferic:

Figure 1: Primary Structure of Triferic

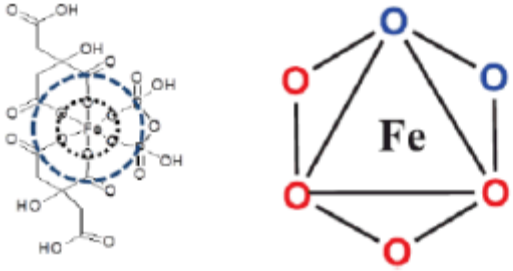
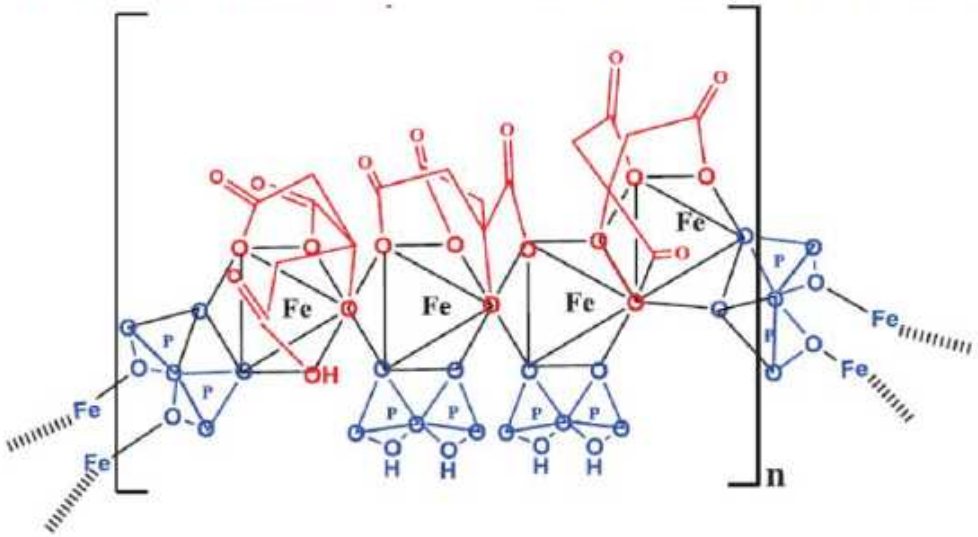


Figure 2: Secondary Structure of Triferic: $Fe_4(cit)_3(H_2Pyr)_2(Pyr)]$ with MW 1301.



Regarding the drug substance manufacturing the CMC review summarizes:

Bulk drug is manufactured by a [redacted]. The synthesis process, process controls and material specifications are adequate for the intended purpose and described in sufficient detail. Packaging for the storage and shipment of bulk material provides [redacted].

Each site proposed for manufacture and testing has been found to meet GMP standards.

The release specification (tests, analytical methods and acceptance criteria) have been described is sufficient detail and the methods have been validated for their intended purpose. The proposed acceptance criteria have been accepted. Appropriate reference standards have been established. A specification for [redacted] is to be established upon after validation of the manufacturing and the analytical method. The criterion for residual solvent will be re-evaluated upon completion of process validation.

The primary stability study data and information is sufficient to support a re-test period of [redacted] months when at stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°C and 86°C) in the proposed packaging system. The post approval stability protocol and commitment are acceptable.

Regarding the drug product manufacturing the CMC review summarizes:

Triferic® (ferric pyrophosphate citrate) Concentrated Solution for Administration by Hemodialysis is a solution of drug substance dissolved in water with a strength of 27.2 mg Fe(III)/5mL. The commercial presentation is a set of five ampules filled with 5 mL of solution which are stored in an opaque, laminate pouch within a cardboard carton.

The product is intended to be admixed into commercially available bicarbonate solution [redacted].

Product manufacture is by a [redacted]. The manufacturing process, process controls and material specifications are adequate for the intended purpose and described in sufficient detail.

Each site proposed for manufacture and testing has been found to meet GMP standards.

The release specification (tests, analytical methods and acceptance criteria) have been described is sufficient detail and the methods have been validated for their intended purpose. The proposed acceptance criteria have been accepted. Appropriate reference standards have been established. A specification for [redacted] is to be established upon after validation of the manufacturing and the analytical method.

The packaging components are the ampule, the pouch and a cardboard carton. Ampules, constructed from low density polyethylene [redacted] form a [redacted] container for the solution. The pouch, formed from a [redacted] aluminum laminate film, provides light protection for the ampules. Materials of composition, dimensions and acceptance specification for the ampule and pouch materials are described in sufficient detail. Extractables and leachables studies are provided to qualify the safety of the ampoule and pouch materials.

In-use stability studies establish that the product-bicarbonate and hemodialysate solutions are stable for up to 24 hours at room temperature.

The primary stability study data and information is sufficient to establish that drug product is stable for 24 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°C and 86°C) when the ampules are maintained within their pouch.

Categorical Exclusion for environmental assessment was provided based on Expected Introduction Concentration (EIC) calculation.

The CMC review does not identify any issues that would preclude approval of Triferic. The review did not make any recommendations on phase 4 postmarketing commitments, agreements or risk management steps. The review conclusion states:

> The application is recommended for APPROVAL from the CMC perspective in that adequate and acceptable information has been provided to establish the quality and stability of the proposed drug substance and drug product.

4. Nonclinical Pharmacology/Toxicology

The primary non-clinical pharmacology toxicology review was conducted by C-J. G. Chang (12/22/2014). Major findings as expressed in that review are as follows:

> Ferric pyrophosphate induced a slight transient increase in blood pressures, increase in heart rate, lengthening of QT and QTc interval and decrease in RR interval duration noted in a safety pharmacology study in Beagle dogs. The magnitude of QT prolongation was <10% as compared to baseline. These nonclinical cardiovascular findings were not noted consistently in trials submitted.
>
> In repeat-dose toxicology studies, rats and dogs were administered ferric pyrophosphate intravenously. Findings in these studies included transient and reversible decreases in body weight and food consumption. Dose-dependent increases in the amounts of element iron were noted in multiple tissues in both rats and dogs, including hepatocytes, Kupffer cells, renal tubular epithelium, and zymogen granules of the pancreas. The exposure (C_{max} and AUC_{0-24}) of iron increased less than proportionally to ferric pyrophosphate dose levels, suggesting saturation of iron binding to transferrin, a rapid removal of unbound iron from serum and an enhanced iron distribution into tissues.
>
> Ferric pyrophosphate was not mutagenic in the bacterial reverse mutation (Ames) test. FP was clastogenic in the chromosomal aberration assay in Chinese hamster ovary (CHO) cells in the presence of metabolic activation, but was not clastogenic in the absence of metabolic activation. FP was not clastogenic in the mouse micronucleus assay.
>
> In a fertility and early embryonic development study in rats at doses up to 40 mg/kg, no adverse effects on fertility or reproduction were noted in males or females. Maternal

> toxicity occurred at 40 mg/kg, but no toxicity was noted in the developing embryos. In embryo-fetal development toxicity studies in rats and rabbits, ferric pyrophosphate did not cause maternal or developmental toxicity at doses up to 30 mg/kg/day in rats and 20 mg/kg/day in rabbits. Maternally toxic doses cause developmental toxicity, resulting in post-implantation loss due to early resorptions, abnormal placentae, decreased fetal body weight and fetal head and vertebral malformations at 90 mg/kg/day in rats and vertebral malformations at 40 mg/kg/day in rabbits. In a pre- and post-natal development study in rats, the maternally toxic dose of 90 mg/kg/day resulted in reductions in the number of live offspring and lower offspring body weights. There were no adverse effects on survival of offspring at doses up to 30 mg/kg/day, or on behavior, sexual maturation or reproductive parameters of offspring at any dose level.

The review did not identify any safety issues regarding impurities or degradants for the drug. In particular, regarding possible presence of [redacted] (b) (4) in the product the review states, "Based on the justification provided by the Applicant, the pharmacology/toxicology team has a low level of concern for the proposed maximum levels of [redacted] (b) (4) that may be formed from administration of Triferic with a specification of [redacted] (b) (4) % in the ampoule solution."

The review concluded, "There are no pharmacology/toxicology issues that would preclude the approval of Triferic for the proposed indication." The secondary pharmacology/toxicology Memorandum by T. Palmby (12/22/2014) and the supervisory pharmacology/toxicology Memorandum by J.K. Leighton (12/23/2014) concurred with the conclusion of the primary review that the application could be approved and no additional nonclinical studies are needed for the indication.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review for this application was completed by O. Okusanya (12/11/2014). Overall, the NDA was found to be acceptable from a clinical pharmacology perspective.

The Clinical Pharmacology Review states:

> The Clinical Pharmacology Section of the NDA is supported by a dose-ranging study in patients with HDD-CKD, a PK study in healthy subjects, and a cross-over study evaluating the effect of different dialysis conditions on the delivery of iron. Dose-response analyses for effectiveness and safety using dose escalation data did not show any relationship between increasing the dose of SFP and an increase in the magnitude of change in hemoglobin (efficacy) or incidence of moderate to severe adverse events. Concentration-response analyses could not be performed because pharmacokinetic sampling was not performed in efficacy and safety studies.

The review comments that no ADME studies were conducted since iron is highly conserved in the body and is not metabolized. Also, no studies of studies of effect of renal impairment or hepatic impairment were done, since the target patient population is the hemodialysis population and patients with hepatic impairment were not likely to undergo chronic hemodialysis.

Important findings of the review were summarized as follows:

The drug is an iron-product administered via dialysis. The dose–escalation trial showed a dose-dependent increase in the concentrations of serum iron for SFP doses of up to 100 µg Fe/L. At doses greater than 100 µg Fe/L, no remarkable increase in serum iron with an increase in dose was observed. The dose for the pivotal phase 3 trials was 1 vial (27.2mg Fe^{3+}/5 mL) in each 2.5 gallon of bicarbonate dialysate yielding hemodialysate iron concentration of 110 µg Fe/L. Dose-response evaluation did not show an increase in efficacy (change in hemoglobin) or moderate to severe adverse events with dose.
Absorbed iron is not metabolized or appreciably excreted, so SFP is not expected to be subject to drug interactions. As SFP is used to maintain plasma iron within a normal range, it is not expected to perpetrate drug interactions.

In patients with HDD-CKD, the impact of varying hemodialysis (HD) conditions such as re-used dialyzers, low bicarbonate, low blood flow rate to dialysis flow rate (Qb/Qd) and polyarylyethersufone (PAES) membrane on the delivery of iron was evaluated. The median cumulative net iron delivered, under standard conditions, was estimated to be 0.348 mg (range = -0.296 to 3.32 mg). The median cumulative net iron delivered with low blood flow rate to dialysis flow rate (Qb/Qd) in the same patients (Qb/Qd of ≥ 350/≥600 mL/min vs. 250/400mL/min) in the aforementioned study was estimated to be 0.130 mg (range= -0.101 to 1.28 mg). The other factors did not appear to remarkably impact the net iron delivered.

No Clinical Pharmacology recommendations were made for post-marketing requirements.

6. Clinical Microbiology

Regarding sterilization process validation, the primary Chemistry, Manufacturing and Controls (CMC) Review by W.M. Adams digitally signed 12/17/2014 states:

Evaluation

Quality Microbiology Review addressed in-process controls, (b) (4) integrity, equipment (b) (4) and in-use stability. Review dated 12/04/14 in Panorama concluded Acceptable.

7. Clinical/Statistical- Efficacy

The Clinical Review of the sNDA was conducted by M. Lu, M.D. (review completed 12/19/2014). The Statistical Review and Evaluation for the application was completed by L. Luo, Ph.D., (review completed 12/24/2015). Please see those reviews for detailed review, analysis and discussion of the efficacy results for the application.

In the Clinical Review Dr. Lu summarizes the efficacy findings of the 2 pivotal studies as follows:

Efficacy Summary

The efficacy of Triferic was evaluated in two randomized controlled phase 3 clinical trials of identical design in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) (305 patients in SFP-4 and 294 patients in SFP-5) for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin. Each study was a multicenter, randomized, single-blind, placebo-controlled study in iron-replete patients with HDD-CKD. Study patients received SFP in dialysate at the concentration of 110 mcg iron/L or standard dialysate without SFP as placebo during each hemodialysis for 3 or 4 times per week. Randomized treatment duration was planned for up to 48 weeks. The mean treatment duration in the randomized phase was 157.7 days in the SFP group and 164.6 days in the placebo group in study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in study SFP-5. About 50% of study patients received study treatment for ≥20 weeks and 20% of study patients received study treatment for 44-47 weeks in the randomized phase.

The primary efficacy endpoint was the change in mean hemoglobin (Hgb) from baseline to the end of treatment period (last one-sixth of the randomized treatment period). In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to 0.38 g/dL in the placebo group in the Intention-to-Treat (ITT) population. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in the ITT population. The primary efficacy analysis used an ANCOVA analysis with baseline hemoglobin as the covariate. The treatment difference in hemoglobin calculated as least square (LS) mean difference was 0.35 g/dL in each study between the SFP (0.06 g/dL in SFP-4 and -0.04 g/dL in SFP-5) and the placebo groups (-0.30 g/dL in SFP-4 and -0.39 g/dL in SFP-5) and was statistically significant (p=0.01) in both studies after adjusting for baseline hemoglobin and ESA stratum. The results of additional analyses in Modified ITT (MITT) population and secondary endpoints in changes in TSAT and serum ferritin level from baseline to the end of treatment were consistent with the results from the primary efficacy analysis in both studies. The results from the two phase 3 clinical studies demonstrated that Triferic was effective to maintain hemoglobin during the treatment period in patients with HDD-CKD.

The Statistical Review (L. Luo, 12/24/2014) confirmed the positive efficacy findings stating, "In Study SFP-4-RC, the mean Hgb decreased 0.03 g/dL in the SFP group as compared to 0.38 g/dL in the placebo group in the intent-to-treat (ITT) population. In Study SFP-5-RC, the mean Hgb decreased 0.09 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in the ITT population. The primary efficacy analysis used an analysis of covariance (ANCOVA) model with baseline Hgb as the covariate. The treatment difference in Hgb calculated as least square (LS) mean difference was 0.35 g/dL between the SFP and the placebo groups in both studies and was statistically significant with a p value of 0.01. The results of sensitivity analyses and key secondary endpoints (mean change from baseline in ferritin, reticulocyte Hgb content (CHr), and transferrin saturation (TSAT)) appear to be supportive of the results from the primary efficacy analysis in both studies."

Although both studies demonstrated efficacy based on the primary efficacy analysis, both the clinical and statistical reviews commented on the fact that while a treatment duration of 48 weeks was planned for patients in the study, less than 20% of patients actually stayed on study treatment for the entire 48 weeks. The Clinical Review (M. Lu, 12/19/2014) comments:

Although treatment duration was planned for up to 48 weeks, it is notable that only a minority o patients completed full 48 weeks treatment, due in large part to protocol-mandated change in anemia management (involving changes in ESA and/or iron dosing). In Study SFP-4 these included 45.4% of patients in the SFP group and 53.6% in the placebo group; in Study SFP-5 these included 46.3% of patients in the SFP-group and 61.2% in the placebo group. Of those, the majority of study patients were due to required ESA dose change for hemoglobin in Study SFP- (42.8% in the SFP group and 45.1% in the placebo group) and in Study SFP-5 (44.2% in the SF group and 46.9% in the placebo group) and a few patients were due to requirement of intravenous iron administration for serum ferritin level <100 mcg/L in Study SFP-4 (2.6% in the SFP group and 9.2% in the placebo group) and in Study SFP-5 (2.0% in the SFP group and 14.3% in the placebo group). A greater percentage of patients in the SFP group (27%) as compared to the placebo group (20.9%) had hemoglobin >12 g/dL prior to withdrawal and more subjects in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively) had hemoglobin <9 g/dL in Study SFP-4. Similarly, in Study SFP-5, there were more subjects with hemoglobin < 9 g/dL prior to withdrawal in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects had hemoglobin >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively) prior to withdrawal. There were also more subjects who had serum ferritin level <100 mcg/L in the placebo group as compared to the SFP group in Study SFP-4 (11.1% vs. 3.3%, respectively) and in Study SFP-5 (15.6% vs. 2.7%, respectively). Although there was unexpected large proportion of patients didn't completed 48 weeks of study treatment mainly due to significant ESA dose changes during the study the final hemoglobin and serum ferritin level between the SFP and placebo groups prior to withdrawal were consistent with the primary efficacy results.

The Statistical Review makes the following comments regarding withdrawal from study treatment for the two studies:

For Study SFP-4 the Statistical Review comments:

- *"For SFP-4-RC, only a total of 54 (17.7%) of the 305 subjects completed 48 weeks of treatment; a total of 135 (44.3%) completed half (24 weeks) of the 48 weeks. At the pre-NDA meeting on September 9th, 2013, this issue raised concerns for intended long-term use of SFP in patients undergoing hemodialysis.*
- *151 out of 305 subjects from SFP-4-RC discontinued the study before the planned 48 weeks due to protocol mandated change. By protocol, these subjects have completed the study despite the fact that they did not reach week 48. These large number of subjects who dropout early but "completed" the study may create bias in estimated results"*

The following table from the Statistical Review summarizes the reasons for treatment discontinuation due to protocol-mandated anemia management changes in Study SFP-4.

Table 9 Reasons for Protocol Mandated Early Withdrawal

	SFP (N=152) N (%)	Placebo (N=153) N (%)	Total (N=305) N (%)
SFP-4-RC			
Overall	69 (45.4)	82 (53.6)	151 (49.6)
Hgb >12 g/dL	41 (27.0)	32 (20.9)	73 (23.9)
Hgb< 9 g/dL	17 (11.2)	27 (17.6)	44 (14.4)
Ferritin < 100 µg/L	5 (3.3)	17 (11.1)	22 (7.2)

For Study SFP-5 the Statistical Review comments:

- *"For SFP-5-RC, a total of 47 (16.0%) of the 294 subjects completed 48 weeks of treatment; a total of 125 (42.5%) completed half (24 weeks). At the pre-NDA meeting on September 9th, 2013, this issue raised concerns for intended longterm use of SFP in patients undergoing hemodialysis.*
- *158 out of 294 subjects from SFP-5-RC discontinued the study before the planned 48 weeks due to protocol mandated change. By protocol, these subjects have completed the study despite the fact that they did not reach week 48. These large number of subjects who dropout early but "completed" the study may create bias in estimated results"*

The following table from the Statistical Review summarizes the reasons for treatment discontinuation due to protocol-mandated anemia management changes for Study SFP-5.

Table 20 Reasons for Protocol Mandated Early Withdrawal

	SFP (N=147) N (%)	Placebo (N=147) N (%)	Total (N=294) N (%)
SFP-5-RC			
Overall	68 (46.3)	90 (61.2)	158 (53.7)
Hgb >12 g/dL	32 (21.8)	21 (14.3)	53 (18.0)
Hgb< 9 g/dL	22 (15.0)	34 (23.1)	56 (19.0)
Ferritin < 100 µg /L	4 (2.7)	23 (15.6)	27 (9.2)

Regarding the proposed claim for use of Triferic to reduce the use of ESA Dr. Lu's Clinical Review (12/19/2014) summarizes the review findings as follows:

The submission also includes a Phase 2 study (NIH-FP-01) to support a labeling statement for reduction of ESA dose in these patients. In this multicenter, randomized, double-blind, placebo-controlled study in 108 patients with HDD-CKD patients received either SFP or placebo during dialysis. The mean treatment duration was 212 days in the SFP group and 222 days in the placebo groups. The primary efficacy endpoint was the percent change from baseline in ESA dose at the end of treatment. The results in ITT population showed that the subjects receiving SFP had a mean increase of 5.0% in prescribed ESA dose at end-of-treatment as compared to a mean increase of 37.3% in the placebo group (p=0.052). It also showed that the subjects receiving SFP had a mean 11.1% increase in actual ESA dose as compared to a mean 40.7% increase in the placebo group in ITT population and the differences between the two treatment groups was again not statistically significant (p=0.111). The secondary efficacy endpoint analysis showed a similar distribution of changes in the prescribed ESA dose between the SFP and the placebo groups (p=0.915). The NIH-FP-01 study protocol stated that this study was exploratory in nature and statistical tests were considered to be descriptive rather than conclusive. No formal sample size determination was provided in the protocol. Because of the exploratory nature of the study, the submitted data is insufficient to support the proposed second indication to reduce the prescribed dose of ESA required to maintain desired hemoglobin levels. Large Phase 3 trials should be conducted to further evaluate the efficacy of Triferic for this indication.

Regarding the results of the NIH-FP-01 Study, the Statistical Review (12/24/2014) states the following, "The results showed that the subjects receiving SFP had a mean increase of 5% in prescribed ESA dose at the EoT as compared to a mean increase of 37.3% in the placebo group (nominal p=0.052). However, the subjects receiving SFP had a mean 11.1% increase in actual ESA dose as compared to a mean 40.7% increase in the placebo group (nominal p=0.111). Both results had nominal P values of greater than 0.05. Based on the study results, this statistical review cannot confirm that Triferic reduces the prescribed dose of ESA required to maintain desired Hgb levels because the study was exploratory in nature, no formal sample size or power calculations planned and difficulties in the interpretation of the efficacy of Triferic over the placebo at the EoT due to the cross-over of the prescribed ESA dose levels between treatment groups."

The overall recommendation from the Statistical Review (L. Luo, 12/24/2014) for the sponsor's requested indication concludes:

> In summary, this statistical review confirms the improvement of the mean change from baseline in Hgb level in favor of the Triferic treated group. However, the data did not support the treatment of iron loss or reduction of ESA use. Whether the positive results of mean change from baseline in Hgb level is beneficial for the HDD-CKD patient population and whether the results have a favorable benefit to risk ratio to support an approval of Triferic will be deferred to clinical judgment.

8. Safety

The Clinical Review of the NDA was conducted by M. Lu, M.D. (review completed 12/19/2014). Please see Dr. Lu's review for detailed review, analysis and discussion of the safety results for the application.

In the Clinical Review Dr. Lu summarizes the safety findings of the application as follows:

The safety of Triferic was evaluated primarily in two randomized placebo-controlled phase 3 clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD (total of 292 patients received SFP). Overall treatment-emergent adverse events (TEAEs) were reported at similar rates for the SFP-treated patients and the placebo-treated patients (78.4% and 75.3%, respectively) during the studies. Non-fatal treatment-emergent serious adverse events (SAEs) were reported at similar rates for the two groups (24.0% in SFP-treated patients and 25.3 % in the placebo-treated patients). Thirteen (4.5%) patients had at least one TEAE that led to treatment discontinuation permanently in the SFP group as compared to 7 (2.4%) the placebo group in the clinical trials.

A total of 17 deaths were reported in the two phase 3 clinical trials including 12 (4.1%) among the SFP-treated patients and 5 (1.7%) among the placebo-treated patients. Among the death cases, the duration of on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days in the placebo-treated patients. Time to event leading to death since the last hemodialysis with study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. Almost all patients had significant underlying cardiac conditions in addition to end-stage renal disease. Six patients in the SFP group and one patient in the placebo group died at home or nursing home without detailed information provided. The events leading to death were cardiac arrest in 8 cases (6 in SFP-treated patients and 2 in placebo-treated patients), sudden death or unknown cause in 5 cases (4 in SFP-treated patients and 1 in placebo-treated patients), acute myocardial infarction in 3 cases (1 in SFP-treated patients and 2 in placebo-treated patients), and one case of bronchopneumonia in the SFP group. No deaths were considered to be related to the study treatment by investigator and cases could be most likely attributed to co-morbid disease and/or disease progression.

In the two phase 3 clinical trials, suspected hypersensitivity reaction was reported in one (0.3%) patient in the SFP group as compared to none in the placebo group (0%). The event was considered as moderate and related to study drug. Five additional cases of suspected hypersensitivity reaction were reported in phase 2 and the phase 3 open-label extension treatment studies. Overall, six (0.4%) cases of suspected hypersensitivity reactions were reported in 1411 SFP-treated patients in clinical trials in the SFP development program. In 2 of the 6 cases events occurred at the first dose, were considered to be study drug related and study treatment was discontinued permanently. The remaining 4 patients continued the SFP treatment without recurrent events and the events were not considered to be related to the study drug. Occurrence of other adverse events of special interest, including intradialytic hypotension, composite cardiovascular events, hemodialysis vascular access thrombotic event, and systemic or serious infection, were similar for the SFP group and the placebo group.

The most common TEAEs (≥3% in the SFP-treated patients) that were reported more frequently in the SFP-treated patients than in the placebo-treated patients were procedural hypotension, muscle spasms, headache, dizziness, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, hyperkalemia, back pain, asthenia, fatigue, arteriovenous fistula site hemorrhage, arteriovenous fistula thrombosis, and hypertension. The nonfatal SAEs that were reported more frequently in the SFP group as compared to the placebo group included: diabetic foot infection (1% vs. 0%), arteriovenous fistula thrombosis (1.7% vs. 0.7%), and pulmonary edema (1.4% vs. 0.3%). The most common TEAEs (occurred in at least 2 subjects) leading to study discontinuation in the SFP group were asthenia, dizziness and headache.

A total of 1411 patients were exposed to Triferic in all clinical trials including open-label extension studies. The safety profile of Triferic in those patients was similar to that observed in the Phase 3 clinical trials.

9. Advisory Committee Meeting

A meeting of the Oncologic Drugs Advisory Committee (ODAC) to discuss the Triferic application was held on November 6, 2014. The majority of the Committee members expressed confidence that the pivotal trials (SFP-4 and SFP-5) supported that ferric pyrophosphate was effective in delivering iron to the patients who received in Triferic in the trials. The Committee voted 8 Yes to 3 No that the studies supported a positive benefit/risk for use of ferric pyrophosphate to treat iron loss. In discussion regarding use of Triferic to reduce ESA use in patients with HDD-CKD, the Committee members generally agreed that additional studies would be needed to establish efficacy. See the Quick Minutes of the November 6, 2014 Meeting of the ODAC and transcripts of the meeting for detailed information regarding the meeting. (See http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM430829.pdf).

10. Pediatrics

No pediatric patients were treated in the studies submitted in the Triferic NDA application. The sponsor has developed under IND 51290 a pediatric development plan for Triferic and as indicated in the Advice/Information Request letter to the sponsor dated 11/25/2014 the Agency has provided an agreed-upon initial Pediatric Study Plan (iPSP). The studies proposed are summarized in the following table from the iPSP.

Table 1: Table of Nonclinical and Clinical Studies for Ferric Pyrophosphate Citrate

PLANNED PEDIATRIC CLINICAL STUDIES			
Pediatric PK Studies			
Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
(b) (4)	Phase 1 PK study	(b) (4)	Y
Clinical Effectiveness and Safety Studies			
Age Group	Type of Study	Comments	Deferral Request Planned for the Study (Y/N)
<18 year (b) (4)	Safety and Efficacy (b) (4)	(b) (4)	Y
(b) (4)			

11. Other Relevant Regulatory Issues

As described in the application and in Dr. Lu's Clinical Review (12/19/2014), for 14 sites in the application financial disclosure forms for the pivotal studies were not available but the sponsor stated they were "confirmed not to have received compensation beyond the value of which could be affected by the outcome of the study". These included one sub-investigator at one site in Study SFP-4 which enrolled (b) (6) patients (b) (6) . (b) (6)

For this application inspections of four clinical sites (2 domestic, 2 foreign [Canada]) and the clinical research organization (CRO) were conducted by the Office of Scientific Investigations (Clinical Inspection Summary, A.J. Orencia, 11/24/2014). The findings of the inspections were summarized as follows:

The final regulatory classification for Dr. Kant Tucker, Dr. Serge Cournoyer, and the sponsor/CRO is No Action Indicated (NAI). The preliminary regulatory classification for Dr. Shayan Shirazian is No Action Indicated (NAI). The final regulatory classification of Dr. Kailash Jindal is Voluntary Action Indicated (VAI). The study data collected from these clinical sites and as reported by the CRO, appear reliable in support of the requested indication.

Review of the proposed proprietary name, Triferic, by the Division of Medication Error Prevention and Analysis (DMEPA)(M.K. Rutledge, 6/24/2014) found the name to be acceptable.

12. Labeling

Final labeling was developed in discussions involving all the review disciplines.

From the Clinical Review (M. Lu, 12/19/2014) recommendations discussed included the following:

1. Section 1 Indication and Usage
   - Revise the indication to: Triferic® is indicated for the treatment of iron loss in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).
   - (b) (4)
2. Section 2 Dosage and Administration
   - Revise to provide clear instruction for all steps involved in preparing Triferic in dialysis solution for use in clinical practice.
3. Section 5 Warnings and Precautions
   - Include 5.1 Hypersensitivity Reactions to add the following standard language as for other intravenous iron products as shown below:

     Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after and after hemodialysis (b) (4) until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions. [see Adverse Reactions (6)].

     Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic® in two randomized clinical trials.

   - (b) (4)

4. Section 6 Adverse Reactions
   - Revise the text and table to be consistent with current labeling guidance to present adverse reactions by body system and frequency of reactions.
   - Refer Hypersensitivity Reactions to Section 5 Warnings and Precautions.
   - Revise adverse reactions leading to treatment discontinuation section to list all adverse reactions leading to treatment discontinuation observed in the clinical trials.
5. Section 8 Use in Specific Populations
   - Revise Pediatric Use and Geriatric Use section to be consistent with current guidance.
6. Section 10 Overdosage
   - Revise to be consistent with current guidance.
7. Section 14 Clinical Studies
   - Revise the text to provide demographics, study endpoint, treatment, and the percentage of patients who completed 48 weeks of the treatment.
   - Revise the efficacy Table to present results from the ITT population analysis.
   - Remove the (b) (4) for the secondary efficacy endpoints.
   - Remove the section describing the (b) (4) (b) (4)

Recommendations from the Clinical Pharmacology Review recommended:

- addition of a Limitation of Use that Triferic® is not intended for use in patients receiving home hemodialysis or peritoneal dialysis
- addition of information to Section 12.3 Pharmacokinetics about delivery of iron from Triferic.

Labeling comments from the CMC review include the following:

- revise the established name from (b) (4) or SFP or soluble ferric pyrophosphate to "ferric pyrophosphate citrate" per the USAN conclusion in the highlights (1), section 8.1 (4), section 11 (3), section 13.1 (4).
- In section 2.1, accept the FDA proposed statement regarding bicarbonate solution in-use stability.
- In section 11, deleted ", an iron replacement product," in line 1; inappropriate statement for this section.
- In section 12.1, delete the statement ", contains iron in the form of ferric pyrophosphate, and " in line 1; inappropriate statement for this section.
- DMEPA noted that, for consistency, product strength should be presented as "27.2 mg iron (III)/5 mL (5.44 mg iron (III)/mL)", throughout the labels and labeling; revise section 16.1 to include the latte part of the strength statement. Carton and Pouch labels already use this strength statement.

CMC comments on the ampule, package and carton labeling also were provided and communicated to the sponsor on 1/16/2015. On 1/19/2015 the sponsor e-mailed updated ampule, package and carton labeling which CMC found acceptable (CMC Review, 01/20/2015).

The Division of Hematology Products (DHP) consulted the Division of Cardiovascular and Renal Products (DCRP) to obtain additional input regarding use of Triferic from a nephrology perspective, comment on the utility and anticipated clinical significance/impact of the product on hemodialysis practice and procedures, and comments on the sponsor's proposed draft labeling with particular attention to the proposed Dosage and Administration section. The DCRP Consult Review was completed by K. Smith (10/17/2014). Regarding the labeling, the DCRP consult review commented that, "Although the trial data suggest that SFP can be used as an exogenous source of iron in patients on dialysis, it is also important to note that the dosing regimen did not adequately replace iron losses in study subjects." Also, the review recommended that because there are different formulations of liquid and powder bicarbonate concentrate that are produced by different manufacturers and different dialysate proportioning systems it is important to address the applicability of the labeled dosing instructions to the various bicarbonate sources and systems in use in the U.S. Finally, the review suggested to include in the label some information on how dialysis conditions such as blood and dialysate flow may affect iron delivery.

The Office of Prescription Drug Promotion (OPDP) (J.S. Dvorsky, 11/20/2014) reviewed the draft labeling and provided comments and recommendations for the package insert. The review commented on the risk for hypersensitivity reactions:

> The draft text in section 5.1 provides information on class labeling for parenteral iron replacement products and hypersensitivity reactions. Similar language can be found in the Feraheme, Ferrlecit and Venofer PIs. However, the draft PI for Triferic (b) (4) (b) (4) We recommend revising the Triferic PI to be consistent with the other iron products and include the bolded information below.
>
> > Serious hypersensitivity reactions, including anaphylactic-type reactions, **some of which have been life-threatening and fatal,** have been reported in patients receiving parenteral iron products.

The Division of Risk Management (DRISK)(J. Weaver, 12/16/2014) reviewed the application and draft labeling to evaluates if a risk evaluation and mitigation strategy (REMS) is needed for Triferic. Regarding the disparity in deaths between the Triferic and placebo treatment arms in the pivotal trials, the review commented, "The disparity in the deaths in the groups was considered by the ODAC [Oncology Drugs Advisory Committee] members to be a chance finding rather than being possibly caused by ferric pyrophosphate." Based on the available information, the DRISK review concluded:

> No serious safety signals have emerged to date for ferric pyrophosphate that would require a REMS to ensure that its benefits outweigh its risks. DRISK and the Division of Hematology Products (DHP) believe that the risks of ferric pyrophosphate that have emerged to date can be communicated through labeling. DRISK and DHP do not recommend a REMS at this time. Should any additional important risk information emerge during the review of the application, we ask that you include DRISK in the discussion of appropriate risk management.

13. Recommendations/Risk Benefit Assessment

The sponsor seeks approval of Triferic (ferric pyrophosphate citrate) for treatment of iron loss or iron deficiency to maintain hemoglobin and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

The sponsor has provided two adequate and well-controlled studies (SFP-4 and SFP-5) that demonstrate the efficacy and safety of Triferic for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). Regarding the benefit/risk for this indication the Clinical Review (M. Lu, 12/19/2014) concludes:

> The overall benefit/risk assessment was favorable for Triferic in clinical trials for the treatment of iron loss to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). Triferic is delivered by dialysate during hemodialysis and provides a new option for parenteral iron administration, with a low iron dose as iron maintenance, to patients with HDD-CKD who require iron supplement due to iron loss during the hemodialysis procedure. The summary of efficacy and safety results for Triferic in clinical trials is included below.

The Division of Cardiovascular and Renal Products (DCRP) Consult Review (K. Smith, 10/17/2014) commented:

> *Many patients on dialysis require regular supplemental iron because of chronic losses related to dialysis (e.g., blood remaining in the dialyzer and blood lines, frequent blood draws) and reduced iron absorption; therefore, exogenous iron is often administered. Although we cannot speak for the nephrology community, we believe that a drug that contributes in a meaningful way to replacing iron losses in dialysis patients has merit, even if it does not meet a patient's full replacement needs.*

For the sponsor's desired claim for use of Triferic to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels, both the Clinical Review (M. Lu, 12/19/2014) and the Statistical Review (L. Luo, 12/242014) found that the information provided by the Phase 2 study NIH-FP-01 was inadequate to demonstrate efficacy of Triferic for this use. The Clinical Review recommended that large Phase 3 trials should be conducted to further evaluate the efficacy of Triferic for this indication.

No CMC, Non-Clinical Pharmacology/Toxicology, Clinical Pharmacology or Office of Scientific Investigation issues were identified that would prevent approval of the application.

During labeling discussions input for the Triferic labeling was obtained from all review disciplines as well as from the Division of Cardiovascular and Renal Products.

There was no recommendation to require postmarketing Risk Evaluation and Mitigation Strategies (REMS) for Triferic.

Conclusion/Recommendation:
The sponsor has provided adequate demonstration of efficacy and an acceptable benefit/risk profile for use of Triferic® (ferric pyrophosphate citrate) 5.44 mg Fe/mL concentrate solution for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). The NDA should be approved for this indication, with the labeling as revised and agreed upon with the sponsor.

Pediatric studies as described in the sponsor's agreed-upon iPSP should be conducted. For PREA these studies should be deferred because the adult indication is ready for approval. There are no additional recommendations for postmarketing requirements and no requirement for REMS is being made.

For a labeling claim to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels, additional adequately designed phase 3 studies are needed.

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/s/

KATHY M ROBIE SUH
01/26/2015