CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVAULATION AND MITIGATION STRATEGY REVIEW

Date:	December 16, 2014
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Naomi Redd, Pharm.D., Acting Team Leader, DRISK
Division Director:	Cynthia LaCivita, Pharm.D., Acting Director, DRISK
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Triferic (ferric pyrophosphate)
Therapeutic class & dosage form:	Iron replacement product; administered via dialysate
OND Review Division:	Division of Hematology Products
Application Type/Number:	NDA 206317
Application received:	March 24, 2014
PDUFA/Action Date:	January 24, 2015
Applicant/sponsor:	Rockwell Medical, Inc.
OSE RCM #:	2014-678

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the iron replacement product, Triferic (ferric pyrophosphate). The tentative indication is treatment of iron deficiency in adult patients with hemodialysis-dependent chronic kidney disease (CKD).

Rockwell Medical, Inc. submitted the application March 24, 2014. Rockwell Medical did not submit a REMS or risk management plan. The application was granted standard review status, with action to be taken on the application by January 24, 2015.

Background

Triferic (ferric pyrophosphate) is proposed for use for the chronic treatment of iron loss, maintenance of hemoglobin, and reduction of erythropoiesis stimulating agent (ESA) in patients receiving hemodialysis. Triferic is supplied in 5 mL ampules each containing 27.2 mg elemental iron. To administer Triferic, the contents of an ampule are added to 2.5 gallons of bicarbonate concentrate solution. The Triferic/bicarbonate mixture is then added to the remainder of the dialysate yielding a final concentration of 110 micrograms Triferic per liter of dialysate.

Other parenteral iron products used for iron replacement in patients receiving hemodialysis are administered intravenously, and comprise a central iron core contained within a carbohydrate shell. The sponsor theorizes that the absence of the carbohydrate component in Triferic could result in a safer iron replacement product, with fewer anaphylactic reactions. (b) (4)

2 REGULATORY HISTORY

The following are milestones important to this application:

- Investigational New Drug (IND) application submitted August 1996
- Rockwell Medical acquires IND December 2002
- Pre-NDA meeting September 9, 2013
- Application submitted March 24, 2014
- Filing date May 23, 2014
- Oncologic Drugs Advisory Committee (ODAC) convened to consider the application November 6, 2014
- PDUFA goal date January 24, 2015

3 MATERIALS REVIEWED

We reviewed the following:

- Application submitted March 24, 2014.

- Discipline presentations at the mid-cycle meeting for NDA 206317, meeting held August 25, 2014.
- Draft labeling, edited by FDA, November 5, 2014.
- FDA briefing document for November 6, 2014 meeting of ODAC
- Sponsor briefing document for November 6, 2014 meeting of ODAC

4 RESULTS OF REVIEW

4.1 OVERVIEW OF CLINICAL PROGRAM[1]

The data submitted in support of efficacy in the application were derived from two randomized multicenter single blind placebo controlled clinical trials enrolling 599 patients. Three or four times each week, patients received either dialysate with ferric pyrophosphate added, or dialysate without ferric pyrophosphate added. Treatment was planned to continue for 48 weeks. The actual average treatment duration in the trials was 22 to 23 weeks, in both the patients receiving dialysate with ferric pyrophosphate and the patients receiving dialysate without ferric pyrophosphate in the two trials. Most patients who discontinued early did so because they required management of anemia that mandated removal from the trial (e.g., change in dose of erythropoiesis-stimulating agents, need for intravenous iron).

The primary efficacy endpoint was change in mean hemoglobin. The mean hemoglobin decreased less in the patients receiving dialysate with ferric pyrophosphate added compared to patients receiving dialysate without added ferric pyrophosphate (0.03 g/dL compared to 0.38 g/dL in the first trial and 0.08 g/dL compared to 0.44 g/dL in the second trial). The differences were significant (p=0.01 in both studies).

4.2 SAFETY CONCERNS

The safety database for ferric pyrophosphate comprises data from 292 patients who received ferric pyrophosphate in the two trials.

Adverse events of special interest from the trials include intradialytic hypotension, hypersensitivity reactions, composite cardiovascular events, hemodialysis vascular access thrombotic events, other thrombotic events, and serious infections. For all the adverse events of special interest, the incidence of the events was similar in the two groups. Intradialytic hypotension occurred in 21.2% in patients receiving ferric pyrophosphate and 19.3% in the placebo group; hypersensitivity reactions 0.3% in patients receiving ferric pyrophosphate and 0% in the placebo group, composite cardiovascular events 8.9% in patients receiving ferric pyrophosphate and 9.1% in the placebo group, hemodialysis vascular access thrombotic events 5.1% in patients receiving ferric pyrophosphate and 3.7% in the placebo group, other thrombotic events 1% in patients receiving ferric

[1] Efficacy and safety summaries presented here are adapted from the data submitted by the sponsor in the application, the discipline presentations by FDA staff at the mid-cycle review meeting, and the briefing packages prepared by the FDA and the sponsor for the November 6, 2014 ODAC meeting.

pyrophosphate and 2% in the placebo group, and serious infections 8.2% in patients receiving ferric pyrophosphate and 8.8% in the placebo group.

There was an imbalance in the 17 deaths that occurred patients in the clinical trials between the treatment groups. Twelve of 292 (4.1%) patients receiving ferric pyrophosphate died compared to 5 of 296 (1.7%) patients in the placebo group. The imbalance comprised cardiac arrest (6 vs 2 patients), and sudden death/unknown cause (4 vs 1). None of the deaths was considered by the investigator to be related to study drug; the deaths were attributed to co-morbid disease and/or disease progression.

4.3 Risk Management Proposed by the Sponsor

The sponsor did not propose risk management measures beyond labeling. The sponsor did not propose any post-marketing studies.

5 DISCUSSION OF A REMS FOR FERRIC PYROPHOSPHATE

The ODAC expressed concern regarding the efficacy data emanating from the two trials, and they expressed concern that the patients in the trials were not dosed with ferric pyrophosphate in a way that reflects clinical practice. Most patients discontinued the trial because they required additional treatment to manage anemia.

The committee did not believe the data demonstrate any concerning safety issues. Overall, the adverse events were similar between the treatment groups. The disparity in the deaths in the groups was considered by the ODAC members to be a chance finding rather than being possibly caused by ferric pyrophosphate.

The committee voted 8 to 3 to recommend approval of ferric pyrophosphate. The committee members who voted against recommending approval did so because the data do not establish a dosing regimen and there are no long term efficacy and safety data, in part due to the large dropout rate in the clinical trials. The committee members who voted in favor of approval stated it would be advantageous to have an iron product that can be delivered via dialysate. Four of the 8 members who voted in favor of approval cited the absence of any concerning safety signals as a factor in their decision to support approval. Three of the committee members who voted to support approval stated that they were concerned about the lack of long term efficacy and safety data, but the necessary data can be obtained after approval.

None of the parenteral iron replacement products currently marketed has a REMS. No concerning safety issues have emerged for Triferic that would require a REMS to insure its benefits exceed its risks. Although Triferic was not compared to intravenous iron replacement products in clinical testing, the incidence of anaphylaxis was low with Triferic in the trials. One patient who received Triferic experienced flushing and hypotension (possibly a hypersensitivity reaction) during clinical testing. Based on the data pertaining to hypersensitivity from the clinical trials, the proposed labeling, as edited by the FDA, [redacted]$^{(b)(4)}$.

6 CONCLUSION/RECOMMENDATION

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.

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/s/

JOYCE P WEAVER
12/16/2014

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