APPLICATION NUMBER:

125545Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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| **Reviewer Name(s)** | **Naomi Redd, Pharm.D.** |
| **Team Leader (Acting)** | **Elizabeth Everhart, MSN, ACNP** |
| **Division Director** | **Cynthia LaCivita, Pharm.D.** |
| **Review Completion Date** | **June 2, 2017** |
| **Subject** | **Evaluation of Need for a REMS** |

| **Established Name** | **Epoetin alfa** |
| **Trade Name** | **Epoetin Hospira** |
| **Name of Applicant** | **Hospira** |
| **Therapeutic Class** | **Erythropoeisis Stimulating Agent (ESA)** |
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the Biologic Licensing Application (BLA) 125545 Epoetin Hospira (epoetin alfa) is necessary to ensure the benefits outweigh its risks. Hospira submitted this BLA under section 351(k) of the Public Health Service Act (PHS Act) as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa; BLA 103234). Hospira is seeking licensure of the biosimilar product for all 4 approved indications of Epogen/Procrit. The applicant’s proposed REMS consists of:

On April 13, 2017 the FDA determined that the ESA Risk Evaluation and Mitigation Strategy (REMS) for Epogen/Procrit and Aranesp, which was limited to treating patients with anemia due to associated myelosuppressive chemotherapy, was no longer necessary to ensure that the benefits outweigh its risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer. Therefore if Epoetin Hospira is approved, a REMS is not necessary to address the risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer. While the REMS is no longer necessary to ensure the benefits outweigh the risks, the serious risks of shortened overall survival and/or increased risk of tumor progression or recurrence associated with these drugs remain. Similar to Epoetin/PROCrit, the prescribing information for Epoetin Hospira will communicate the increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access..

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the Biologic Licensing Application (BLA) 125545 Epoetin Hospira (epoetin alfa) is necessary to ensure the benefits outweigh its risks. Hospira submitted this BLA under section 351(k) of the Public Health Service Act (PHS Act) as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa; BLA 103234). This application is under review in the Division of Hematology Products (DHP). The applicant’s proposed REMS consists of:

2 Background

2.1 PRODUCT INFORMATION
Epoetin alfa belongs to the class of erythropoiesis stimulating agents (ESAs), which stimulates the production of red blood cells in the bone marrow by binding to erythroid progenitor cells. The applicant is seeking licensure of Epoetin Hospira for the same indications as US-licensed Epogen/Procrit:
1. For the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion
2. For the treatment of anemia due to zidovudine administered at <4200mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤500mUnits/mL
3. For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
4. To reduce the need for allogenic RBC transfusions among patients with perioperative hemoglobin >10 to ≤13 g/dL who are at high risk for perioperative blood loss from elective, non-cardiac, nonvascular surgery.

Epoetin Hospira will be supplied as single-dose vials in 2000, 3000, 4000, 10,000, and 40,000 Units/mL, and strength and duration of treatment is dependent upon which indication it is prescribed. The intended setting in which the drug is likely to be administered is the inpatient hospital setting.

Epogen/Procrit (epoetin alfa) and Aranesp (darbopoetin) were previously approved with a REMS known as the ESA APPRISE Oncology Program (ESA REMS). The ESA REMS for was approved in February 2010, implementation was under common program called the ESA Apprise Oncology Program. On April 13, 2017 the ESA REMS for Epogen/Procrit and Aranesp were eliminated. The Agency determined that the REMS was no longer necessary to ensure that the benefits outweigh the risks of Epogen/Procrit and Aranesp for patients with cancer because the REMS Assessments indicated that prescribers have a good understanding of the risks, and ESA utilization appears to reflect appropriate use consistent with the approved indication. Please see the reviews written by Dr. Redd in DARRTS on January 5, 2017 and March 31, 2017 for more detailed information on the removal rationale. While the REMS is no longer necessary to ensure the benefits outweigh the risks, the serious risk of shortened overall survival and/or increased risk of tumor progression or recurrence with these drugs remain and will be included in the Boxed Warning and prescribing information for Epoetin Hospira.

This application is submitted as a BLA under section 351(k) of the Public Health Service Act (PHS Act) for “Epoetin Hospira” which is the proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa, BLA 103234), and is being reviewed under the six-month Biosimilar User Fee Act (BsUFA). In December 2007 the European Commission (EC) authorized Hospira to market EU-approved Retacrit, as a biosimilar to EU-approved Eprex for the treatment of anemia associated with chronic renal failure and chemotherapy.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history relevant to this review:

- 12/16/2009: FDA receives IND 100685 for Epoetin zeta (Epoetin Hospira)

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[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
• 12/16/2014: FDA receives formal submission of BLA 125545 Epoetin Hospira
• 10/16/2015: Complete Response (CR) letter that included analytical and clinical issues were sent to the sponsor
• 01/06/2016: A Type 1 Meeting was granted to address the CMC quality and analytical items identified in the CR letter received by the applicant on October 16, 2015
• 01/05/2017: FDA Acknowledges resubmission of the BLA, and assigns the user fee goal date as June 22, 2017
• 05/25/2017: The Oncologic Drug Advisory Committee (ODAC) Meeting was convened to discuss whether the totality of evidence supports licensure of Epoetin Hospira as a biosimilar to US licensed Epogen/Procrit provided that:
  o Epoetin Hospira is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components,
  o There are no clinically meaningful differences between Epoetin Hospira and US-licensed Epogen/Procrit, and
  o Whether there is adequate scientific justification to support licensure for all of the proposed indication.

The voting question: Does the totality of the evidence support licensure of Epoetin Hospira as a biosimilar product to US-licensed Epogen/Procrit for all of the indications for which US-licensed Epogen/Procrit is currently licensed and for which the Sponsor is seeking licensure resulted in a vote of 14-yes, 1-no. Since the ESA REMS had been released on April 13, 2017, there was no discussion about the need for a REMS.

3 Therapeutic Context of Biosimilars

The applicant is seeking licensure of Epoetin Hospira for the same indications as US-licensed Epogen/Procrit. The following section below is information related to licensure of biosimilar products in the United States:¹

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “ interchangeable” with an FDA-licensed biological product (the “reference product”). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.
Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

As FDA stated in the ODAC backgrounder, “to support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences.”

4 Benefit Assessment

Hospira submitted two clinical studies that evaluated efficacy and safety endpoints in support of licensure of “Epoetin Hospira”. Both studies were randomized, double-blinded, parallel group studies that enrolled patients with chronic kidney disease on hemodialysis and receiving epoetin maintenance treatment with co-primary endpoints of difference between arms in mean weekly hemoglobin and mean weekly dose. One study (EPOE-10-13) used subcutaneous epoetin, and the other study (EPOE-10-01) used intravenous epoetin. The FDA review of the data from both studies supports the Applicant’s contention that there are no clinically meaningful differences between “Epoetin Hospira” and US-
licensed Epogen/Procrit, and confirms the findings made in the FDA analysis of the phase 1 PK/PD trials. Please see the clinical statistical review which will be finalized in DARRTS for the full analysis of these data.

5 Risk Assessment & Safe-Use Conditions

The Safety Populations in the randomized phase 3 studies consisted of all subjects who received at least one dose of study drug. The frequency of TEAE, serious events, and events leading to discontinuation of study drug or death was not different between the treatment arms. Major events of interest which are listed as Warnings and Precautions in the prescribing information for US-licensed Epogen/Procrit include myocardial infarction, stroke, and thromboembolism. Events in these categories occurred in both studies with no imbalances between treatment arms, and there were no cases of pure red cell aplasia (PRCA) in the randomized trials. There were no clinically meaningful differences in safety between Epoetin Hospira and US-licensed Epogen/Procrit. Epoetin Hospira will also have a the Box Warning in the label that is the same as US-licensed Epogen/Procrit which outlines risk in the chronic kidney disease population, cancer, and peri-surgery. Please see the review written by the clinical reviewers which will be finalized in DARRTS for a full analysis of the safety data of this application.¹

6 Expected Postmarket Use

Epoetin Hospira will likely be used in the same inpatient settings and prescribed by the same healthcare prescribers as US-licensed Epogen/Procrit.

7 Risk Management Activities Proposed by the Applicant

7.1 Review of Applicant’s Proposed REMS

The applicant submitted a REMS on December 16, 2014. The REMS submission was similar to the formerly approved REMS for Epogen/Procrit and included:

(b) (4)
The Sponsor submitted their proposed REMS which was prior to the release of the REMS requirement for Epogen/Procrit.

8 Discussion of Need for a REMS

A REMS is a required risk management plan that uses risk minimization strategies beyond professional labeling that is designed to ensure that the benefits of certain prescription drugs outweigh their risks. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), the FDA has the authority to require a manufacturer to develop and implement a REMS to manage a known or potential serious risk associated with a drug and enable patients to have continued access to the drug. The Biologics Price Competition and Innovation Act states that biosimilars must comply with REMS Program requirements if the approved reference listed product has an approved REMS. Therefore, if a reference listed product has a currently approved REMS program, based on previous determination that a REMS is needed to ensure that the benefits outweigh the risk(s) of the approved reference listed product, the biosimilar product must also submit a REMS that is comparable to the REMS program for the reference listed product.

In 2010, FDA approved the ESA REMS to ensure patients were informed about the risks and benefits of ESAs prior to beginning treatment and to ensure prescribers were trained about the risks and safe and appropriate use of the ESAs in cancer patients. The ESA REMS became fully implemented in 2011. Since its implementation, the REMS assessments have consistently shown that prescribers have a strong knowledge of risks and the need to counsel their patients on these risks. Drug utilization patterns have also shown that appropriate prescribing of ESAs, consistent with the FDA approved labeled indication is occurring and has been occurring prior to implementation of the REMS.

Based on the results of the REMS Assessments, and because ESA utilization is consistent with the intended use as a treatment alternative to RBC transfusion for anemia associated with myelosuppressive chemotherapy. DRISK and DHP determined that a benefit-risk discussion is no longer necessary to ensure the benefits outweigh the risks.2,3

On April 13, 2017 the REMS requirement for Epoetin/Procrit was eliminated, therefore if Epoetin Hospira is approved, a REMS is not necessary to address the risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer. However, while the REMS for the ESAs is no longer necessary, the risks remain. Therefore the prescribing information and Medication
Guide will communicate an increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.

9 CONCLUSION & RECOMMENDATIONS

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Epoetin Hospira to ensure the benefits outweigh the risks. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated.

10 Materials Reviewed

1. Hospira REMS Submission, December 16, 2014

11 Appendices

11.1 REFERENCES

1 ODAC Epoetin Hospira FDA Background Document, May 25, 2017

2 Redd N. ESA REMS Removal, submitted in DARRTS, January 5 2017

3 Redd N ESA REMS removal addendum submitted in DARRTS, March 31 2017
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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NAOMI B REDD
06/02/2017

CYNTHIA L LACIVITA
06/02/2017
Concur
Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 14, 2015
Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)
Team Leader: Naomi Redd, Pharm.D, Acting Team leader, DRISK
Division Director Cynthia LaCivita, Pharm.D, Acting Director, DRISK
Drug Name(s): “Epoetin Hospira” Injection (Retacrit™)¹
Therapeutic Class: Erythropoiesis stimulating agent
Dosage and Route: Being developed for the same dosing regimens and route of administration as US-licensed Epogen
Application Type/Number: BLA 125545
Submission Number: Seq. No. 0000 (1) and 0007 (8)
Applicant/sponsor: Hospira, Inc.
OSE RCM #: 2014-2609 and 2014-2610

¹ For purposes of this review, we generally refer to Hospira’s proposed product by the Hospira descriptor “Epoetin Hospira.” FDA has not yet designated a nonproprietary name for Hospira’s proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).
1 INTRODUCTION

This review documents the Division of Risk Management’s (DRISK) evaluation of Hospira’s proposed risk evaluation and mitigation strategy (REMS) for “Epoetin Hospira” received by FDA on December 16, 2015 (Seq. No. 0000 (1)) and amended on February 13, 2015 (Seq. No. 0007). “Epoetin Hospira” is a recombinant erythropoietin developed as a biosimilar to US-licensed Epogen/Procrit, the reference product. The proprietary name, Retacrit™, was granted by FDA on April 6, 2015.

Hospira is seeking approval of “Epoetin Hospira” for the following indications:

- For the treatment of anemia due to Chronic Kidney Disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.
- For the treatment of anemia due to zidovudine administered at < 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of < 500 mUnits/mL.
- For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- To reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to < 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

For the oncology indication, “Epoetin Hospira” is intended for intravenous administration at a starting dose of 40,000 Units weekly or 150 Units/kg 3 times weekly for adults or 600 Units/kg intravenously weekly for children > 5 years. It comes in single-dose vials of 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL.

In December 2007 the European Commission (EC) authorized Hospira to market EU-approved Retacrit, as a biosimilar to EU-approved Eprex for the treatment of anemia associated with chronic renal failure and chemotherapy.

1.1 BACKGROUND

ESAs Approved in the USA for Anemia of Chemotherapy. Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa) are erythropoiesis stimulating agents (ESAs) which are indicated for the treatment of anemia due to (1) chronic kidney disease and (2) the effects of concomitant myelosuppressive chemotherapy, (3) the effects of zidovudine in HIV-infected patients (Epogen and Procrit only), and for (4) reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery (Epogen and Procrit only).

In 2007, the FDA held an advisory committee meeting to discuss the risks associated with the use of ESAs and approved a boxed warning for the increased risk of death and tumor progression based on ESA clinical trial evidence. Based on the boxed warning and evidence of these serious harms associated with ESAs, the Centers for Medicare & Medicaid Services (CMS) made a National Coverage Determination (NCD) in 2007 to limit coverage of the ESAs to cancer patients whose hemoglobin level is less than 10 mg/dL, in addition to other safe use conditions.
REMS for Aranesp and Epogen/Procrit. In 2010, just two years after FDA began implementing its new REMS authorities, FDA determined that a risk evaluation and mitigation strategy (REMS) was necessary due to evidence demonstrating that the effects of concomitant myelosuppressive chemotherapy with an ESA do not outweigh the risks of shortened overall survival and increased risk of tumor progression or recurrence. The Aranesp and Epogen/Procrit REMS programs are referred to as the ESA REMS and jointly fall under a common implementation program, the ‘ESA APPRISE Oncology Program’. The goal of the approved ESA REMS Program, modified on December 2013, is to support informed discussions between patients with cancer and their healthcare providers by: (1) educating healthcare providers about ESAs’ risks and safe use conditions for patients with cancer and (2) informing patients about the risk of shortened overall survival and/or increased risk of tumor progression or recurrence when ESAs are used to treat anemia due to concomitant myelosuppressive chemotherapy.

The initial REMS approved on February 2010, consisted of a Medication Guide (MG), a communication plan (CP), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU and the implementation system were only applicable to healthcare providers who prescribe and/or dispense ESAs to patients with cancer. The ETASU consisted of prescriber and hospital certification and documentation of safe use conditions (i.e., completion of the Acknowledgement Form). ESA REMS communication tools included: a Dear Healthcare Provider letter, REMS program flashcard, prescriber and hospital designee training modules, prescriber and hospital designee enrollment forms, Patient-Prescriber Acknowledgement Form (Acknowledgement Form), and a REMS website. Immediately following the ESA REMS approval in 2010, all ESA prescribers and hospitals dispensing ESAs were afforded 12 months to become certified.

The ESA REMS was modified on June 24, 2011. The modifications to the REMS consisted of revisions to the REMS document, MG, and REMS materials. These modifications intended to provide consistency with the recently revised product label and to revise the REMS document and the ESA APPRISE Oncology Program REMS materials, including the REMS website, to facilitate implementation of the program (e.g., allowable changes to the Acknowledgement Form) and to more concisely and effectively present important information safety information.

On May 31, 2012, the ESA REMS was revised to incorporate the name and logo change of the marketer and distributor of Procrit from Centocor Ortho Biotech to Janssen Products, LP. The REMS was modified again on March 27, 2013 to remove the prescriber re-enrollment requirement.

The most recent modification of the REMS on December 31, 2013 consisted of: (1) revision of goal statement (focus on oncology indication), (2) removal of the MG from the REMS, (3) revision of the Acknowledgement Form to be used as the primary oncology patient counseling tool, (4) removal of the CP and relocation of all communications activities under the corresponding ETASU, (5) revision of all training modules, (6) simplification of the risk messages communicated through the

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2 Claudia Karwoski, DRISK review, dated February 9, 2010.

3 APPRISE = Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs
Acknowledgement Form, (7) revision of audit sampling methodology to assess compliance with Acknowledgement Form, (8) elimination of clinic requirement to return Acknowledgement Forms to REMS Program Call Center, (9) enforcement of noncompliance with Acknowledgement Form by placement of the private clinic or hospital on the Suspension List, (10) added requirement that a copy of the Acknowledgement Form must be given to the patient, and (11) revision of REMS Assessment Plan.

1.2 REGULATORY HISTORY

The regulatory history of “Epoetin Hospira”, in pertinent part, is as follows:

- **December 16, 2009**: FDA Receives IND 100685 for Epoetin zeta (“Epoetin Hospira”).
- **February 9, 2010**: DRISK review providing the rationale for the need of a REMS for ESAs.
- **January 7, 2014**: Retacrit™ Proprietary name was conditionally approved by FDA.
- **July 18, 2014**: Hospira submitted a request for FDA feedback on the REMS proposal.
- **August 14, 2014**: FDA provides Hospira with comments regarding their high-level REMS proposal and informed Hospira that the proposed REMS should take into consideration the particular safety concerns associated with the use of the reference product and its class, as reflected in the Aranesp and Epogen/Procrit REMS.
- **December 16, 2014**: FDA received BLA125545, which included a REMS similar to that approved for Epogen/Procrit and Aranesp.
- **January 26, 2015**: BLA Orientation Meeting. DRISK requests Hospira submits details of the process for [redacted].
- **February 13, 2015**: FDA received an amendment to the REMS including methodology.
- **February 24, 2015**: REMS Oversight Committee meeting to discuss REMS for biosimilar products.
- **February 27, 2015**: FDA sends filing comments to Hospira including the following comment: “We noted that you submitted a risk evaluation and mitigation strategy (REMS) in your application. Although there is no requirement for a product licensed under section 351(k) of the Public Health Service Act and its reference product to utilize a single, shared system REMS, the sponsors for both products may do so voluntarily. If this is an option you intend to pursue, please advise the agency accordingly.” Hospira responded on **March 13, 2015** as follows: “Hospira is currently not pursuing a single, shared system REMS. However, Hospira is favorable to pursuing a single, shared system REMS post-approval if requested by FDA.”
- **April 6, 2015**: Proprietary name Retacrit granted.
• **May 5, 2015:** Mid-cycle meeting. Limitations of the proposed REMS and REMS Assessment Plan were presented to the review team.

• **October 16, 2015:** BSUFA date.

### 2 MATERIALS REVIEWED

#### 2.1 DATA AND INFORMATION SOURCES

- Retacrit REMS submission received by FDA on December 16, 2014.
- Retacrit REMS Audit Plan received by FDA on February 13, 2015.
- ESA REMS, last modified December 31, 2013.
- Draft DHP Clinical Review from August 11, 2015.

### 3 REVIEW FINDINGS

#### 3.1 CLINICAL DEVELOPMENT PROGRAM

The studies conducted to support that “Epoetin Hospira” is a biosimilar of US-licensed Epogen/Procrit include the following:

1. **Study EPOE-10-13:** A Therapeutic Equivalence Study Comparing the Efficacy and Safety of Subcutaneous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment.

2. **Study EPOE-10-01:** A Therapeutic-Equivalence Study Comparing the Efficacy and Safety of Intravenous “Epoetin Hospira” and Epoetin Alfa (Amgen) in Patients with Chronic Renal Failure Requiring Hemodialysis and Receiving Epoetin Maintenance Treatment.

3. **Studies EPOE-12-02 and EPOE-14-01:** These are PK/PD studies cross-over studies conducted in healthy volunteers.

FDA reviewers identified the following issues with this application:

1. Serious concerns regarding data integrity – FDA inspectors found that multiple clinical sites that enrolled subjects in the core studies submitted in support of this application were Good Clinical Practice (GCP) non-compliant. Hospira’s audit certification regarding the GCP compliance contradicts FDA inspections’ findings raising concerns over the integrity of the data.

2. **Adverse event report** – a case report of pure red cell aplasia (PRCA) was reported in a patient who was enrolled in a long-term, non-interventional, observational post approval study with EU approved Retacrit™.

3. **Immunogenicity assay validation** – is not complete.

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4 Draft DHP Clinical Review from August 11, 2015.
Assessment of Biosimilarity: DHP determined that an assessment to determine if Retacrit does not have any clinically meaningful differences to US-licensed Epogen/Procrit (reference product) cannot be completed until the final population for the comparative efficacy and safety analyses is finalized.

3.2 REMS PROGRAM PROPOSED BY HOSPIRA

FDAAA does not require 505(b) and BLA applications to form single, shared systems with other applications with similar risks. The REMS proposed by Hospira is similar to the REMS Program for Aranesp and Epogen/Procrit in that it includes the same elements and addresses the same risks. Hospira’s REMS proposal includes the following components:
4 CONCLUSIONS AND RECOMMENDATIONS

DHP determined that the data included in this application do not support biosimilarity between “Epoetin Hospira” and US-licensed Epogen/Procrit; therefore, FDA will issue a complete response letter. DRISK will provide comments to the sponsor regarding their proposed REMS program during the next review cycle.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMARILYS VEGA
09/10/2015

CYNTHIA L LACIVITA
09/14/2015
I concur