

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
May 25, 2017

DRAFT QUESTIONS

BLA 125545

**“Epoetin Hospira”, a proposed biosimilar to
US-licensed Epogen/Procrit**

Applicant: Hospira Inc., a Pfizer Company

PROPOSED INDICATIONS:

- 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 ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/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 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
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Hospira, Inc. (Applicant) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for "Epoetin Hospira", a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa) (BLA #103234).

Background. 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.”

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.

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The Applicant conducted the following clinical studies to support the application:

Study ID	Design	Route	Number	Study Population	Dose	Dosing Schedule	Primary Endpoint
EPOE-12-02	Cross-over	Subcutaneous	81	Healthy subjects	100 U/kg	Single dose	PK and PD similarity (reticulocyte count)
EPOE-14-01	Parallel	Subcutaneous	129	Healthy subjects	100 U/kg	3 times / week for 4 weeks	PD similarity (Hb)
EPOE-10-13	Parallel	Subcutaneous	246	Patients with CKD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose
EPOE-10-01	Parallel	Intravenous	612	Patients with CKD	Variable	1-3 times / week	Mean weekly Hb Mean weekly dose

PK: pharmacokinetic, PD: pharmacodynamic, Hb: hemoglobin, CKD: chronic kidney disease

Summary of FDA Review

Chemistry, Manufacturing, and Controls. “Epoetin Hospira”, a proposed biosimilar to US-licensed Epogen/Procrit was evaluated and compared to US-licensed Epogen/Procrit using multiple orthogonal physicochemical and functional methods. The totality of the analytical similarity data and publicly available information support the conclusion that the two products are highly similar, notwithstanding minor differences in clinically inactive components. The data indicate that the amino acid sequences of “Epoetin Hospira” and US-licensed Epogen/Procrit are the same. The results from secondary and tertiary structures and the biological activity analyses met the predefined analytical similarity acceptance criteria. In addition, the stability profile of “Epoetin Hospira” was shown to be similar to that of US-licensed Epogen/Procrit with respect to degradation products and degradation pathways. Differences in the levels of some glycosylation species and higher levels of a Cys29-Cys33 trisulfide species were identified in “Epoetin Hospira”, however, these differences did not impact biological activity, in vitro, and in vivo specific activity. As noted in subsequent sections, the additional clinical studies confirm this assessment.

Pharmacology/Toxicology. The nonclinical pharmacology and toxicology data submitted demonstrate similar pharmacodynamic effects in dogs and the same target organs of toxicity in rats and dogs administered “Epoetin Hospira” or US-licensed Epogen/Procrit. Except in instances in rats with lower exposure to US-licensed Epogen/Procrit, exposure to “Epoetin Hospira” was generally lower in animals compared to US-licensed Epogen/Procrit after the dose on Day 1. This may be related to the fact that the “Epoetin Hospira” lot used for the comparative

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animal toxicology studies had lower protein content. Therefore, there are residual uncertainties as to the similarity of the proposed biosimilar to the reference product based on the differences that were observed in the nonclinical data. However, these observed differences did not have an observable impact on pharmacokinetic/pharmacodynamic similarity in the clinical studies.

Immunogenicity. Immunogenicity for erythropoietin is linked to the development of life-threatening pure red cell aplasia. The incidence of immunogenicity for “Epoetin Hospira” and US-licensed Epogen/Procrit was compared in 3 multiple-dose, parallel-arm studies in 849 patients with chronic kidney disease (EPOE-10-01 and EPOE-10-13) and 129 healthy volunteers (EPOE-14-01). The results indicate similar rates and titers of anti-drug antibodies (ADA) for both products. No neutralizing ADA were detected in any of the clinical studies and no apparent impact of ADA on safety, pharmacokinetic, or pharmacodynamic endpoints were observed. Therefore, the data support a determination of no clinically meaningful differences in immunogenicity risk for “Epoetin Hospira” as compared to reference product US-licensed Epogen/Procrit.

Clinical Pharmacology. Overall, the submitted clinical pharmacology studies adequately demonstrated similarity of pharmacokinetics (PK) and pharmacodynamics (PD) (reticulocyte count and hemoglobin level) between “Epoetin Hospira” and US-licensed Epogen/Procrit. Studies EPOE-12-02 and EPOE-14-01, conducted in healthy subjects using a subcutaneous administration route, are considered sufficiently sensitive to detect clinically significant differences in PK and PD (reticulocyte count and hemoglobin level) among the products. Single-dose PK and PD (reticulocyte count) and multiple-dose PD (hemoglobin level) similarity pre-specified margins were met. The demonstration of similar PK and PD (reticulocyte count and hemoglobin level) exposure supports a demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit.

Efficacy and Safety. The Applicant 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 conclusion that there are no clinically meaningful differences in efficacy and safety between “Epoetin Hospira” and US-licensed Epogen/Procrit.

Extrapolation Across Indications. The Applicant seeks licensure for all indications for which US-licensed Epogen/Procrit is licensed (listed in Introduction section above). The “Epoetin Hospira” clinical program, however, provides clinical efficacy and safety data from a clinical program in patients with chronic kidney disease on hemodialysis. Scientific justification for extrapolation include the following considerations: same mechanism of action across indications, demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit based on

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extensive analytical characterization data, and no clinically meaningful differences based on clinical data on pharmacodynamics, pharmacokinetics, efficacy, safety, and immunogenicity.

QUESTIONS:

1. **DISCUSSION:** Please discuss whether evidence from analytical studies supports a demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components.
2. **DISCUSSION:** Please discuss whether there are no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit based on the results from the clinical studies.
3. **DISCUSSION:** Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.
4. **VOTE:** Does the totality of the evidence support licensure of “Epoetin Hospira” as a biosimilar product to US-licensed Epogen/Procrit for the following indications for which US-licensed Epogen/Procrit is currently licensed and for which the Applicant is seeking licensure?

PROPOSED INDICATIONS FOR “EPOETIN HOSPIRA”:

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Please explain the reasons for your vote.