CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	206317
Applicant Name	Rockwell Medical Inc.
Date of Submission	March 24, 2014
PDUFA Goal Date	January 24, 2015
Proprietary Name / **Established (USAN) Name**	Triferic/soluble ferric pyrophosphate
Dosage Forms / Strength	Triferic® ampule contains 27.2 mg of elemental iron (III) as soluble ferric pyrophosphate citrate in 5 mL water for injection at a concentration of 5.44 mg Fe/mL.
Proposed Indication(s)	the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD). Triferic® can reduce the ESA and (b) (4) requirements in CKD 5HD patients.
Action/Recommended Action:	**Approval – see label for final wording of indication**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Min Lu, M.D./ Kathy Robie-Suh, M.D., Ph.D.
Statistical Review	Lola Luo, Ph.D./Yuan-Li Shen, Ph.D.
Pharmacology Toxicology Review	George Chang, Ph.D./Todd Palmby, Ph.D.
CMC Review/OBP Review	W. Michael Adams, M.S../Ali Al-Hakim, Ph.D.
Microbiology Review	Neal Sweeney, Ph.D./John Metcalfe, P.h.D.
Clinical Pharmacology Review	Olanrewaju Okusanya, Pharm.D./Jee Eun Lee, Ph.D./Gene Williams, Ph.D.
DDMAC	James Dvorsky/Katie Davis
OSI	Anthony Orencia, M.D./Janice Pohlman, M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Review	Kathy Robie-Suh, M.D., Ph.D.
OSE	Joyce Weaver, Pharm.D.
Other -DCRP	Kimberly Smith, M.D./Aliza Thompson, M.D./Norman Stockbridge, M.D.

Signatory Authority Review Template

1. Introduction

This application for NDA 206317 for Triferic™ (ferric pyrophospohate citrate) is proposed for the following indication: the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD).

Also the applicant proposes that the data support the following claim: Triferic® can reduce the ESA and (b) (4) requirements in CKD 5HD patients.

Triferic is not approved in any country or region.

The PDUFA goal date is January 24, 2015.

2. Background

The Applicant proposes that Triferic will treat both absolute iron deficiency as well as functional iron deficiency. The absolute iron deficiency arises from chronic blood loss as a result of whole blood loss with each dialysis treatment which is estimated at 15-25 mL/dialysis treatment. The functional iron deficiency is iron-restricted erythropoiesis (IRE) where iron is sequestered in the reticuloendothelial system (RES).

Patients with CKD 5HD are typically given small doses of intravenous iron replacement products during hemodialysis. The list of iron replacement products approved for use in patients with CKD includes: InFeD, Dexferrum, Ferrlecit, Venofer, Feraheme, and Injectafer.

3. CMC/Device

No issue which would preclude approval was identified. The following text is from the CMC reviews:

The primary stability study data and information is sufficient to support a re-test period of (b) (4) 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.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the primary review the following was identified:

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 (Cmax and AUC0-24) 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.

5. Clinical Pharmacology/Biopharmaceutics

The following text is from the Clinical Pharmacology review:

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 applicant did not conduct a human ADME study or a metabolism study, given that absorbed iron is not metabolized and is highly conserved within the body. In addition, renal or hepatic studies were not conducted as patients with chronic renal disease requiring hemodialysis are the target population and patients with significant hepatic impairment requiring dialysis are more likely to receive kidney transplant rather than maintained by chronic dialysis.

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

From the primary clinical review:

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 (HDDCKD)(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.

Although treatment duration was planned for up to 48 weeks, it is notable that only a minority of patients completed full 48 weeks treatment, due in large part to protocol-mandated change inanemia 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-4 (42.8% in the SFP group and 45.1% in the placebo group) and in Study SFP-5 (44.2% in the SFP 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 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.

I concur with the statistical review team regarding the following:

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.

I concur with the consult from Division of Cardiovascular and Renal Products that this product provides iron.

8. Safety

From the primary clinical review:

Safety Summary:
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.

Overall, SFP was reasonably tolerated in patients with HDD-CKD.

I concur with the primary reviewer that deaths, hypersensitivity reactions were more frequent in the SFP arm compared with the placebo arm. I also note that additional non-fatal SAES of concern include graft/A-V fistula thrombosis.

9. Advisory Committee Meeting

This application was presented at an ODAC meeting on 11/6/14 due to its novel mechanism of delivery and increased deaths and arteriovenous thrombosis observed on the ferric pyrophosphate arm. The ODAC committee voted in favor of approval of this product 8 to 3.

10. Pediatrics

This product has received a deferral and the Applicant is in the process of negotiating studies to conduct.

11. Other Relevant Regulatory Issues

From the OSI review:
The study data collected from these clinical sites and as reported by the CRO, appear reliable in support of the requested indication.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval

- Risk Benefit Assessment

Triferic is an iron replacement product that provides iron. Due to the fact that not all patients treated with SFP were able to avoid intravenous iron use despite being compliant with the product, it is difficult to use the terms such as treat iron loss. What this product really does is provides iron. As with all iron replacement products an increased number of deaths and hypersensitivity reactions were noted. In addition, possibly because of the manner of administration, graft thromboses were noted.

- Recommendation for Post marketing Risk Management Activities
  None

- Recommendation for other Post marketing Study Requirements/ Commitments
  Pediatric study(ies) – see approval letter for specifics

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/s/

ANN T FARRELL
01/23/2015