APPLICATION NUMBER:

125545Orig1s000

OTHER REVIEW(S)
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 10, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 125545
Product Name and Strength: Retacrit* ("Epoetin Hospira"**) Injection
2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL and 40,000 units/mL
Applicant/Sponsor Name: Hospira
FDA Received Date: May 4, 2018
OSE RCM #: 2017-2418-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM
The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Retacrit (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

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¹ Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). The proprietary name Retacrit is conditionally approved only with approval of “Epoetin Hospira.”
** "Epoetin Hospira" is used throughout this review in place of the nonproprietary name for this product. Epoetin alfa-aafi is conditionally approved only with the approval of Epoetin Hospira.
¹ Garrison N. Label and Labeling Review for Retacrit (BLA 125545). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 April 04. RCM No.: 2017-2418.

Reference ID: 4261100
Reference ID: 4266940
2 CONCLUSION

The revised container labels and carton labeling for Retacrit is acceptable from a medication error perspective. We have no further recommendations at this time.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE B GARRISON 05/10/2018

HINA S MEHTA 05/10/2018
MEMORANDUM
NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: April 25, 2018
Responsible OND Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 125545
Product Name and Strength: Retacrit (epoetin alfa-epbx)
Injection
2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL and 40,000 units/mL

Product Type: Single-Ingredient Product
Applicant/Sponsor Name: Hospira
FDA Received Date: November 17, 2017
OSE RCM #: 2017-2416
DMEPA Primary Reviewer: Nicole Garrison, PharmD, BCPS
DMEPA Deputy Director: Danielle Harris, PharmD, BCPS
1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Hospira for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 125545.

1.1 REGULATORY HISTORY

Hospira previously submitted a list of 10 suffixes, in their order of preference, to be used in the nonproprietary name of their product on December 22, 2016. The Division of Medication Error Prevention and Analysis (DMEPA) found the suffixes unacceptable in OSE# 2016-2975a. Subsequently, we informed Hospira of our intention to designate a suffix since they did not propose additional suffixes for our evaluationb. On June 2, 2017, Hospira submitted a list of 10 new suffixes, to be used in the nonproprietary name of their productc, but they were not evaluated because the application received a complete response on June 21, 2017. On November 17, 2017, Hospira submitted a response to the complete response for BLA 125545 and included proposed suffixes in the submission.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On November 17, 2017, Hospira submitted a list of 10 suffixes, in their order of preference, to be used in the nonproprietary name of their productd. Hospira also provided findings from an external study conducted by evaluating the proposed four-letter suffixes in conjunction with the nonproprietary name, for our consideration. Table 1 presents a list of suffixes submitted by Hospira:

![Table 1. Suffixes submitted by Hospira***](image)

<table>
<thead>
<tr>
<th>1.</th>
<th>2.</th>
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</thead>
<tbody>
<tr>
<td>3.</td>
<td>4. -epbx</td>
</tr>
<tr>
<td>5.</td>
<td>6.</td>
</tr>
<tr>
<td>7.</td>
<td>8.</td>
</tr>
<tr>
<td>9.</td>
<td>10.</td>
</tr>
</tbody>
</table>

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a Garrison, N. Proprietary Name Review for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 May 11. OSE RCM No.: 2016-2975.
We reviewed Hospira’s proposed suffixes in order of preference listed by Hospira, along with the supporting data they submitted, using the principles described in the applicable guidance.  

2.4 Epoetin alfa-epbx

Hospira’s fourth proposed suffix, -epbx, contains some letters that represent common medical abbreviations (EP is an abbreviation for etoposide and cisplatin [Platinol]). We considered whether the inclusion of the letters (ep) within the suffix could be misleading or a source of confusion and errors, but we could not identify a plausible risk based on the expected us of this product or, based upon known causes of medication errors.

We also determined that -epbx is not too similar to any other products’ suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA’S ANALYSIS

These findings were shared with OPDP, TBBS and ORP. The workgroup concurred with DMEPA’s assessment and conclusion. DMEPA also communicated our findings to the Division of the Division of Hematology Products via e-mail on April 25, 2018.

4 CONCLUSION

We find Hospira’s proposed suffix -epbx acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to epoetin alfa-epbx.

4.1 RECOMMENDATIONS FOR HOSPIRA

We find the nonproprietary name, epoetin alfa-epbx, conditionally acceptable for your proposed product. Should your 351(k) BLA be approved during this review cycle, epoetin alfa-epbx will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your suffix unacceptable upon our re-evaluation, we would inform you of our finding.

We also note that the first three proposed suffix candidates are unacceptable for the following reasons:
FDA finds that this suffix is meaningful as it connotes (b) [4] Additionally, the suffix, (b) [4] contains the USAN stem (b) [4]. Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE B GARRISON
04/25/2018

DANIELLE M HARRIS
04/25/2018
LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: April 4, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 125545
Product Name and Strength: Retacrit (“Epoetin Hospira”*)
Injection
2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL and 40,000 units/mL
Product Type: Single-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Hospira
FDA Received Date: November 17, 2017 and January 9, 2018
OSE RCM #: 2017-2418
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMPEA Team Leader: Hina Mehta, PharmD
DMEPA Associate Director (Acting): Mishale Mistry, PharmD, MPH

*Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). The proprietary name Retacrit is conditionally approved only with approval of “Epoetin Hospira.” Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, Prescribing Information (PI) and Instructions for Use (IFU) for Retacrit (“Epoetin Hospira*”) injection (BLA 125545) for areas of vulnerability that may lead to medication errors. The Division of Hematology Products (DHP) requested this review as part of their evaluation of the 351(k) BLA class 2 re-submission for Retacrit (“Epoetin Hospira*”) injection.

1.1 REGULATORY HISTORY


2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C- N/A</td>
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<tr>
<td>ISMP Newsletters</td>
<td>D- N/A</td>
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<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E</td>
</tr>
<tr>
<td>Other</td>
<td>F- N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

* Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). The proprietary name Retacrit is conditionally approved only with approval of “Epoetin Hospira.” Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
Table 1. Materials Considered for this Label and Labeling Review

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A=not applicable for this review</td>
<td></td>
</tr>
</tbody>
</table>

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3  OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, PI, and IFU for Retacrit (“Epoetin Hospira”) to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We note that Retacrit has the same route of administration, dosing, indications, strength, and storage requirements as the reference product, US-licensed Epogen/Procrit (BLA 103234). We also note that Retacrit will only be supplied in single-dose vials, which differs from US-licensed Epogen/Procrit as it is supplied in both single-dose and multiple-dose vials containing benzyl alcohol (20,000 units/2 mL and 20,000 units/mL). The Retacrit IFU follows the same steps and injection technique as the reference product, US-licensed Epogen/Procrit.

We searched FAERS database and identified 15 medication error cases (see Appendix E for a detailed description of the cases) relevant to this review as follows:

- Incorrect route of administration (n = 6)
- Wrong technique during drug usage process (n = 7)
- Inappropriate schedule of administration (n = 1)
- Incorrect dose administration (n = 1)

In the cases of incorrect route of administration, it was reported that Epogen was administered as an intramuscular injection or orally instead of a subcutaneous injection. The cases did not report root causes, contributing factors, or patient outcomes. We note that the proposed Retacrit labels and labeling clearly and prominently state that the product should only be administered intravenously or subcutaneously.

The cases involving wrong technique of US-licensed Epogen/Procrit reported that Epogen/Procrit was administered to a hemodialysis patient in 70 mL of 0.9% sodium chloride injection, filtered with a five-micron filter, and unit dose syringes were prepared using a single-dose vial. Another case described a patient receiving Epogen that was previously frozen. The reporter did not know what the freeze indicators looked like and administered doses from four or five vials into an unknown number of patients. Other cases described a patient who was administered Procrit with a previously used syringe, administered 80,000 units of Procrit that was warmed prior to administration, and one case described delayed administration and storage of Procrit in a syringe for 4 days after it was withdrawn from the vial. We evaluated the Retacrit labels and labeling, considering the wrong technique Epogen/Procrit medication errors, to ensure that information regarding dose preparation and administration is clear and prominent. Our review of the proposed PI identified warnings on storage and use of frozen Retacrit, in addition to advising not to mix Retacrit with other drug solutions. Therefore, we do
not believe that labeling revisions are needed at this time. To mitigate the risk of the preservative free vials being used to prepare more than one dose, we recommend adding the statement “Discard unused portion” after “Sterile Solution- No Preservative” on the Principal Display Panel of the carton labeling.

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. We recommend changes to the carton labeling and container labels to improve readability and prominence of important information. Specifically, we recommend the inclusion of information such as lot number, expiration date, and finished dosage form. Additionally, we note that the labels and labeling contains the term, “single-use”, which is not consistent with the draft guidance\(^a\) and we defer to the Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term on labels and labeling.

4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed container labels and carton labeling, is vulnerable to confusion that can lead to medication errors. We provide recommendations in sections 4.1 to be implemented prior to approval of BLA 125545.

4.1 RECOMMENDATIONS FOR HOSPIRA

We recommend the following be implemented prior to approval of this BLA:

A. Container labels
   1. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 610.60.
   2. Include the finished dosage form below the proper name on the principal display panel (PDP)\(^b\).
   3. For numbers greater than or equal to 1,000, we recommend including a comma to mitigate the risks that users misinterpret thousands “1000” as hundreds “100” or ten thousands “10000.”

A. Carton labeling
   1. See A.1 through A.3 and revise the carton labeling accordingly.

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2. Include the statement “Discard unused portion” after “Sterile Solution- No Preservative” on the Principal Display Panel. We recommend this to mitigate the risk of the vial being used to prepare more than one dose.

3. Relocate the routes of administration and package information statements below the statement of strength on the principal display panel to bring prominence to this important information.

   For example:
   Retacrit
   Epoetin alfa-xxxx
   Recombinant Injection
   2,000 units/mL
   For Intravenous or Subcutaneous Use only
   Sterile Solution- No Preservative

4. Re-arrange the locations of route of administration statement and the storage information on the principal display panel to bring prominence to the route of administration.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Retacrit received on November 17, 2017 and January 9, 2018 from Hospira, and US-licensed Epogen/Procrit.

| Table 2. Relevant Product Information for Retacrit and US-licensed Epogen/Procrit |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Product Name**                | **Retacrit**                     | **US-licensed Epogen/Procrit**  | **Active Ingredient**           |
| **Initial Approval Date**       | N/A                              | June 1, 1989                    | “Epoetin Hospira”               |
| **Active Ingredient**           | “Epoetin Hospira”*               | Epoetin alfa                    | **Indication**                  |
| **Indication**                  | Treatment of anemia due to:      | **Indication**                  | Treatment of anemia due to:     |
|                                 | • Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis | • Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis | • Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis |
|                                 | • Zidovudine in HIV-infected patients | • Zidovudine in HIV-infected patients | • Zidovudine in HIV-infected patients |
|                                 | • Chemotherapy in patients with Cancer | • Chemotherapy in patients with Cancer | • Chemotherapy in patients with Cancer |
|                                 | Reduction of allogenic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery | Reduction of allogenic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery |
| **Route of Administration**    | Intravenous and subcutaneous     | Intravenous and subcutaneous    | **Route of Administration**     |
| **Dosage Form**                 | Injection                        | Injection                        | **Dosage Form**                 |
| **Strength**                    | Single-dose vials: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL | Single-dose vials: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL | Single-dose vials: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL |
|                                 |                                 | Multi-dose vials: 20,000 units/2 mL and 20,000 units/mL | Multi-dose vials: 20,000 units/2 mL and 20,000 units/mL |

*Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). The proprietary name Retacrit is conditionally approved only with approval of “Epoetin Hospira.” Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.

Reference ID: 4244375
Reference ID: 4266940
Dose and Frequency

*Treatment of anemia due to Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis*

- Adult patients: 50 to 100 units/kg 3 times weekly intravenously or subcutaneously.
- Pediatric patients: 50 units/kg 3 times weekly subcutaneously or intravenously is recommended.
- The intravenous route is recommended for patients on hemodialysis.

*Treatment of anemia due to Zidovudine in HIV-infected patients*

- The recommended starting dose in adult patients is 100 units/kg as an intravenous or subcutaneous injection 3 times per week.

*Treatment of anemia due to chemotherapy in patients with cancer*

- Adults: 150 units/kg subcutaneously 3 times per week until completion of a chemotherapy course or 40,000 units subcutaneously weekly until completion of a chemotherapy course.
- Pediatric patients (5 to 18 years): 600 units/kg intravenously weekly until completion of a chemotherapy course.

*Treatment of anemia due to Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis*

- Adult patients: 50 to 100 units/kg 3 times weekly intravenously or subcutaneously.
- Pediatric patients: 50 units/kg 3 times weekly subcutaneously or intravenously is recommended.
- The intravenous route is recommended for patients on hemodialysis.

*Treatment of anemia due to Zidovudine in HIV-infected patients*

- The recommended starting dose in adult patients is 100 units/kg as an intravenous or subcutaneous injection 3 times per week.

*Treatment of anemia due to chemotherapy in patients with cancer*

- Adults: 150 units/kg subcutaneously 3 times per week until completion of a chemotherapy course or 40,000 units subcutaneously weekly until completion of a chemotherapy course.
- Pediatric patients (5 to 18 years): 600 units/kg intravenously weekly until completion of a chemotherapy course.
| **How Supplied** | **Preservative-free, single-dose vials (in phosphate-buffered formulation):** 1 mL of solution contains 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, or 40,000 units/mL of Epoetin Hospira. | **Epogen (epoetin alfa) injection is a sterile, clear, and colorless solution available as:**  |
| | | - Single-dose, preservative-free vial: 1 mL of solution contains 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL supplied in dispensing packs containing ten 1 mL single-dose vials.  |
| | | - Preserved, multiple-dose vial: 20,000 units/2 mL (10,000 units/mL) supplied in dispensing packs containing then 2 mL multiple-dose vials.  |
| | | - Preserved, multiple-dose vial: 20,000 units/mL supplied in dispensing packs then 1 mL multiple-dose vials. |

**Treatment of anemic patients (hemoglobin > 10 to <13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions**  
- The recommended regimens are 300 units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.  
  Alternatively, 600 units/kg can be administered subcutaneously in 4 doses on 21, 14, and 7 days before surgery and on the day of surgery.  

**Treatment of anemic patients (hemoglobin > 10 to <13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions**  
The recommended regimens are 300 units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.  
Alternatively, 600 units/kg can be administered subcutaneously in 4 doses on 21, 14, and 7 days before surgery and on the day of surgery.
| Storage                      | Store at 36°F to 46°F (2°C to 8°C). Do not freeze. Do not shake. Do not use Retacrit that has been shaken or frozen. Store Retacrit vials in the original carton until use to protect from light. | Store at 36°F to 46°F (2°C to 8°C). Do not freeze. Do not shake. Do not use Epogen that has been shaken or frozen. Store Epogen vials in the carton until use to protect from light. |
APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 30, 2018, we searched DMEPA’s previous reviews using the terms, Retacrit. Our search identified four proprietary name reviews\(^c,d,e,f\), two label and labeling reviews\(^g,h\) and one nonproprietary name review\(^i\). Our recommendations were not considered or implemented because the application receive a Complete Response.

\(^c\) Gao, T. Proprietary Name Review for Retacrit (IND 100685). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Dec 17. OSE RCM No.: 2013-2199.

\(^d\) Vora, N. Proprietary Name Review for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Apr 03. OSE RCM No.: 2015-47422.

\(^e\) Garrison, N. Proprietary Name Review for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Mar 17. OSE RCM No.: 2016-11762660.

\(^f\) Garrison, N. Proprietary Name Memorandum for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 Jan 23. OSE RCM No.: 2017-19145298.

\(^g\) Mena-Grillasca, C. Label and Labeling Review Memo for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 Jan 17. 1 p. OSE RCM No.: 2014-2611.

\(^h\) Garrison, N. Label and Labeling Review for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 May 22. 20 p. OSE RCM No.: 2016-2973.

\(^i\) Garrison, N. Nonproprietary Name Suffix Memorandum for Retacrit (BLA 125545). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 May 11. OSE RCM No.: 2016-2975.
APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On January 30, 2018, we searched FAERS using the criteria in the table below and identified 278 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.¹

We excluded 278 cases because they described errors involving: accidental exposure (n = 7), drug dose omission (n = 69), error not related to Epogen (n = 6), expired drug administered (n = 10), wrong patient (n = 2), wrong drug (n = 1), off-label use (n = 1), product quality issue (n = 3) and incorrect product storage (n = 163).

<table>
<thead>
<tr>
<th>Criteria Used to Search FAERS</th>
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<tbody>
<tr>
<td>Initial FDA Receive Dates:</td>
</tr>
<tr>
<td>February 28, 2017 to January 30, 2018</td>
</tr>
<tr>
<td>Product Name:</td>
</tr>
<tr>
<td>Epogen, Procrit</td>
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<tr>
<td>Product Active Ingredient (PAI):</td>
</tr>
<tr>
<td>Epoetin alfa</td>
</tr>
<tr>
<td>Event:</td>
</tr>
<tr>
<td>SMQ Medication errors (Narrow)</td>
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<tr>
<td>Country (Derived):</td>
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<td>USA</td>
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</table>

E.2 Results

Our search identified 278 cases, of which 15 described errors relevant for this review.

Incorrect route of administration (n = 6)

- Six cases reported inappropriate route of administration of US-licensed Epogen/Procrit (FAERS Case No. 13619306, 13619434, 14159862, 14421780, 13618926, 14159922).
  o Four of the cases described patients who received US-licensed Epogen/Procrit via an intramuscular injection instead of a subcutaneous injection. The cases did not provide contributing factors or patient outcomes.
  o One case described a patient who received Procrit via the oral route. The patient did not experience any adverse effects. Contributing factors were not reported for this case.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Epogen/Procrit indications that the route of administration is clearly listed. The route of administration information in the Prescribing Information for Retacrit is similar to the reference

product and does not appear vulnerable to medication errors. Additionally, the proposed IFU for Retacrit depicts intravenous and subcutaneous administration. Labeling revisions are not necessary at this time.

Wrong technique during drug usage process (n=7)

- Seven cases reported wrong technique during drug usage process of US-licensed Epogen/Procrit (FAERS Case No. 13619095, 13619136, 13619368, 14159724, 13618993, 13619159, 14159981).
  - One case described Epogen was administered to a hemodialysis patient in 70 mL of 0.9% sodium chloride injection. Contributing factors or patient outcome was not reported.
  - One case described a pharmacist filtering Epogen with a five-micron filter because they found a particulate in a Epogen vial years ago. Patient outcome was not reported.
  - One case described a pharmacist withdrawing unit doses of Epogen from single dose vials into syringes and refrigerating the syringes. The syringes were not protected from light. The pharmacist stated that he worked at a pediatric hospital where they prepared unit doses. Patient outcomes was not reported.
  - One case described patients receiving Epogen that was previously frozen. The reporter did not know what the freeze indicators looked like and administered doses four or five vials into an unknown number of patients. Patient outcomes was not reported.
  - One case described a patient who was administered Procrit with a syringe and needle that was used one week earlier from a nurse. It was reported that the needles from the package were either misplaced or not shipped. Patient outcome was not reported.
  - One case described administration of 80,000 units of Procrit that warmed prior to subcutaneous injection and administered slow. Contributing factors or patient outcome was not reported.
  - One case described Procrit that was withdrawn from the vial into the syringe and administered four days later. It was not clarified why the patient did not receive the dose at the time medication was withdrawn into the syringe or why the reporter would administer dose to the patient which was stored in the syringe. Contributing factors or patient outcome was not reported.

A review of Section 2.6 Preparation and Administration of the Prescribing Information for US-licensed Epogen/Procrit indicates “Do not mix with other drug solutions” and “Do not use Epogen that has been shaken or frozen.” Our review of the proposed PI contains the exact warnings on use of shaken or frozen Retacrit, in addition to advising not to mix Retacrit with other drug solutions. Labeling revisions are not necessary at this time.
A review of Section 16 How Supplied/Storage and Handling of the Prescribing Information for US-licensed Epogen/Procrit indicates to store Epogen vials in the original carton until use to protect from light. A review of Section 17 Patient Counseling Information instructs patients who self-administer Epogen of the dangers of reusing needles, syringes, or unused portions of single-dose vials. In addition, the Instructions For Use advises to “use only disposable syringes and needles. Use the syringes and needles only one time and throw them away as instructed by your healthcare provider.” The storage, handling, patient counseling, and Instructions for Use for Retacrit is similar to the reference product and does not appear vulnerable to medication errors.

Inappropriate schedule of administration (n=1)

- One case described a patient who received Procrit whenever her hemoglobin was low. The patient stated it could be "1-2 months for each shot" but it was not clarified if she meant she received Procrit injections for one or two months at a time or she went between doses one or two months. Patient outcome was not reported.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Epogen/Procrit indicates that the dosing schedule is clearly listed. The dosing information in the Prescribing Information for Retacrit is similar to the reference product and does not appear vulnerable to medication errors.

Incorrect dose administration (n =1)

- One case described a patient who had questions about drawing up her Procrit. She stated she had issues getting the needle through the rubber top of the vial. In addition, she said that some of the medication is spilled during injection under the skin, so she is probable not getting the full dose. The patient was provided education on the proper technique for needle insertion.

A review of the proposed Instructions for Use (IFU) instructs patients or caregivers to not administer Retacrit until training has been received. In addition, users are instructed ask their healthcare provider for help if they have questions about giving the injection. In Steps 10 and 11 of the proposed IFU, users are instructed to insert the needle straight down through the grey stopper of the Retacrit and push the plunger of the syringe down to inject air into the vial of Retacrit. The IFU clearly depicts subcutaneous and intravenous administration of Retacrit. Labeling revisions are not necessary at this time.
E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

<table>
<thead>
<tr>
<th>FAERS Case Number</th>
<th>Manufacturer Control Number</th>
<th>Version Number</th>
<th>FAERS Case Number</th>
<th>Manufacturer Control Number</th>
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</table>

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA’s postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA’s Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm).
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Retacrit labels and labeling submitted by Hospira.

- Container label received on November 17, 2017
- Carton labeling received on November 17, 2017
- Instructions for Use received on January 9, 2018
- Medication Guide received on January 9, 2018
- Prescribing Information (Image not shown) received on January 9, 2018

G.2 Label and Labeling Images

Container labels

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NICOLE B GARRISON
04/04/2018

HINA S MEHTA
04/05/2018

MISHALE P MISTRY
04/09/2018
Memorandum

Date: March 22, 2018

To: Beatrice Kallungal, Senior Regulatory Health Project Manager, Division of Hematology Products (DHP)
    Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
      Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Retacrit (epoetin alfa-xxxx) injection, for intravenous or subcutaneous use

BLA: 125545

In response to DHP’s consult request dated January 5, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Retacrit.

**PI and Medication Guide and IFU:** OPDP’s comments on the proposed labeling are based on the draft PI, Medication Guide, and IFU received by electronic mail from DHP (Beatrice Kallungal) on February 16, 2018. OPDP’s comments for the draft PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on March 20, 2018.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 17, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

41 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
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/s/

ROBERT L NGUYEN
03/22/2018
MEMORANDUM

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs

Through: John Alexander, M.D., M.P.H., Deputy Director
DPMH, ODE IV, OND

To: Division of Hematology Products (DHP)

Drug: Epoetin Hospira/Retacrit (proposed biosimilar to US-licensed Epogen/Procrit [epoetin alpha])

Application Number: BLA 125545 (IND 100685)

Applicant: Hospira, Inc.

Proposed Indications: Treatment of anemia due to:
- Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis.
- Zidovudine in HIV-infected patients.
- The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
• Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

Proposed Dosage Form & Route of Administration:
Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL; Intravenous and subcutaneous administration

Proposed Dosing Regimen:
• CKD Patients:
  Initial dose:
  Adults (on dialysis and non-dialysis): 50 to 100 Units/kg 3 times weekly.
  Pediatric patients (on dialysis only): 50 Units/kg 3 times weekly.
  Individualize maintenance dose.

• Zidovudine-treated HIV-infected Patients:
  Adults: 100 Units/kg 3 times weekly.

• Cancer Patients on Chemotherapy:
  Adults: 40,000 Units weekly or 150 Units/kg 3 times weekly.
  Pediatric patients (5 years and older): 600 Units/kg intravenously weekly.

• Surgery Patients:
  Adults: 300 Units/kg daily for 15 days or 600 Units/kg weekly.

Consult Request: DHP consulted DPMH to review this Complete Response resubmission and to provide recommendations for pediatric use information in labeling.

Materials Reviewed:
- Division of Pediatric Maternal Health (DPMH) consult request
- Agreed upon initial Pediatric Study Plan (iPSP) for Epoetin Hospira, IND 100685 (January 20, 2015)
- Current US-licensed Epogen/Procrīt (epoetin alpha) labeling (September 29, 2017) per Drugs @FDA
- Prior DPMH reviews for Epoetin Hospira (BLA 125545/IND 100685) dated September 1, 2015 and August 25, 2017 and in DARRTS
- Applicant’s proposed labeling for Epoetin Hospira (January 9, 2018)
Consult and Regulatory Background:
On December 16, 2014, Hospira, Inc. submitted a BLA for Epoetin Hospira/Retacrit under the 351(k) pathway as a proposed biosimilar to U.S.-licensed Epogen/Procrit (epoetin alpha). U.S.-licensed Epogen/Procrit (epoetin alpha) is an erythropoiesis-stimulating agent (ESA) licensed by Amgen, Inc. and was first approved in 1989. Epoetin alpha stimulates erythropoiesis similar to endogenous erythropoietin.1

US-licensed Epogen/Procrit has the following indications for which Hospira plans to seek approval:
- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis.
  - Zidovudine in HIV-infected patients.
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

On September 29, 2017, US-licensed Epogen/Procrit labeling was updated to incorporate changes pertaining to severe cutaneous reactions and risk of serious adverse reactions due to benzyl alcohol preservative in the multi-use vial presentation. With the approval of this labeling supplement, information was also included in the pediatric use section describing the data supporting the use of US-licensed Epogen/Procrit for CKD in pediatric patients not requiring dialysis. Furthermore, there are no outstanding pediatric postmarketing requirements for US-licensed Epogen/Procrit, and following the approval of this labeling supplement, US-licensed Epogen/Procrit is considered fully labeled for pediatric use.

The Epoetin Hospira/Retacrit application was issued a Complete Response for this BLA due to biopotency, immunogenicity, and product quality issues on October 16, 2015 (see the prior DPMH review for Epoetin Hospira [BLA 125545/IND 100685] dated September 1, 2015 in DARRTS for further regulatory background.) The applicant resubmitted the application on December 22, 2016. However, the application received a second Complete Response on June 21, 2017 due to manufacturing facility deficiencies. The applicant resubmitted the application for a third time on November 17, 2017. DHP requested DPMH-Pediatrics Team assistance in providing labeling recommendations for pediatric use.

---

1 Current US-licensed Epogen/Procrit (epoetin alpha) labeling (September 29, 2017)
**Pediatric Assessment:**
Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new “active ingredient” for purposes of PREA, and a pediatric assessment is required unless waived or deferred. The Agency confirmed agreement with the agreed initial Pediatric Study Plan (iPSP) on January 20, 2015. The agreed upon plan is summarized in the table below.

<table>
<thead>
<tr>
<th>Approved Indications</th>
<th>Pediatric Information in Package Insert Labeling for US-licensed Epogen/Procrit</th>
<th>Proposal for the Pediatric Study Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia due to CKD in patients on dialysis and not on dialysis</td>
<td>Epogen is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established.</td>
<td>No additional studies are needed for patients 1 month to 16 years of age. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 1 month of age and older. Request a partial waiver for &lt; 1 month of age because studies would be impossible or highly impracticable.</td>
</tr>
<tr>
<td>Anemia due to concomitant myelosuppressive chemotherapy</td>
<td>Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established.</td>
<td>No additional studies are needed for patients 5 to 18 years of age. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 5 years of age and older. Request a partial waiver for &lt; 5 years of age because studies would be impossible or highly impracticable.</td>
</tr>
<tr>
<td>Anemia due to Zidovudine in HIV-infected patients</td>
<td>Published literature has reported the use of Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of red blood cell transfusions were observed.</td>
<td>No additional studies are needed for patients 8 months to 17 years of age. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 8 months of age and older. Request a partial waiver for &lt; 8 months of age because studies would be impossible or highly impracticable.</td>
</tr>
</tbody>
</table>
The pediatric plan provided in the BLA submissions is unchanged from the agreed iPSP,

Reviewer Comment: DPMH recommends DHP continue with the approach for this indication that was outlined in the agreed iPSP as described in the table above. The pediatric assessment for this indication in patients 8 months to 17 years of age would be considered complete and a partial waiver should be granted for patients less than 8 months of age.

**DPMH Review of Pediatric Use Labeling**

This DPMH-Pediatric team labeling review will specifically focus on edits to 8.4 (Pediatric Use). The following recommendations are based on labeling discussions between DHP and DPMH. Additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text.

**Applicant’s Proposed Labeling:**

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information
5 WARNINGS AND PRECAUTIONS

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

Pediatric Patients with CKD

Epoetin alfa RETACRIT is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established [see Clinical Studies (14.1)].

Use of epoetin alfa products in pediatric patients with CKD not requiring dialysis is supported by efficacy in pediatric patients requiring dialysis. The mechanism of action of epoetin alfa products is the same for these two populations. Published literature also has reported the use of epoetin alfa in pediatric patients with CKD not requiring dialysis. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

The safety data from the pediatric studies and postmarketing reports are similar to those obtained from the studies of epoetin alfa in adult patients with CKD [see Warnings and Precautions (5) and Adverse Reactions (6.1)]. Postmarketing reports do not indicate a
difference in safety profiles in pediatric patients with CKD requiring dialysis and not requiring dialysis.

**Pediatric Patients with Cancer on Chemotherapy**

Epoetin alfa RETACRIT is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established [see Clinical Studies (14.3)]. The safety data from these studies are similar to those obtained from the studies of epoetin alfa in adult patients with cancer [see Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)].

**Pediatric Patients with HIV Infection Receiving Zidovudine**

Published literature has reported the use of epoetin alfa in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of RBC transfusions were observed.

**Pharmacokinetics in Neonates**

Limited pharmacokinetic data from a study of 7 preterm, very low birth weight neonates and 10 healthy adults given intravenous erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.

_DPMH Comments: Based on the biosimilar development plan, Hospira is able to extrapolate the pediatric data included throughout US-licensed Epogen/Procrit’s labeling. Thus, Retacrit labeling should incorporate similar labeling language regarding pediatric use for all proposed pediatric indications. Language pertaining to data specifically obtained from studies conducted with US-licensed Epogen/Procrit will include the term “epoetin alpha”. Language pertaining to general information regarding epoetin alpha that is not specific to US-licensed Epogen/Procrit will include the term “epoetin alpha products”. Use statements specifically referencing this proposed biosimilar epoetin alpha product will include the term “RETACRIT”._

**Conclusion:**

DPMH agrees with the pediatric plan provided in the BLA submission including waivers and extrapolation of pediatric data from the reference product, US-licensed Epogen/Procrit, based on the biosimilar development program,
No pediatric postmarketing requirements are necessary for this BLA.

DPMH reviewed the applicant’s draft labeling, and participated in the team internal meetings from January to February 2018. DPMH’s recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv). DPMH’s input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.
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/s/

ERICA D RADDEN
03/21/2018

JOHN J ALEXANDER
03/21/2018
Date: March 20, 2018

To: Ann Farrell, MD
   Director
   Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
   Senior Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (Medication Guide (MG) and Instructions for Use (IFU))

Drug Name (established name): RETACRIT (epoetin alfa-xxxx)¹

Dosage Form and Route: injection, for intravenous or subcutaneous use

Application Type/Number: BLA 125545

Applicant: Hospira Inc., a Pfizer company

¹ A four letter suffix for the nonproprietary name for RETACRIT has not been determined. FDA is using “-xxxx” as a placeholder for the suffix. “-xxxx” is not intended to be included in the final printed labels and labeling.
INTRODUCTION
On November 17, 2017, Hospira Inc., a Pfizer company submitted for the Agency’s review a Complete Response (class 2 resubmission) of their original Biologic License Application (BLA) 125545 submitted under section 351(k) of the Public Health Service Act for “Epoetin Hospira”, in response to the Agency Complete Response (CR) Letter dated June 21, 2017. On January 26, 2018 the Agency notified the Applicant that the proposed proprietary name RETACRIT (epoetin alfa-xxxx) is conditionally acceptable. The Applicant seeks approval for RETACRIT (epoetin alfa-xxxx) for injection, for intravenous or subcutaneous use as a biosimilar product to the reference product EPOGEN/PROCRIT (epoetin alfa), licensed under BLA 103234.

The Applicant proposes RETACRIT (epoetin alfa-xxxx) injection for the following indications:

Anemia Due to Chronic Kidney Disease
- 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.

Anemia Due to Zidovudine in Patients with HIV-infection
- for the treatment of anemia due to zidovudine administered at ≤ 4,200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL.

Anemia Due to Chemotherapy in Patients With Cancer
- 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.

Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Elective, Noncardiac, Nonvascular Surgery
- 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. RETACRIT is not indicated for patients who are willing to donate autologous blood pre-operatively.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on January 5, 2018 for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) and Instructions for Use (IFU) for RETACRIT (epoetin alfa-xxxx) injection.
2 MATERIAL REVIEWED

- Draft RETACRIT (epoetin afa-xxxx) injection MG and IFU received on November 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 16, 2018.

- Draft RETACRIT (epoetin alfa-xxxx) Prescribing Information (PI) received on November 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 16, 2018.

- Approved EPOGEN (epoetin alfa) MG dated September 29, 2017.


3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10 and 11 respectively.

In our collaborative review of the MG and IFU we:

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- reviewed the MG and IFU for consistency with FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the presentation of information in the MG is consistent with the format of the approved MG for the reference product where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.
5 RECOMMENDATIONS

• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

• Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.
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/s/

SHARON R MILLS
03/20/2018

ROBERT L NGUYEN
03/20/2018

LASHAWN M GRIFFITHS
03/20/2018
Date: June 16, 2017

To: Ann Farrell, MD
   Director
   Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
   Team Leader, Patient Labeling
   Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
   Senior Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): RETACRIT (epoetin alfa)

Dosage Form and Route: injection, solution for intravenous or subcutaneous use

Application Type/Number: BLA 125545

Applicant: Hospira Inc., a Pfizer company
1 INTRODUCTION

On December 22, 2016, Hospira Inc., a Pfizer company, re-submitted for the Agency’s review an original Biologics License Application (BLA) 125545 for RETACRIT (epoetin alfa) injection in response to the Agency’s Complete Response Letter that was issued on October 16, 2015. RETACRIT (epoetin alfa) is a biosimilar to EPOGEN/PROCRIT with the proposed indications for:

- Treatment of anemia due to:
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis,
  - Zidovudine in HIV-infected patients,
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

On May 15, 2017, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant’s proposed Medication Guide (MG) and Instructions for Use (IFU) for RETACRIT (epoetin alfa) injection.

This memorandum documents the DMPP review deferral of the Applicant’s proposed MG and IFU for RETACRIT (epoetin alfa) injection.

2 CONCLUSIONS

Due to outstanding deficiencies, DHP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant’s patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

Please notify us if you have any questions.
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/s/

----------------------------------------------------
SHARON R MILLS
06/16/2017

BARBARA A FULLER
06/16/2017

LASHAWN M GRIFFITHS
06/16/2017
*Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, Prescribing Information (PI) and Instructions for Use (IFU) for Retacrit (“Epoetin Hospira*”) injection (BLA 125545) for areas of vulnerability that may lead to medication errors. The Division of Hematology Products (DHP) requested this review as part of their evaluation of the 351(k) BLA class 2 re-submission for Retacrit (“Epoetin Hospira*”) injection.

1.1 REGULATORY HISTORY


2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C- N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D- N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-</td>
</tr>
<tr>
<td>Other</td>
<td>F- N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, PI, and IFU for Retacrit (“Epoetin Hospira*”) to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We note that Retacrit has the same route

* Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
of administration, dosing, indications, strength, and storage requirements as the reference product, US-licensed Epogen/Procrit (BLA 103234). We also note that Retacrit will only be supplied in single dose vials, which differs from US-licensed Epogen/Procrit as it is supplied in both single-dose and multi-dose vials containing benzyl alcohol (20,000 units/2 mL and 20,000 units/mL). The Retacrit IFU follows the same steps and injection technique as the reference product, US-licensed Epogen/Procrit.

We searched FAERS database and identified 30 medication error cases (see Appendix E for a detailed description of the cases) relevant to this review as follows:

- Incorrect route of administration (n = 18)
- Incorrect dose administration (n = 1)
- Wrong technique during drug usage process (n = 7)
- Incorrect schedule of administration (n = 4)

In the cases of incorrect route of administration, it was reported that Epogen was administered as an intramuscular injection or orally instead of a subcutaneous injection. The majority of cases did not report root causes, contributing factors, or patient outcomes. However, one case reported that the prescriber did not indicate the route of administration on the prescription, which resulted in the patient experiencing burning at the injection site. The proposed Retacrit labels and labeling clearly states that the product should only be administered intravenously or subcutaneously.

One case involving the incorrect dose administered was related to a pediatric patient receiving an adult dose of US-licensed Epogen/Procrit. Root causes, contributing factors, or patient outcomes were not reported. In the cases involving the incorrect schedule of administration, patients received Procrit on a schedule that is not in accordance with the PI. Root causes and contributing factors were not reported. Our review of the proposed PI determined that the dosage and frequency of administration information is clear and prominent; thus, we do not recommend any changes to the labeling at this time.

The cases involving wrong technique of US-licensed Epogen/Procrit reported that US-licensed Epogen/Procrit preservative free vials were used to prepare more than one dose. Additionally, reports of wrong technique also included the introduction of bubbles into the syringe and shaking the vial during dose preparation. Most of the cases did not indicate root causes, contributing factors, or patient outcomes. However, one case reported that the medication error was related to the use of a smaller needle to withdraw the dose. We evaluated the Retacrit labels and labeling in light of the US-licensed Epogen/Procrit medication errors to ensure that information regarding the route of administration, dosage, and dose preparation is clear and prominent. To mitigate the risk of the preservative free vials being used to prepare more than one dose, we recommend adding the statement “Discard unused portion” after “Sterile Solution- No Preservative” on the Principal Display Panel. We will continue to monitor for wrong technique errors.

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we recommend the revision of a strength statement under Section 3 Dosage Forms and Strengths of the PI. Additionally, we
note that the labels and labeling contains the term, “single-use”; which is not consistent with
the draft guidance\(^a\); we defer to CMC for the determination of the appropriate package type
term on labels and labeling.

For the Applicant, we recommend changes to the carton and container labels to improve
readability and prominence of important information. Specifically, we recommend inclusion of
required information such as lot number, expiration date, and finished dosage form.

4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed PI, container labels, and carton labeling, is vulnerable to
confusion that can lead to medication errors. We provide recommendations in sections 4.1 and
4.2 below, to be implemented prior to approval of BLA 125545.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. Dosage Forms and Strengths
      a. Revise the ‘40,000 units/1 mL’ concentration statement to “40,000
         units/mL” in accordance with USP General Chapter <1>\(^b\).

4.2 RECOMMENDATIONS FOR HOSPIRA

We recommend the following be implemented prior to approval of this BLA:

A. Container labels
   1. Please indicate where the required lot number and expiration date will appear as
      required per 21 CFR 610.60.
   2. Include the finished dosage form below the proper name on the principal display
      panel (PDP)\(^c\).
   3. Consider stating number greater than or equal to 1,000 with a comma to prevent
      the reader from misinterpreting thousands “1000” as hundreds “100” or ten
      thousands “1000.”

B. Carton labeling
   1. See A.1 through A.3 and revise the carton labeling accordingly.

\(^a\) Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling
Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human
Use. 2015. Available from

\(^b\) United States Pharmacopoeia (USP). General Chapter <1> Injections

\(^c\) Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Draft Guidance
[Internet].FDA. April 2013 [cited 2017 March 17]. Available from:
2. Include the statement “Discard unused portion” after “Sterile Solution- No Preservative” on the Principal Display Panel. We recommend this to mitigate the risk of the vial being used to prepare more than one dose.

3. Relocate the routes of administration and package information statements below the statement of strength on the principal display panel to bring prominence to this important information.

For example:

Retacrit
“Epoetin Hospira”
Recombinant Injection
2,000 units/mL
For Intravenous or Subcutaneous Use only
Sterile Solution- No Preservative
Discard unused portion

4. Switch the locations of route of administration statement and the storage information on the principal display panel to bring prominence to the route of administration.

________________________________________

* Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Retacrit that Hospira submitted on December 22, 2016, and the listed drug (LD).

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Retacrit</th>
<th>US-licensed Epogen/Procrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval Date</td>
<td>N/A</td>
<td>June 1, 1989</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>“Epoetin Hospira*”</td>
<td>Epoetin alfa</td>
</tr>
<tr>
<td>Indication</td>
<td>Treatment of anemia due to: Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis, Zidovudine in HIV-infected patients, Chemotherapy in patients with Cancer. Reduction of allogenic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery.</td>
<td>Treatment of anemia due to: Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis, Zidovudine in HIV-infected patients, Chemotherapy in patients with Cancer. Reduction of allogenic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery.</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Intravenous and subcutaneous</td>
<td>Intravenous and subcutaneous</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Injection</td>
<td>Injection</td>
</tr>
<tr>
<td>Strength</td>
<td>Single-dose vials: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL</td>
<td>Single-dose vials: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL Multi-dose vials: 20,000 units/2 mL and 20,000 units/mL</td>
</tr>
<tr>
<td>Dose and Frequency</td>
<td>Treatment of anemia due to Chronic Kidney Disease (CKD) in</td>
<td>Treatment of anemia due to Chronic Kidney Disease (CKD) in</td>
</tr>
</tbody>
</table>

* Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
patients on dialysis and not on dialysis

- Adult patients: 50 to 100 units/kg 3 times weekly intravenously or subcutaneously.
- Pediatric patients: 50 units/kg 3 times weekly or intravenously is recommended. The intravenous route is recommended for patients on hemodialysis.

Treatment of anemia due to Zidovudine in HIV-infected patients

- The recommended starting dose in adult patients is 100 units/kg as an intravenous or subcutaneous injection 3 times per week.

Treatment of anemia due to chemotherapy in patients with cancer

- Adults: 150 units/kg subcutaneously 3 times per week until completion of a chemotherapy course or 40,000 units subcutaneously weekly for 4 weeks.
- Pediatric patients (5 to 18 years): 600 units intravenously weekly until completion of a chemotherapy course.

Treatment of anemic patients (hemoglobin > 10 to <13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery}

patients on dialysis and not on dialysis

- Adult patients: 50 to 100 units/kg 3 times weekly intravenously or subcutaneously.
- Pediatric patients: 50 units/kg 3 times weekly or intravenously is recommended. The intravenous route is recommended for patients on hemodialysis.

Treatment of anemia due to Zidovudine in HIV-infected patients

- The recommended starting dose in adult patients is 100 units/kg as an intravenous or subcutaneous injection 3 times per week.

Treatment of anemia due to chemotherapy in patients with cancer

- Adults: 150 units/kg subcutaneously 3 times per week until completion of a chemotherapy course or 40,000 units subcutaneously weekly for 4 weeks.
- Pediatric patients (5 to 18 years): 600 units intravenously weekly until completion of a chemotherapy course.

Treatment of anemic patients (hemoglobin > 10 to <13 g/dL) scheduled to undergo elective,
to reduce the need for allogeneic blood transfusions

- The recommended regimens are 300 units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery. Alternatively, 600 units/kg can be administered subcutaneously in 4 doses on 21, 14, and 7 days before surgery and on the day of surgery.

The recommended regimens are 300 units/kg per day subcutaneously for 15 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery. Alternatively, 600 units/kg can be administered subcutaneously in 4 doses on 21, 14, and 7 days before surgery and on the day of surgery.

### How Supplied

<table>
<thead>
<tr>
<th></th>
<th>Single-dose, preservative-free vial: 1 mL of solution contains 2000, 3000, 4000, 10,000, or 40,000 units of “Epoetin Hospira*”</th>
</tr>
</thead>
</table>

### Storage

<table>
<thead>
<tr>
<th></th>
<th>Store at 36°F to 46°F (2°C to 8°C). Do not freeze. Do not shake. Protect from light; store Retacrit in the carton until use. Do not use Retacrit that has been shaken or frozen.</th>
</tr>
</thead>
</table>

* Retacrit has been developed as a proposed biosimilar to US-licensed Epogen/Procrit (epoetin alfa). Since the proper name for Retacrit has not yet been determined, “Epoetin Hospira” is used throughout this review in place of the nonproprietary name for this product.
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 2, 2017, we searched the L:drive and AIMS using the terms, Retacrit to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one label and labeling review memo\(^d\). We did not have any recommendations in the review because the application was receiving a Complete Response.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on February 27, 2017 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.\(^{\text{e}}\)

<table>
<thead>
<tr>
<th>Table 3: FAERS Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial FDA Receive Dates</strong></td>
</tr>
<tr>
<td><strong>Product Name</strong></td>
</tr>
<tr>
<td><strong>Product Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Event (MedDRA Terms)</strong></td>
</tr>
</tbody>
</table>

E.2 Results

Our search identified 409 cases, of which 30 cases described medication errors relevant for this review. Some cases described more than one type of medication error.

**Incorrect route of drug administration (n = 18)**

- Eighteen cases reported inappropriate route of drug administration of US-licensed Epogen/Procrit (FAERS Case No. 10226430, 10226531, 12440151, 12440309, 12440380, 10226407, 10226493, 10226534, 10226545, 11172428, 1172443, 11172484, 11172493, 11172521, 11172534, 12440211, 12440386, 12443117).
  - Seventeen of the cases described patients who received US-licensed Epogen/Procrit via an intramuscular injection instead of a subcutaneous injection. One patient complained of burning sensation at the site of injection. One nurse reported that the prescriber did not indicate the route of administration on the prescription, which contributed the medication error. The remaining cases did not provide contributing factors or patient outcomes.
  - One case described a patient who received Procrit via oral route by his family. The patient did not experience any adverse effects. Contributing factors were not reported for this case.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Epogen/Procrit indications that the route of administration is clearly listed. The route of administration information in the Prescribing Information for Retacrit is similar to the reference

product and does not appear vulnerable to medication errors. Additionally, the proposed IFU for Retacrit depicts intravenous and subcutaneous administration. Labeling revisions are not necessary at this time.

Incorrect dose administration (n =1)

- One case (FAERS Case No. 10226440) described a 3-year-old patient who was not responding to Epogen therapy for one month. It was stated that the patient was using an adult dose. Patient outcomes were not reported.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Epogen/Procrit indicates that the dosing information is clearly listed. Additionally, we note the PI contains directives for dose modifications based on hemoglobin lab values. The dosing information in the Prescribing Information for Retacrit is similar to the reference product and does not appear vulnerable to medication errors.

Wrong technique during drug usage process (n =7)

- Seven cases reported wrong technique during drug usage process of US-licensed Epogen/Procrit (FAERS Case No. 12440130, 12440152, 10226564, 12440138, 12440141, 12440219, 12440261).
  - Three cases described preservative free vials being used twice for two different doses. Contributing factors or patient outcomes were not reported.
  - One case described the syringe used by the patient was broken and stayed inside the patient’s body. It was reported that the physician advised to use a second vial to get the dose. Contributing factors or patient outcomes were not reported.
  - Two cases described air bubbles were introduced into the syringe during dose preparation of the product. One of the cases reported a missed dose because of the wrong technique. The other case contributed the wrong technique to the use of a smaller needle to withdraw the dose.
  - One case described a nurse flicking the vial of Procrit before administering the dose to the patient. The patient experienced a decline in the hemoglobin value and was unsure if the nurse’s technique may have contributed to the drop in hemoglobin. Contributing factors to the medication error were not reported.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Epogen/Procrit indicates to discard unused portions of Epogen in preservative-free vials. The PI further states “Do not re-enter preservative-free vials.” Our review of the proposed IFU for Retacrit recommends for users not to shake the vial and provides instructions on how to remove air bubbles from the syringe. Additionally, the proposed PI clearly depicts intravenous and subcutaneous administration. Labeling revisions are not necessary at this time.
Incorrect schedule of administration (n =4)

- One case (FAERS Case No. 11172515) described a patient was administered Procrit only when her blood count drops. No additional information was provided.
- One case (FAERS case No. 11233352) described a patient receiving Procrit 40 (unit not provided) subcutaneously every other week to raise her blood count. Approximately three years later in April 2015, the patient was not receiving adequate blood circulation to her foot, causing her toes to look black. As a result, the patient had couple of toes removed in May 2015.
- Another case (FAERS case No.10722575) described a patient on Procrit 4000 units subcutaneous weekly if needed in January 2014. The baseline hemoglobin (Hgb) was not provided. It was reported that the patient received Procrit depending on her Hgb level; so for some weeks, she received Procrit and for others she did not.
- One case (FAERS case No.11172552) described a patient on Procrit subcutaneously as needed (the dose and unit was not provided) on an unknown date. In April 2015, the patient experienced drop in her hemoglobin five months after her last injection. No treatment information was reported. The outcome of the events drop in her hemoglobin and receiving Procrit as need was reported as ongoing. Procrit therapy was continued.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Epogen/Procrit indicates that the dosing schedule is clearly listed. Additionally, we note the PI contains directives for dose modifications based on hemoglobin lab values for all indications. The dosing information in the Prescribing Information for Retacrit is similar to the reference product and does not appear vulnerable to medication errors.

We excluded 379 cases because they described errors involving: accidental exposure (n = 11), drug dose omission (n = 77), error not related to Epogen (n = 8), expired drug administered (n = 34), extra dose administered (n =3), incorrect dose not related to labeling (n = 3), incorrect vial fill volume (n = 8), incorrect product storage (n = 234), and accidental overdose (n = 1).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

<table>
<thead>
<tr>
<th>FAERS Case Number</th>
<th>Manufacturer Control Number</th>
<th>Version Number</th>
<th>FAERS Case Number</th>
<th>Manufacturer Control Number</th>
<th>Version Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>10226430</td>
<td>US-AMGEN INC.-USASP2013050589</td>
<td>1</td>
<td>12440130</td>
<td>US-AMGEN-USASP2015100263</td>
<td>1</td>
</tr>
<tr>
<td>10226531</td>
<td>US-AMGEN INC.-USASP2013082666</td>
<td>1</td>
<td>12440152</td>
<td>US-AMGEN-USASP2015098911</td>
<td>1</td>
</tr>
</tbody>
</table>
### E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA’s postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA’s Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded
using the FAERS Product Dictionary. More information about FAERS can be found at: 

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Retacrit labels and labeling submitted by Hospira on December 22, 2016.

- Container label
- Carton labeling
- Prescribing Information
- Instructions for Use
- Medication Guide

G.2 Label and Labeling Images

Container labels

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE B GARRISON
05/22/2017

HINA S MEHTA
05/23/2017

MISHALE P MISTRY
05/23/2017
I. Background

This is a follow up memo to the Clinical Inspection Reports (CISs) dated July 10, 2015 and August 7, 2015, for the applicant’s Epoetin Hospira. As requested by the Agency in the Complete Response (CR) letter received on October 16, 2015, the applicant provided sponsor and CRO audit reports performed during the conduct of the clinical investigative studies EPOE-10-01 and EPOE-10-13, and monitoring records from clinical investigator sites closed during the conduct of the trials.

<table>
<thead>
<tr>
<th>Date</th>
<th>May 19, 2017</th>
</tr>
</thead>
</table>
| From | Anthony Orencia, M.D., F.A.C.P., GCPAB Medical Officer  
Cynthia, Kleppinger, M.D., GCPAB, Acting Team Leader  
Janice Pohlman, M.D., M.P.H., GCPAB Team Leader  
Kassa Ayalew, M.D. M.P.H., GCPAB Branch Chief  
Division of Clinical Compliance Evaluation/OSI |
| To | Lori Ehrlich, M.D., Ph.D., Medical Officer  
R. Angelo de Claro, M.D., Cross Discipline Team Leader  
Ann Farrell, M.D., Division Director  
Beatrice Kallungal, Regulatory Project Manager  
Division of Hematology Products/OHOP |
| BLA # | 125545 S-044 (Complete Response Submission) |
| Applicant | Hospira, a Pfizer Company |
| Drug | Epoetin Hospira |
| NME (Yes/No) | No (Complete Response Submission) |
| Therapeutic Classification | Colony stimulating factor |
| Proposed Indication(s) | Treatment of anemia in patients with:  
• Chronic kidney disease  
• Anemia in HIV due to zidovudine treatment  
• Non-myeloid malignancies  
• Perioperative hemoglobin > 10 to < 13 g/dL at high risk for perioperative blood loss from elective, non-cardiac, nonvascular surgery |
| Consultation Request Date | February 13, 2017 (signed) |
| Goal Date | May 18, 2017 (original)  
May 22, 2017 (extension) |
| Action Goal Date | June 22, 2017 |
| BsUFA/PDUFA Date | June 22, 2017 {BsUFA [351 k, biosimilar application]} |
The Division consulted the Office of Scientific Investigations (OSI) on February 13, 2017 to review the audit and monitoring reports submitted by the Applicant to verify that GCP compliance items were adequately addressed during the course of the study.

During the initial review cycle, two clinical trials, studies EPOE-10-01 and EPOE-10-13, submitted in support of the sponsor’s 351(k) (biosimilar) application were selected for clinical site inspections by FDA. Five clinical investigator (CI) sites and the sponsor were inspected. Four of the five CI sites inspected were classified as voluntary action indicated (VAI) and one CI site, No Action Indicated (NAI). The sponsor inspection was classified as VAI. For details of those inspections, refer to the Clinical Inspection Summary entered into DARRTS July 10, 2015.

The application included seven unique investigators closed by the sponsor during study conduct for GCP noncompliance [Note: Through the post-study GCP assessment, the Sponsor identified two additional investigators, Dr. Chiang and Dr. Liss, to be excluded from study-level sensitivity analyses for EPOE-10-01]. Of these seven unique investigators, three participated in both EPOE-10-13 and EPOE-10-01 [Drs. Devidoss, El-Shahawy, and Moustafa].

- Closures for two clinical investigators without conduct of a Hospira clinical investigator audit
  - Dr. Sakhrani for EPOE-10-01
  - Dr. Shapiro for EPOE-10-01
- Closures for three clinical investigators with conduct of a routine Hospira clinical investigator audit
  - Dr. El-Shahawy for EPOE-10-01 and EPOE-10-13
  - Dr. Espinosa-Melendez for EPOE-10-01
  - Dr. Moustafa for EPOE-10-01 and EPOE-10-13
- Closures for two clinical investigators with conduct of a for-cause Hospira clinical quality audit
  - Dr. Devidoss for EPOE 10-01 and EPOE 10-13
  - Dr. Baer for EPOE-10-01

Additionally, there were six CI sites that were inspected related to the two studies under IND 100685 because of complaints submitted to OSI. Four of the CI site inspections were classified as VAI and one CI site as NAI. One of the six CI sites, Dr. Mohammed El-Shahawy, was classified as Official Action Indicated (OAI) and an Untitled Letter was issued on July 8, 2015 to the investigator for failure to maintain adequate records of disposition of study drug, including dates, quantity, and use by subjects, specifically with respect to temperature logs for the study drugs (part of the drug disposition records for this protocol). For details of the for-cause inspection observations, refer to the Clinical Inspection Summary Addendum entered into DARRTS on August 7, 2015.

On October 16, 2015, a Complete Response letter was issued to the sponsor of BLA 125545. In part, the Agency requested the following: “...auditing reports for studies EPOE-10-01 and EPOE-10-13. The reports must include a description of the GCP compliance issues that you identified and measures taken to address the GCP compliance issues. For sites closed due to
GCP compliance issues, you must include the details of the GCP compliance issues.”
The Post-Study GCP Assessment Report was submitted as a component of the sponsor’s Complete Response to the first review cycle CR letter issued by the review division on October 16, 2015.

OSI reviewed the available audit reports (described below) for clinical studies EPOE-10-01 and EPOE-10-13. The comments made by the OSI reviewer about the audit findings are based only on the sponsor’s audit findings, which do not contain exhibits from the clinical investigator sites.

**Audit Findings:**
The clinical package for Epoetin Hospira is comprised of seven clinical studies. The focus of the Post-Study GCP Assessment Report was Study EPOE-10-01 (N=612 randomized into the ITT) and Study EPOE-10-13 (N=246 randomized into the ITT maintenance period).

For Study EPOE-10-01, 27 CI site audits (23 routine and four for-cause audits) were conducted and for Study EPOE-10-13, 13 CI sites audits (12 routine and one for-cause audits) were conducted by Hospira. The monitoring CRO, also conducted three routine CI site audits for study EPOE-10-01 and two routine CI site audits for study EPOE-10-13.

### Clinical Investigator Sites and Audits Conducted by Hospira and in Studies EPOE-10-01 and EPOE-10-13

<table>
<thead>
<tr>
<th></th>
<th>EPOE-10-01</th>
<th>EPOE-10-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Investigator Sites</td>
<td>95</td>
<td>68</td>
</tr>
<tr>
<td>Clinical Investigators*</td>
<td>78</td>
<td>52</td>
</tr>
<tr>
<td>Total Clinical Investigator Audits Conducted</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

*Some clinical investigators participated in both EPOE-10-01 and EPOE-10-13.
A Clinical Investigator could have more than one site within a study and an investigator could have sites in both studies. (From: Table 2. Clinical Investigator Sites and Audits Conducted by Hospira and in Studies EPOE-10-01 and EPOE-10-13, Post-Study GCP Assessment Report).

The Post-Study GCP Assessment Report included a review of overall study controls while studies were ongoing, observations from sponsor audits and contract research organization audits, monitoring reports from CI sites that were audited, FDA-inspected, or directly closed for GCP non-compliance without audits, and additional documentation from data sources from the trial master file, and clinical and safety databases. Audit site profiles encompassing critical and major observations representing a significant departure from written policy or procedure were also submitted with this report. Detailed outlines of identified issues and attempted corrective measures were provided, along with dates of the letters notifying the FDA of CI site closures.

For the Post-Study GCP Assessment, multiple teams of two persons who had not participated in the studies and were familiar with quality assurance and clinical development gathered information from the sources noted above. Summary reports for each of the sites were

Reference ID: 4100767
Reference ID: 4266940
developed and an initial assessment was made as to the overall quality and reliability of information. This information was presented to a core team of five individuals with expertise in areas of quality, operations, regulatory affairs, and clinical development; four members were from Pfizer and had not participated in the studies, while the fifth member was from Hospira and had been involved in clinical trial conduct. Final review and conclusions on clinical site disposition were determined by the four members from Pfizer.

The clinical investigator sites that were closed for GCP non-compliance by the sponsor are described below in the table, followed by further discussion.

**Clinical Investigator Sites Closed During Study Conduct by Hospira for GCP Noncompliance in Studies EPOE-10-13 and EPOE-10-01**

<table>
<thead>
<tr>
<th>Investigator/Site #</th>
<th>Study # / Randomized Intent-to-Treat Subjects (n)</th>
<th>GCP noncompliance sponsor comment/s*</th>
</tr>
</thead>
</table>
| Chakkungal Devidoss, M.D. EPOE-10-13 Site 21020 EPOE-10-01 Site 11098 | EPOE-10-13 ITT=0 EPOE-10-01 ITT=9 | • Informed consent documentation discrepancies  
• Source documentation inconsistencies; ALCOA principles not followed  
• Multiple protocol deviations, including  
  - Randomized subjects who did not meet eligibility  
  - Study drug temperature issues  
  - Significant delay in first dose administration after subject randomization  
  - Week 2 dosing administration occurred less than 7 days after the Week 1 dosing administration  
  - Laboratory samples not obtained per the protocol  
• Lack of PI oversight / Delegation of Duties not properly executed  
• ICH/GCP issues, lack of site understanding / background  
• Regulatory document deficiencies / discrepancies |
| Mohamed El-Shahawy, M.D. EPOE-10-13 Site 21012 EPOE-10-01 Site 11095 | EPOE-10-13 ITT=14 EPOE-10-01 ITT=5 | • SAEs not fully reported  
• EDC data entry not up to date  
• Insufficient documentation to support dosing and reconciliation of study drug  
• Lack of training and follow through on ICH/GCP/ Good Documentation Practices for study personnel  
• Lack of PI oversight |
| Moustafa Moustafa, M.D. EPOE-10-13 Sites 24020 EPOE-10-01 Site 14028 | EPOE-10-13 ITT=6 EPOE-10-01 ITT=12 | • SAEs have not been reported within 24 hours of knowledge on multiple occasions  
• Over 80 protocol deviations including misdosing of patients, potential unblinding of staff, randomization outside of protocol window, out of temperature range medication administered to patients and multiple dosing errors on 14 subjects  
• Lack of documentation to show qualifications of delegated unblinded study coordinator tasks  
• Unblinded coordinator was incorrectly drawing |
<table>
<thead>
<tr>
<th>Investigator/Site #</th>
<th>Study # / Randomized Intent-to-Treat Subjects (n)</th>
<th>GCP noncompliance sponsor comment/s*</th>
</tr>
</thead>
</table>
| Harold Baer, Jr., M.D. EPOE-10-01 Site 11100 | EPOE-10-01 ITT=14 | up IP, filling the syringes based on a visual assessment of volume and not differentiating between the 2,000 U and 10,000 U vials  
• Improper monitoring of storage temperature requirements for IP.  
  - The site’s thermometer was due for calibration on Nov. 11, 2011; however, the thermometer had not been calibrated as of the last unblinded monitoring visit on Sept. 11, 2012.  
  - IP which had been out of the required range of 2°-8°C was dispensed to 4 subjects.  
  - The min/max temperature data loggers used to track the refrigerator temperatures were not re-set each day so the temperature logs may not accurately reflect the minimum and maximum temperatures for the IP storage refrigerator.  
• Informed consent documentation discrepancies  
• Source documentation inconsistencies; ALCOA principles not followed  
• Multiple protocol deviations, including subjects not dosed per protocol, and failure to report SAEs per requirements (one)  
• Laboratory samples not obtained or processed per the protocol (unable to trace to origin due to mis-labeling)  
• Lack of PI oversight / Delegation of Duties not properly executed  
• ICH/GCP issues, lack of site understanding / background  
• Regulatory document deficiencies / discrepancies |
| Enrique Espinosa-Melendez, M.D. EPOE-10-01 Site 11005 | EPOE-10-01 ITT=7 | • Lack of PI oversight  
  - No written progress notes for any study subject for any visits  
  - No documented assessment of adverse event severity or relationship to study drug  
  - Incomplete assessment and/or unreported protocol deviations  
  - Delegation of duties not properly executed  
  - Laboratory results not reviewed or out of range results not assessed by PI for clinical significance  
• Serious adverse events not reported/ followed up  
• Data entry non-compliance  
• Improper monitoring of storage temperature requirements for study drug |
| Lakhi Sakhrani, M.D. EPOE-10-01 Site 14048 | EPOE-10-01 ITT=5 | • Data entry non-compliance  
• Unreported study drug temperature excursions  
• Laboratory samples not obtained or processed per the protocol  
• Lack of PI oversight; laboratory results not reviewed or out of range results not assessed by PI |
<table>
<thead>
<tr>
<th>Investigator/Site #</th>
<th>Study # / Randomized Intent-to-Treat Subjects (n)</th>
<th>GCP noncompliance sponsor comment/s*</th>
</tr>
</thead>
</table>
| Warren Shapiro, M.D. EPOE-10-01 Site 14015 | EPOE-10-01 ITT=1 | • Source documentation inconsistencies, ALCOA principles not followed  
• Study drug issues including accountability discrepancies, improper disposal, inadequate supply on site, issues with temperature monitoring, study drug labeling  
• Data entry non-compliance  
• Multiple protocol deviations including study drug temperature issues, laboratory samples not obtained per the protocol  
• Lack of PI oversight and delegation of duties not properly executed  
• Training non-compliance including but not limited to Protocol, ICH/GCP and IP  
• ICH/GCP issues, lack of site understanding/background  
• Regulatory document deficiencies/ discrepancies  
• Lack of responsiveness |
| Wen-Yuan Maricenne Chiang, M.D. EPOE-10-01 Site 11083 | EPOE-10-01 ITT=5 | Insufficient documentation to support drug dosing and drug reconciliation (IP documentation done months later “from memory” with retroactive dating placed/Post-it notes on vials instead of labels). |
| Kenneth A. Liss EPOE-10-01 Site 11094 | EPOE-10-01 ITT=7 | • Source documentation inconsistencies, ALCOA principles not followed  
• Multiple protocol deviations including  
• Randomized subjects who did not meet eligibility criteria  
• Study drug temperature issues  
• Failure to report SAEs per requirements  
• Lack of PI oversight and delegation of duties not properly executed  
• Study drug issues including  
  • Unblinding of all seven patients  
  • Inadequate documentation of maintenance of IP temperature  
  • IP vial labeling  
• Inadequate informed consent process  
• Data entry non-compliance  
• Lack of responsiveness |

*From: Table 3 of applicant’s Post-Study GCP Assessment for Studies EPOE-10-13 and EPOE-10-01.  
Legend: ALCOA=Attributable, Legible, Contemporaneous, Original, Accurate. ICH=International Conference on Harmonization. EDC=electronic data capture. PI=principal investigator. IP=investigational product (i.e., Epoetin Hospira).
**Chakkungal Devidoss, M.D.:** Two of 20 consents were signed and dated by the PI almost three months after the patients were consented. Signature dates on documents occurred before the date the information was obtained. The signature date for PI signature authorizing study responsibilities indicated that PI backdated signatures. Three subjects did not meet inclusion criteria. There was no documentation showing PI’s review of screening labs or eligibility for any patient. The site experienced multiple temperature excursions that were not reported and not clearly documented. There were many changes to source data observed for all subjects enrolled which were not properly lined through, initialed and dated by the individual making the change. Source worksheets for all subjects were completed in a way that it is not possible to determine which checkbox was checked. Many source worksheets for all subjects are completed in two different colors of ink and different handwriting; however, there is only one signature on the worksheet. Site was closed February 6, 2013 but FDA was not notified until November 14, 2013.

**Mohamed El-Shahawy, M.D.:** Numerous deficiencies and discrepancies were noted between the source documents and the eCRFs, including missing adverse events (AEs) and concomitant medications. Access to the second floor, where the study drug refrigerator was located, was not secure. Facility was freely accessible by non-personnel. The former unblinded Study Coordinator (SC) did not hand over keys to the facility and IP refrigerators upon termination of employment and locks to the facility and IP refrigerators had not been changed since the former SC’s departure. Two days after resigning, the unblinded SC brought several empty vials into the LA Dialysis Unit and gave them to the Blinded Coordinator, who refused to accept them. Two SAE Follow-up Reports were not submitted. The chairside dialysis flow sheet noted that a subject was dosed from September 15 to 25, 2012 with ‘11000’ units which on June 12, 2013 all doses were changed to ‘14300’ units by the blind SC (no explanation). Non-variability in the handwriting on the Study Drug Preparation and Administration Worksheets indicated that the worksheets were written after the fact. This was confirmed by the blind SC. Discrepancies were noted between investigational product (IP) accountability records, IP inventory on site, and data recorded in the Drug Dispensation eCRFs. Shipment Confirmations were missing for six out of twelve shipments. Reconciliation of the dispensation of ten vials of study drug could not be achieved due to the lack of proper IP return documentation. Five dispensing log errors were noted where entries of vials dispensed were not recorded. Five discrepancies were noted between the Dispensing Logs and the data recorded in the Drug Dispensation eCRFs. The site was closed August 30, 2013 but FDA was not notified until November 14, 2013.

**Moustafa Moustafa, M.D.:** Critical errors related to receipt, storage, and preparation of the study drug were documented on 11 of 12 patients by unqualified site staff. There was inadequate documentation to determine whether the drug had been consistently maintained between 2°C-8°C. Dose calculations and doses of study drug administered were not accurately recorded. Dose preparation errors resulted in under-dosed subjects. Syringe labels were missing dose prepared. Documentation errors in vial concentration were noted on Patient Dispensing Logs. Inventory errors were noted during reconciliation against subject specific IP dispensing records and physical count. The site was closed October 31, 2012 and FDA was notified November 21, 2012.
Harold Baer, Jr., M.D.: Source documents filed in the blinded patient research binders contained information that had the potential to unblind every patient enrolled in the study. The potential existed for the blinded staff to have visibility to a ‘Note’ contained in the electronic medical record, if they chose to print the dialysis flow sheets or access the order system, that would unblind the study. This issue was not identified by Clinical Research Associates (CRAs). The site was closed June 25, 2013 but the FDA was not notified until February 19, 2014.

Enrique Espinosa-Melendez, M.D.: IRB requires notification of screening or enrollment hold either by the site or sponsor. Such documentation, which was documented as sent to the site, was not available at the site and was not sent to the IRB. Over a 5-month period, the study drug, which was administered to subjects, was not maintained within the range of 2°-8°C. These temperature excursions went unreported. Several subjects had screening labs collected prior to consent. The site was closed January 2, 2013 and the FDA was notified March 21, 2013.


Wen-Yuan Marianne Chiang, M.D.: Site's process for documenting the dispensing and administering of study drug did not include completing the Study Drug Preparation and Administration Worksheets or Patient Dispensing Logs in real time. Labeling of used vials was performed using post-it notes, which were then placed in a locked box in a locked refrigerator. Labeled vials of study drug dispensed had patient identification labels affixed in a manner that obscured the product label. A discrepancy in the number and concentration of vials dispensed was noted for subject . Documentation of the PI's assessment of severity and relatedness of AEs and SAEs was not contemporaneous. Discrepancies in IP accountability and the IP accountability process were not adequately identified and/or resolved by the monitors and sponsor/CRO staff. This site was not pre-maturely closed.

Kenneth A. Liss: Informed consent forms (ICFs) were not signed by the PI contemporaneously when the consent process was conducted for nine of 11 subjects. The PI evaluation of eligibility for all patients was supposedly conducted before randomization, but not documented until July 18, 2012 in a note to file. There is inadequate documentation available to determine whether study drug was consistently maintained between 2°-8°C. Two known temperature excursions occurred at the site. The thermometer used at site 11094 stopped working on August 10, 2012 and temperature documentation was missing for several days in August and September 2012. The site did not label the majority of study drug vials with the patient randomization number, date and time medication was withdrawn from the vial as required by the Study Drug Accountability Instructions dated November 14, 2011. Though there was no evidence of unblinding by the site, there were study wide procedures that could compromise the maintenance of the blind at study sites: If study drug had to be quarantined due to a temperature excursion, and drug was dispensed on that day, by default the drug had to
be Epogen Amgen since resupply of Epoetin Hospira took a minimum of 1-2 days. All seven enrolled patients received standard of care (SOC) following enrollment due to either an unplanned facility closure from June 9 to 19, 2012, or due to patent vacations.

In addition, there were critical audit findings of sites that were not closed.

- **Dr. Chong**, EPOE-10-01, Site # 14050, 14051, 14058: Inadequate maintenance of study blind. All three patients enrolled at Site 14058 received study drug that was prepared and administered by the same nurse. Two subjects did not meet eligibility criteria. These deviations were sent to the Medical Monitor and IRB.

- **Dr. Christiano**, EPOE-10-01, Site # 13062: Study drug doses were not reduced or interrupted for hemoglobin greater than 11 g/dL as required by Protocol Section 5.1.6 Study Dosing During the Treatment Period.

- **Dr. Diamond**, EPOE-10-01, Site # 11003, 11116: Inadequate maintenance of study blind by . Inappropriate un-blinding information relating to the study drug assignment for Patients were provided to the PI in the blinded follow up letter of the unblinded interim monitoring visit (IMV) 4, dated February 8, 2013. It was later replaced with a corrected, blinded version.

- **Dr. Dua**, EPOE-10-01, Site # 14040, 14041: Potential compromise of study blind for EPOE-10-01 by . Study drug for both EPOE-10-01 and EPOE-11-03 were stored in the same refrigerator at each site. No blinded site staffers for EPOE-10-01 were delegated responsibilities for EPOE-11-03; however, blinded CRAs who were assigned to the sites for EPOE-10-01 also conducted visits for EPOE-11-03, including performing drug accountability and returning used study drug for EPOE-11-03. Study drug for both studies was stored within the lockbox and outside the lockbox in the locked refrigerator. It is possible that while performing drug accountability for EPOE-11-03, the CRA was exposed to study drug from EPOE-10-01.

- **Dr. Kazmi**, EPOE-10-13, Site # 24035: Blinded study nurse or blinded coordinator prepared study drug, conducted assessments and administered IP. This occurred for three subjects. The situation was reported to the IRB, who directed the site to ensure blinded nurse did not administer IP in the future; however, blinded nurses continued to conduct assessments and administer IP.

- **Dr. Lee**, EPOE-10-01, Site # 11015, 11016: The PI did not follow recommendations listed in Protocol Section 5.1.6 for study dosing during the treatment period.

- **Dr. Martinez**, EPOE-10-01/ EPOE-10-13. Site # 11018/ 21002: Dialysis flow sheets were only printed for one day when the subject received investigational product but not for the other two days of the week when dialysis was performed. Data deficiencies and discrepancies noted between source documents and electronic CRFs.
• **Dr. Matalon**, EPOE-10-01, Site # 15004, 15007: Inadequate maintenance of study blind. Unblinded Study Coordinators (SCs) at the sites prepared study drug, administered study drug and documented dialysis treatment evaluations for most patients enrolled in the study. They provided patient care as required to cover for nurses who called in sick or who were on break. There was non-compliance with the Site Specific Blinding Plan version 5.0. The plan requires that the study drug be stored in a lockable refrigerator with access restricted to unblinded site personnel only as required. Blinded study nurses had access to the key which unlocked this refrigerator.

• **Dr. Smith**, EPOE-10-13, Site # 24008, 24009, 24036: The site did not label the majority of study drug vials with the patient randomization number, date and time medication was withdrawn from the vial as required by the Study Drug Accountability Instructions dated November 4, 2011.

Several audit reports of the sites made the observation that the study monitoring was critically inadequate. Hospira contracted with [redacted] to perform site monitoring of the EPOE-10-13 and EPOE-10-01 studies and monitoring was conducted according to [redacted] SOPs. In March 2013, Hospira reviewed the conduct of monitoring for studies EPOE-10-13 and EPOE-10-01 and agreed on a plan for corrective measures with [redacted]. These corrective measures included adding CRA staff and a plan for re-monitoring a subset of data at select sites. The re-monitoring took place between October 2013 and February 2014 and was conducted by [redacted] according to a plan they defined; a total of 33 sites had re-monitoring conducted. Observations related to drug administration, AE/SAE reporting and concomitant medications were identified in many of the site audits and therefore selected for review during the plan for re-monitoring.

Re-monitoring resulted in the identification of additional previously unreported AEs, including two SAEs and concomitant medications. In addition, corrections were identified to previously entered and monitored data regarding dosing. All findings were discussed with site staff in the course of the re-monitoring visit and updates and additions were made to the electronic CRF as appropriate.

In October 2013, Hospira contracted with a second CRO, [redacted] and a subset of clinical investigator sites were transitioned from [redacted] for the conduct of monitoring.

In summary, 121 unique sites enrolled patients (68 sites in EPOE-10-13 and 95 sites in EPOE-10-01). FDA inspected a total of 11 clinical sites and the sponsor for the application, resulting in one OAI classification for Dr. Mohammed El-Shahawy, a site that had been closed by the sponsor.

For study EPOE-10-01, five clinical investigator sites were closed by the sponsor for GCP non-compliance based on audits and two additional sites were closed due to GCP non-compliance issues identified by monitors. The five sites closed (as a subset of the 27 audited) accounted for half (30 of the 60) critical observations. Per the Applicant, these critical observations represent a significant departure from written policy or procedure (Hospira Corporate Policy, Hospira SOPs, Quality System Documents), appropriate regulation or
guideline that would be cited by a regulatory agency and would have a serious impact on the validity of the Applicant’s data or on the system or process. The most common critical observations were related to the investigational product and monitoring.

For study EPOE-10-13, three clinical investigator sites were closed for GCP non-compliance based on the audits. These three closed sites accounted for 20 of the 34 critical observations, with the most common problem related to Epotin Hospira.

The sponsor addressed the inadequate monitoring cited in the audit reports with corrective actions.

**OSI Reviewer Comments:**
Sponsor and CRO audits performed while studies EPOE-10-01 and EPOE-10-13 were ongoing and additional monitoring records from CI sites closed during the conduct of the trials were provided as requested by DHP in the CR letter. The sponsor (Hospira, a Pfizer Company) appears to have conducted this review in a thorough manner. The Post-Study GCP Assessment review was conducted by Applicant’s core team, which comprised senior corporate management representatives. The core team’s decisions about the clinical study sites were arrived via a consensus process. A final post-study GCP descriptive evaluation was conducted. This group reviewed the study site audit reports and documentations, without recommendation, as to a study site disposition for the Applicant’s post-study GCP sensitivity analyses.

Additional study-level sensitivity analyses have been conducted to address the FDA request for sensitivity analyses that exclude the patients from sites closed due to GCP noncompliance issues. The reported non-compliances identified by the sponsor at these clinical investigator sites reflected in the Post-Study GCP Assessment review are concerning, such as Mohamed El-Shahawy, M.D. and Enrique Mendoza-Melendez, M.D. Therefore, the sensitivity analysis requested by the review division is reasonable.

Limitations of this Post-Study GCP Assessment include the fact that this was only a partial look at clinical investigator sites, although the sites were selected in accordance with the sponsor’s standard operating procedures. Additionally, the review was retrospective (after initial study analysis and unblinding), and the review was conducted by representatives from the sponsor, although these senior reviewers were not involved in the conduct of these particular studies. There appeared to be no singular prominent or systemic problems that emerged other than the fact that the initial monitoring done by the contract research organization was inadequate. As diverse, multiple GCP non-compliance issues were identified in the course of the studies, the Applicant sought corrective actions and re-evaluation of the selected clinical investigator sites.

**II. CONCLUSION**
The sponsor (Hospira, a Pfizer Company) appears to have conducted this review in a thorough manner and reported the GCP violations and the sponsor’s monitoring process.

In the Applicant’s Post-Study GCP Assessment Report, the review was based on retrospective evaluation (after initial study analysis and un-blinding of the clinical sites) of the audits and monitoring records. A retrospective, qualitative review of the GCP compliance issues was conducted by non-independent representatives from the sponsor.

The GCP compliance items and other noncompliance items were addressed adequately in this Post-Study GCP Assessment Report. They also do not appear to result in an alteration of findings described in the original Clinical Inspection Reports.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Cynthia, Kleppinger, M.D., GCPAB, Acting Team Leader, for Janice Pohlman, M.D., M.P.H.
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OSI/DCCE/GCP MO Reviewer/Anthony Orencia
OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
05/19/2017

CYNTHIA F KLEPPINGER
05/19/2017

KASSA AYALEW
05/19/2017
1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the suffixes proposed by Hospira for the nonproprietary name and communicates our recommendation for the nonproprietary name.
2 ASSESSMENT OF THE NONPROPRIETARY NAME

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Hospira’s Retacrit product is necessary to distinguish this proposed product from Epogen/Procrit (epoetin alfa). As explained in FDA’s Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name for Retacrit include a distinguishing suffix that will facilitate safe use and optimal pharmacovigilance.

On December 22, 2016, Hospira submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of their product. The Applicant also provided for our consideration findings from an external study conducted by [redacted] evaluating the proposed four letter suffixes in conjunction with the nonproprietary name. We note that the Applicant submitted a total of six proposed suffixes, three labeled as “meaningful” suffixes and three labeled as “random” suffixes.

After this submission proposing a list of suffixes for this product, FDA published the final guidance on the Nonproprietary Naming of Biological Products on January 13, 2017 describing our current thinking that that the suffix be devoid of meaning and composed of four lowercase letters. Therefore, we did not evaluate the suitability of those suffixes that were listed as meaningful as these suffixes are plainly inconsistent with our final guidance. We reviewed Hospira’s proposed “random” suffixes in the order of preference listed by the Applicant, along with the supporting data they submitted, against the criteria described in the final guidance. a

A. Proposed “Random” suffixes:

1. We note that the [redacted] inconsistent with FDA’s final guidance on this topic which recommends that the suffixes be composed of at least three unique letters.

2. We note that [redacted] FDA finds that this suffix is meaningful [redacted].” Thus, we find that these suffixes are not devoid of meaning [redacted].

The use of a distinguishing suffix that is product-specific is less likely to be associated with a specific manufacturer, thus alleviating potential confusion among the health care providers (HCPs) and patients as to the license holder's identity if ownership of the product changes following licensure. Alternatively, if, to avoid such confusion, FDA designated a new suffix following a change in BLA ownership, whether on its own initiative or in response to a license holder’s requests, this too could result in confusion amongst health care providers and patients who could mistakenly conclude that the new suffix indicated a material change in the product or discontinuation of the product, as

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opposed to merely a change in ownership. While suffixes shared across a sponsor’s products may be more likely to be memorable than suffixes that are unique to each product, the increasing prevalence of electronic systems in the ordering, prescribing, and dispensing process reduces the potential utility of such memorability.

Collectively, the proposed suffixes [redacted] if approved, would result in inconsistency in the nonproprietary names of biological products if other sponsors’ products continue to bear suffixes that align with the naming convention described in the final guidance. The inconsistency could lead to confusion among the HCPs and patients as well as industry stakeholders, potentially detracting from our pharmacovigilance and safe use goals.

5. CONCLUSIONS

For the reasons described above, we find that Hospira’s proposed suffixes are unacceptable for the proposed nonproprietary name, epoetin alfa. Therefore, the decision to deny the suffixes will be communicated to the Applicant via letter.

6. COMMENTS TO THE APPLICANT

1. We find your proposed nonproprietary name, [redacted], unacceptable, as the proposed suffixes [redacted] inconsistent with FDA’s final guidance on this topic which recommends that the suffixes be composed of at least three unique letters.

2. We find your proposed nonproprietary name, [redacted], unacceptable [redacted] FDA finds that this suffix is meaningful [redacted].” Thus, we find that these suffixes are not devoid of meaning [redacted].

3. We note that you have not proposed any additional suffixes for our evaluation. Since your proposed suffixes were found unacceptable, please be informed that in the absence of other alternative proposals, we intend to designate the proper name with an FDA generated suffix should your 351(k) BLA be licensed this review cycle. Should you wish to avoid licensure of a proper name that includes an FDA-generated suffix, any alternatives should be communicated to FDA at your earliest convenience and no later than June 5, 2017.
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/s/

NICOLE B GARRISON
05/11/2017

LUBNA A MERCHANT
05/12/2017
This memo is in response to your labeling consult request on February 2, 2015. DHP issued a Complete Response (CR) letter on October 16, 2015. Therefore, OPDP defers comment on the Applicant’s labeling at this time. A comprehensive review of the proposed patient labeling will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.
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/s/

JAMES S DVORSKY
11/05/2015
DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Office of New Drugs /
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD  20993
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M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Lynne Yao, M.D., Division Director
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

To: Division of Hematology Products (DHP)

Drug: Epoetin Hospira (proposed biosimilar to Epogen [epoetin alpha])

Application Number: IND 100685/ BLA 125545

Re: Review of the initial Pediatric Study Plan (iPSP) and PSP

Applicant: Hospira, Inc.

Proposed Indications:
• Treatment of anemia due to:
  - Chronic Kidney Disease (CKD) in patients on
dialysis and not on dialysis.
  - Zidovudine in HIV-infected patients.
  - The effects of concomitant myelosuppressive
chemotherapy, and upon initiation, there is a
minimum of two additional months of planned
chemotherapy.
• Reduction of allogeneic red blood cell (RBC)
transfusions in patients undergoing elective, noncardiac,
nonvascular surgery.
Proposed dosage forms & route of administration: Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL. Intravenous and subcutaneous administration.

Proposed Dosing Regimen:

- **CKD Patients:**
  
  **Initial dose:**
  
  *Adults (on dialysis and non-dialysis):* 50 to 100 Units/kg 3 times weekly.
  *Pediatric patients (on dialysis only):* 50 Units/kg 3 times weekly.

  Individualize maintenance dose.

- **Zidovudine-treated HIV-infected Patients:**
  *Adults:* 100 Units/kg 3 times weekly.

- **Cancer Patients on Chemotherapy:**
  *Adults:* 40,000 Units weekly or 150 Units/kg 3 times weekly.
  
  *Pediatric patients (5 years and older):* 600 Units/kg intravenously weekly.

- **Surgery Patients:**
  *Adults:* 300 Units/kg per day daily for 15 days or 600 Units/kg weekly.

**Consult Request:** DHP requests assistance in evaluating the sponsor’s Pediatric Study Plan and preparing for the Pediatric Review Committee (PeRC) meeting.

**Materials Reviewed:**

- Epoetin Hospira initial Pediatric Study Plan (iPSP) (June 11, 2014)
- Revised Epoetin Hospira iPSPs (September 24, 2014 and December 17, 2014)
- DPMH consult request
- Current Epogen (epoetin alpha) labeling (December 31, 2013) per Drugs @FDA
- Approval letters and associated labeling for Epogen, BLA 103234 dated July 26, 1999; May 21, 2004; and July 30, 2004
- Pediatric Review Committee meeting minutes from the November 19, 2104 meeting (dated December 1, 2014 in DARRTS)

**Consult and Regulatory Background:**

Hospira, Inc. is developing Epoetin Hospira as a proposed biosimilar to Epogen (epoetin alpha). Epogen (epoetin alpha) is an erythropoiesis-stimulating agent (ESA) licensed by Amgen, Inc. and was first approved in 1989. Epoetin alpha stimulates erythropoiesis similar to endogenous erythropoietin.\(^1\)

Epogen has the following indications for which Hospira plans to seek approval:

---

\(^1\) Current Epogen (epoetin alpha) labeling (December 31, 2013)
- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis.
  - Zidovudine in HIV-infected patients.
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

Epogen was approved prior to the Pediatric Research Equity Act (PREA); therefore, Amgen was not required to conduct pediatric studies. However, following a supplemental new drug application (sNDA) from Amgen, labeling was updated on July 26, 1999 to include information on pediatric use regarding the following populations:

- pediatric patients on dialysis (1 month to 16 years of age based on clinical studies),
- pediatric patients not requiring dialysis (of age based on literature),
- pediatric HIV-infected patients (8 months to 17 years of age based on literature)
- pediatric cancer patients on chemotherapy (to 18 years based on literature).

The approval letter notes a commitment made by Amgen on May 11, 1999 to complete a literature search to find additional references to support the pharmacokinetic (PK) profile of epoetin alfa in neonates. Consequently, labeling was updated in November, 2004 to include PK information in neonates in the Pharmacokinetics subsection of the Clinical Pharmacology section.

Reviewer comment: The approval letter does not specify the patient population in which the neonatal PK information was requested. Furthermore, whether this postmarketing commitment was required under the Pediatric Rule or simply agreed upon with the sponsor is unclear.

An alternative weekly dosing regimen for the treatment of anemia due to chemotherapy in patients with non-myeloid malignancies was approved in June, 2004. PREA had been enacted by this time, and was triggered by this new dosing regimen. Pediatric study requirements were deferred for all ages as follows:

- patients 0 to < 5 years of age: to evaluate the feasibility of conducting a study in patients 0 to < 5 years of age, and if appropriate, submit a pediatric study plan or request a waiver by June, 2005.
Labeling was updated in March, 2007 to provide additional information on use in pediatric cancer patients on chemotherapy including the results of the PREA PMR study in patients 5 to 18 years of age.

Reviewer comment: Based on the approval for pediatric cancer patients on chemotherapy ages 5 to 18 years, the PREA postmarketing requirement (PMR) for that age group appears to have been fulfilled. However, whether the PREA PMR for patients 0 to <5 years of age was fulfilled is not clear. Nevertheless, the division agrees that studies would now be waived for this indication in patients < 5 years of age because erythropoietin is rarely used in pediatric cancer patients (see the Discussion below).

In June, 2011, Epogen labeling was updated based on the results of six multicenter, randomized trials assessing the effect of ESAs in patients with cancer that demonstrated or suggested decreased survival or more rapid tumor progression/ recurrence. Additionally, labeling was converted to the Physician Labeling Rule (PLR) format. During this conversion to the PLR format, the data in the Pediatric Use subsection describing use in pediatric patients not requiring dialysis was omitted from labeling; however, information on use in pediatric HIV-infected patients 8 months to 17 years of age was retained. Additionally, the following statement was placed in the Highlights, Pediatric Use subsection: “Safety and effectiveness have not been established in CKD patients undergoing dialysis who are less than 1 month old, pediatric patients with cancer less than 5 years old, pediatric patients with CKD not on dialysis, and pediatric patients with HIV infection”. Of note, labeling explicitly states that Epogen is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis and in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy.

Reviewer comment: The initial submission by Amgen to support pediatric approval included information from 17 published studies with a total of 133 pediatric CKD patients not on dialysis. These findings may not have been considered with the 2011 PLR conversion and thus, the inclusion of the statement that safety and effectiveness have not been established in pediatric patients with CKD not on dialysis appears to be an error. DHP and DPMH agree that the CKD indication in the pediatric population should therefore include both dialysis and non-dialysis patients, and the pediatric assessment is complete. (See the Discussion below.)

Of note, Amgen submitted a supplemental BLA (BLA 103951/S5363) for Aranesp (darbepoetin alpha) to provide labeling on the use of Aranesp in pediatric CKD patients for initial treatment of anemia or when transitioned from treatment with epoetin alfa to Aranesp. This supplement was approved on July 23, 2015. Aranesp is approved for the treatment of anemia due to both CKD and chemotherapy in patients with cancer. Dosing recommendations are provided for all pediatric patients with CKD and labeling describes conversion of epoetin alpha to Aranesp for pediatric patients with CKD receiving or not receiving dialysis.
Reviewer comment: DHP believes that this data supports that the Epogen indication includes the entire pediatric CKD population (dialysis and non-dialysis) and plans to seek alignment in the labeling between the two products (Epogen and Aranesp). (See the Discussion below.)

Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Biosimilar products that have not been determined to be interchangeable, such as Epoetin Hospira, are considered new active ingredients, and are subject to PREA. Applicants must submit an initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting as required by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). However, given that Epoetin Hospira is a proposed biosimilar product, no phase 2 or phase 3 studies are planned, and an EOP2 meeting will not take place for this product. Under FDASIA, in the absence of an EOP2 meeting, and if a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, an iPSP should be submitted as soon as feasible, including as early as the pre-IND phase. However, the iPSP must be submitted no later than 210 days prior to the submission of the NDA/BLA, and an agreed iPSP must be submitted with the NDA/BLA. Failure to include an agreed iPSP in an NDA/BLA or efficacy supplement may be considered grounds for a Refuse to File Action.

Hospira submitted their iPSP on June 11, 2014 and their BLA on December 16, 2014, without an agreed iPSP. Hospira was issued an agreed iPSP letter on January 20, 2015, prior to the filing meeting for the BLA on February 3, 2015.

Reviewer comment: Failure to include an agreed upon iPSP at the time of NDA or BLA submission may be grounds for a refuse-to-file action. Although correspondence with Hospira prior to submission of their BLA encouraged them to submit their iPSP as soon as feasible and allow up to 210 days for review, they were not explicitly advised that they must submit their iPSP at least 210 days prior to submission of their BLA or that they must have an agreed iPSP prior to submission of their BLA. Ultimately, because agreement was reached on the iPSP prior to the filing meeting, the application was filed.

DHP consulted DPMH for assistance in reviewing the sponsor’s iPSP and preparing for the Pediatric Review Committee (PeRC) meeting.

**Pediatric Study Plan and Biosimilar Extrapolation:**
In the iPSP submitted June 11, 2104, for the proposed indications of anemia due to (1) CKD in patients on dialysis and not on dialysis, (2) concomitant myelosuppressive chemotherapy, and (3) Zidovudine in HIV-infected patients, Hospira proposed to demonstrate biosimilarity to Epogen (epoetin alpha) and extrapolate pediatric data from the reference product based on the biosimilar development program. Hospira suggests that the assessment should be considered complete for all the proposed indications for the treatment of anemia because in an FDA Medical Review of the submission to support
pediatric approval in 1999, the FDA reviewer recommended that Epogen be granted approval in pediatric patients for the analogous approved adult indications. Therefore, Hospira did not plan to perform clinical studies in pediatric patients. However, Hospira did not completely address PREA for the treatment of anemia due to CKD (which appears to have a gap in pediatric labeling based on the statement that …). For the remaining indication related to the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery, Hospira planned to request a full waiver of pediatric studies because overall use for this indication is limited, and use of ESAs in the pediatric preoperative setting is not standard of care.

The iPSP was reviewed by the Pediatric Review Committee (PeRC) on August 20, 2014. PeRC agreed with DHP's edits and comments to Hospira embedded within the iPSP. FDA provided the following advice to Hospira regarding the approach to the pediatric study plan for each proposed indication in correspondence dated September 9, 2014:

Hospira addressed the majority of FDA’s comments and submitted a revised iPSP on September 24, 2014; however justification for the requested waivers was not provided. Therefore, in correspondence dated December 11, 2014, FDA advised Hospira to resubmit their iPSP including rationale to support each proposed waiver.

**Discussion:**
Under PREA, a waiver can be granted for the following reasons:

1. necessary studies are impossible or highly impracticable;
2. evidence suggests the drug or biologic would be ineffective or unsafe (Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling);
The approach for each proposed indication will be discussed below.
The table below summarizes the specific recommendations to address PREA for the proposed indications.

<table>
<thead>
<tr>
<th>Approved Indications</th>
<th>Pediatric Information in Package Insert Labeling for Epogen</th>
<th>Recommendations for the Pediatric Study Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia due to CKD in patients on dialysis and not on dialysis</td>
<td>Epogen is indicated in pediatric patients, ages 1 month to 16 month years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established.</td>
<td>The pediatric assessment is complete for patients 1 month to 16 years of age. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 1 month and older. Request a partial waiver for &lt; 1 month of age because studies would be impossible or highly impracticable.</td>
</tr>
</tbody>
</table>
### Approved Indications

| Anemia due to concomitant myelosuppressive chemotherapy | Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established. | The pediatric assessment is complete for patients 5 to 16 years of age. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 5 years and older. Request a partial waiver for < 5 years of age because studies would be impossible or highly impracticable. |
| Anemia due to Zidovudine in HIV-infected patients | Published literature has reported the use of Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of red blood cell transfusions were observed. | The pediatric assessment is complete for patients 8 months to 17 years of age. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 8 months and older. Request a partial waiver for < 8 months of age because studies would be impossible or highly impracticable. |
| Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery | No information for pediatric use in the reference product label | Request a full waiver because studies would be impossible or highly impracticable. |

### Conclusion/Recommendations:

The revised iPSP was reviewed by the Pediatric Review Committee (PeRC) on November 19, 2014. With PeRC’s concurrence, DHP provided feedback and recommendations regarding the proposed waiver rationale, in addition to potential supporting data for each proposed indication in correspondence dated December 11, 2014. The approach to address PREA for the pediatric CKD indication and associated Epogen labeling inaccuracies is still being determined. The division plans to request Amgen to revise the Epogen label in order to achieve consistency in pediatric labeling between Epogen and Aranesp.

An agreed iPSP letter was issued on January 20, 2015, in which general agreement with the proposed plan was conveyed. DPMH agrees with the proposed pediatric development plans as outlined above. DPMH participated in the internal meetings from August, 2014 to June, 2015, assisted in PeRC preparation, and provided comments on the iPSPs and the Advice Letters to the sponsor. Our input is reflected in the written comments in the iPSPs and the Advice Letters dated September 9, 2014; December 11, 2014; and January 20, 2015 (DARRTS Reference IDs: 3624219, 3671695 and 3689752, respectively). DPMH will continue to participate in the PSP review process for the BLA.

Of note, DHP plans to issue a Complete Response for this BLA due to biopotency, immunogenicity and product quality issues.
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/s/

ERICA D RADDEN
09/01/2015

HARI C SACHS
09/01/2015
I agree with these recommendations.

LYNNE P YAO
09/02/2015
DATE: August 21, 2015

TO: Ann Farrell, M.D.
Director, Division of Hematology Products (DHP)
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance

AND

Michael F. Skelly, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Acting Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Inspection of covering:
BLA 125545 (Retacrit Epoetin, sponsored by Hospira)

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of analytical portions of the following immunogenicity studies conducted by:

Study Number: EPOE-12-02
Study Title: “A phase I, randomized, single-dose, crossover study evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) of Epoetin Hospira compared
to Epogen® (Amgen) following subcutaneous (SC) administration to healthy male volunteers”

**Study Number:** EPOE-14-01  
**Study Title:** “A randomized, open-label, multiple-dose, parallel group study evaluating the pharmacodynamics and Pharmacokinetics of Epoetin Hospira compared to Epogen (Amgen) following subcutaneous administration to healthy volunteers”

**Study Number:** EPOE-10-01  
**Study Title:** “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”

**Study Number:** EPOE-10-13  
**Study Title:** “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”

The pharmacokinetic portions of studies EPOE-12-02 and EPOE-14-01 were audited by DNDBE pharmacologists Seongeun (Julia) Cho and Srinivas R. Chennamaneni at [redacted]. The review of this audit was loaded into DARRTS on 5/7/2015.

Inspection of the immunogenicity portions of these studies was conducted by DGDBE pharmacologists Michael F. Skelly and [redacted]. The audit included a thorough examination of facilities and equipment, review of method validation and study records including correspondence, and interviews and discussions with management and staff.

Following the inspection of [redacted], Form FDA-483 was not issued. However, several findings were discussed throughout the inspection, and during the inspection close-out meeting. These findings, and an evaluation of observations and discussions with management follow. In addition, we note in DARRTS and EDR
that the sponsor Hospira has submitted additional information on these studies.
Kara A. Scheibner, Ph.D.
DGDBE

Michael F. Skelly, Ph.D.
DGDBE

**Final Classification:**

**VAI** -

DARRTS CC:
OTS/OSIS/Taylor/Dejernett/Nkah/Fenty-Stewart/Johnson
OTS/OSIS/DGDBE/Haidar/Skelly/Choi/Scheibner
OTS/OSI/DNDEB/Bonapace/Dasgupta/Cho
CDER/OND/DHP/Sensie/Farrell
Draft: KAS 7/30; 8/14/2015
Edits: MFS 8/3/2015; 8/14/2015; SHH 8/14/2015
OSI: File#: [Redacted]
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/

**FACTS:**

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/s/

MICHAEL F SKELLY
08/21/2015
Primary author = Kara A. Scheibner
Co-author = Michael F. Skelly

KARA A SCHEIBNER
08/21/2015

SAM H HAIDAR
08/21/2015

Reference ID: 3809684
Reference ID: 4266940
MEMORANDUM
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: August 17, 2015
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 125545
Product Name and Strength: Retacrit (“Epoietin Hospira”)* Injection, 2000 units/mL, 3000 units/mL, 4000 units/mL, 10,000 units/mL and 40,000 units/mL
Submission Date: December 16, 2014
Applicant/Sponsor Name: Hospira
RCM #: 2014-2611
DMEPA Primary Reviewer: Carlos M Mena-Grillasca, RPh
DMEPA Team Leader: Yelena Maslov, PharmD
DMEPA Associate Director: Lubna Merchant, MS, PharmD

This memo serves to close out the label and labeling consult request from the Division of Hematology Products for Retacrit (“Epoietin Hospira”)*, BLA 125545.

DMEPA was notified by the Division of Hematology Products (DHP) on August 13, 2015 that a Complete Response (CR) action will be taken on BLA 125545 and that the review division will defer label and labeling comments to the next review cycle.

Therefore, DMEPA will provide comments regarding label and labeling for this application during a subsequent review cycle. DMEPA requests that DHP submit a new consult request during the subsequent review cycle.

* Retacrit has been developed as a proposed biosimilar to the US-licensed Epogen®/Procrit® (epoetin alfa). Since the core name for Retacrit has not yet been determined, “Epoietin Hospira” is used throughout this review as the nonproprietary name for this product.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARLOS M MENA-GRILLASCA
08/17/2015

YELENA L MASLOV
08/17/2015

LUBNA A MERCHANT
08/19/2015
CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: August 6, 2015

TO: Beatrice Kallungal, Regulatory Project Manager
Saleh Ayache, M.D., Medical Officer
R. Angelo de Claro, M.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: BLA: 125545
APPLICANT: Hospira, Inc.
DRUG: Epoetin Hospira
NME: 351(k) biosimilar

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: Treatment of anemia in patients with:
- Chronic kidney disease
- Anemia in HIV due to zidovudine treatment
- Non-myeloid malignancies
- Perioperative hemoglobin > 10 to < 13 g/dL at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery

DIVISION ACTION GOAL DATE October 15, 2015

PDUFA DATE: February 09, 2016
**I. BACKGROUND:**

Human erythropoietin is a single chain, monomeric, glycosylated polypeptide that is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal interstitial cells. Erythropoietin for clinical use (originally in anemic patients with chronic kidney disease) is produced by recombinant deoxyribonucleic acid technology using mammalian cells as an expression system.

Two clinical trials, Studies EPOE-10-01 and EPOE-10-13, submitted in support of the sponsor’s 351(k) (biosimilar) application were selected for clinical site inspections. Three clinical investigator sites were selected for each study based on a large number of enrolled subjects. The sponsor of the BLA, Hospira, Inc., was also inspected, focusing on the conduct of these two studies. The final classification (one clinical site, Dr. Lee, is preliminary) of these inspections are listed in the table in Section II below. Descriptions of the scope, observations, and assessment of data integrity for the inspected clinical sites remain unchanged and can be reviewed in the original Clinical Inspection Summary (CIS) entered into DARRTS on July 10, 2015.

Following the entry of the original CIS for BLA 125545 into DARRTS, the Good Clinical Practice Assessment Branch (GCPAB), Division of Clinical Compliance Evaluation, within the Office of Scientific Investigations was made aware of an Official Action Indicated (OAI) Untitled Letter issued to Dr. Mohammed El-Shahawy entered into DARRTS under IND 100685 on July 8, 2015 by OSI’s Division of Enforcement and Safety Compliance, Compliance Enforcement Branch (CEB). Dr. El-Shahawy had participated as a clinical investigator in the two clinical studies noted above (EPOE-10-01 and EPOE-10-13), as well as an additional Hospira study, EPOE-11-04, also submitted in support of BLA 125545. The inspection of Dr. Shahawy’s site had been conducted because of a complaint received by the Good Clinical Practice (GCP) For-Cause Team (previously Good Clinical Practice Enforcement Branch) within OSI about Dr. El-Shahawy’s conduct of these studies. Regulatory violations were observed during inspection.

A meeting between members of OSI and Division of Hematology Products (DHP) was held on July 16, 2015, to address an error in OSI CEB recommendations regarding the overall reliability of data from Studies EPOE-10-01 and EPOE-10-13 reported to IND 100685 (specifically internal Notes to Review Division (NTRD) section of the OAI Untitled Letter issued to Dr. El-Shahawy). Based upon this discussion, OSI CEB agreed to update the IND correspondence for Dr. El-Shahawy with a corrected NTRD. OSI GCPAB will provide DHP with the findings of all inspections conducted at clinical sites participating in the Hospira studies submitted with the BLA in an addendum to the Clinical Inspection Summary.

This Addendum contains information regarding clinical site inspections conducted in response to complaints received by the GCP For-Cause Team for six clinical
investigators who participated in Hospira studies conducted under IND 100685. Inspections were conducted at five of these six clinical sites (covering six clinical investigators) and details of these inspections will be described below. One clinical site (Dr. Coyne, Washington University, St. Louis, MO) reported by the IRB for overdosing a single subject (specific Hospira study not identified) was not inspected as the issue was isolated, had caused no harm to the subject, and the IRB accepted the Corrective Action Plan of the investigator.

Additionally, the Addendum contains information related to a routine surveillance inspection of an IRB responsible for approving conduct of two clinical studies of Hospira Epoietin conducted under IND 100685 and the Voluntary Action Indicated (VAI) letter of correspondence that was issued to this IRB.

### II. PDUFA-RELATED INSPECTIONS FOR BLA 125545

#### RESULTS:

<table>
<thead>
<tr>
<th>Name of CI Location</th>
<th>Study Site/Protocol /Number of Subjects Enrolled (n)</th>
<th>Inspection Date</th>
<th>Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steven Zeig, M.D.</td>
<td>Site #24011 Protocol EPOE-10-13 Subjects=20</td>
<td>March 3 - 16, 2015</td>
<td>VAI</td>
</tr>
<tr>
<td>Pines Clinical Research Inc.</td>
<td>601 N. Foamingo Road, #104 Pembroke Pines, FL 33028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anant J. Desai, M.D.</td>
<td>Site #24005 Protocol EPOE-10-13 Subjects=18</td>
<td>March 26-27, 2015</td>
<td>VAI</td>
</tr>
<tr>
<td>Renal Consultants Medical Group</td>
<td>16907 Devonshire Street Granada Hills, CA 91344</td>
<td></td>
<td></td>
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<tr>
<td>Kamal Ghandhi, M.D.</td>
<td>Site #14011 Protocol EPOE-10-01 Subjects=28</td>
<td>March 24-27, 2015</td>
<td>VAI</td>
</tr>
<tr>
<td>Renal Consultants Medical Group</td>
<td>16907 Devonshire Street Granada Hills, CA 91344</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santa Fe Springs Dialysis</td>
<td>11147 Washington Blvd. Whittier, CA 90606</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susan Adele Diamond, M.D.</td>
<td>Site #11003 Protocol EPOE-10-01 Subjects=29</td>
<td>April 20 – May 1, 2015</td>
<td>NAI</td>
</tr>
<tr>
<td>San Antonio Kidney Disease Center Physicians Group, PLLC</td>
<td>8042 Wurzbach Road, Suite 500 San Antonio, TX 78229</td>
<td></td>
<td></td>
</tr>
<tr>
<td>275 North Field Drive Dept. 389 Bldg. H2</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Hospira, Inc.
600 North Field Drive
Lake Forest, IL 60045

(Revised inspection observations and OSI assessment following review of EIR received by OSI on July 27, 2015)

What was inspected:
The inspection evaluated the following: organization and personnel, contracts for vendor services, selection and monitoring of clinical sites, completed Form FDA 1572s, financial disclosures, documents related to study monitoring visits and correspondence, safety and adverse event reporting, and drug accountability.

The inspection focused on Studies EPOE-10-01 and EPOE-10-13. Documents related to conduct of the studies at the following clinical sites were examined:

1. Site #24011 Steven Zeig (EPOE-10-13)
2. Site #24005 Anant Desai (EPOE-10-13)
3. Site #21001 Susan Diamond (EPOE-10-13)
4. Site #14011 Kamal Ghandi (EPOE-10-01)
5. Site #11015 Mark Lee (EPOE-10-01)
6. Site #11003 Susan Diamond (EPOE-10-01)

Documents related to two of seven sites terminated from participation in Study EPOE-10-01 were also examined:

1. Site #11100 Harold Baer
2. Site #14015 Warren Shapiro

General observations and commentary:
As noted in the original CIS, monitoring deficiencies were identified during the course of inspection. These deficiencies included delays in initiating interim monitoring visits.
based on the Clinical Management Plans, clinical investigators being associated with more than one type of operational site (some sites were designated as satellite sites which were not defined in the Plan), scope of monitoring capabilities at different types of operational sites (such as at a clinical practice site versus a dialysis center), and how a centralized monitoring process would be performed.

Hospira terminated seven sites for non-compliance in Study EPOE-10-01 and three sites for Study EPOE-10-13 as reported in the BLA.

A Form FDA 483 was issued at the end of the sponsor inspection for (1) failure to ensure proper monitoring of the study and (2) failure to adequately transfer obligations to a Contract Research Organization for the conduct of any clinical study.

1. Failure to ensure proper monitoring of the study. Specifically,
   a. Study-specific Clinical Management Plans specified that Interim Monitoring Visits (IMVs) were to begin approximately two weeks after the first randomization at each site, to ensure subject safety, data accuracy, protocol adherence, and adherence to FDA regulations.

   Interim Monitoring Visit Records were reviewed for seven (of 95) enrolling clinical sites for Study EPOE-10-01 and three (of 68) enrolling clinical sites for Study EPOE-10-13. For Study EPOE-10-01, the median number of days between initial Blinded and Un-blinded IMVs was 37 and 36, respectively (averages 42 and 36 days, respectively). For Study EPOE-10-13, the median number of days between initial Blinded and Un-blinded IMVs was 28 days for both (averages 38 days).

   b. The Clinical Management Plans for EPOE-10-01 specified that all sites were to have Site Initiation Visits (SIVs) prior to subject enrollment. This was to ensure that all CIs and site personnel were ready to participate in the study and had appropriate equipment to conduct the study. However, the sponsor did not conduct adequate monitoring procedures as outlined in their plans at the study sites.

   Specifically, for Study EPOE-10-01, a CI listed two sites (Sites 11002-a and 11003) on a Form FDA 1572. A SIV was held at these sites February 29 to March 1, 2012. The CI subsequently added a third site (Site 11116) on April 25, 2012, but an SIV was not performed. Subsequently the first Interim Monitoring Visit Reports showed dosing-related protocol deviations at this site.

   c. The Clinical Management Plan for EPOE-10-13 specified that Blinded and Un-blinded Interim Monitoring Visits be conducted separately and routinely, each with different objectives, schedules and associated study staff. However, the sponsor did not conduct adequate monitoring procedures at the study sites.
For example, a CI had two sites (Sites 24010-a and 24011) listed on a Form FDA 1572. All subjects were enrolled at Site 24011 (Site 24010-a indicated that this was an administrative site for Site 24011). All 18 blinded Interim Monitoring Visits for Site 24011 showed that the blinded monitor visited Site 24010-a exclusively throughout the study. There was no evidence that the blinded monitor visited Site 24011 at any point during the study.

**OSI Comment:**
Studies EPOE-10-01 and EPOE-10-13 were performed in subjects receiving hemodialysis. Monitoring was performed by blinded and unblinded monitors. The unblinded monitors were responsible for assessing drug accountability, storage, and dispensing of investigational product.

The clinical investigators could each be involved with multiple sites (e.g., hemodialysis center(s) and a clinical medical practice facility). The actual site where monitoring took place was determined by the blinding status of the monitors (and site personnel) and availability of adequate space to review records. Specifically, unblinded monitors visited the hemodialysis centers where investigational product was received, stored, and dispensed. Blinded monitors visited the dialysis center(s) and/or “administrative” sites (i.e. medical offices) if sufficient space was not available at the dialysis center to accommodate review of records.

There is some concern about how thorough or accurate an assessment of some aspects of actual conduct of the study would be, based upon remote review of copies of source records at a remote administrative (medical office) site. Examples would be the ability to assess whether a site had adequate, qualified personnel available to conduct the study and how actual operational aspects of the study were proceeding.

2. Failure to notify FDA in a timely fashion regarding transfer of obligations for a study including site monitoring, including clinical and safety management to a contract research organization for site management including the conduct of any clinical study. Specifically, the sponsor failed to report to FDA the contracting to (a CRO) parts of the clinical study until March 29, 2012. Transfer of obligations was also reported later on January 21, 2013.

**Assessment of data integrity:**
Despite the regulatory deficiencies described above, based upon inspection findings at the clinical sites selected for inspection and noted in the table above, the sponsor adequately reported protocol deviations to the BLA. Therefore, data from the clinical sites inspected as submitted by this sponsor appear acceptable in support of the requested indication.

**III. CLINICAL SITE INSPECTIONS RELATED TO COMPLAINTS FOR STUDIES CONDUCTED UNDER IND 100685**
As previously discussed in the background above, there are six complaints in the OSI database associated with IND 100685. Inspection of five of the clinical sites (two investigators participated at one of the sites, so six CIs were inspected) associated with the complaints was requested by Good Clinical Practice For-Cause Team (previously Good Clinical Practice Enforcement Branch). Three of these clinical sites had been closed by the sponsor for GCP-related violations (Drs. El-Shahawy, Moustafa, and Shapiro) and reported to the BLA.

Five clinical sites related to IND 100685 were referred for inspection. Establishment Inspection Reports (EIRs) for these sites have been reviewed by EB and GCP For-Cause reviewers. Findings are summarized below.

**RESULTS:**
(Reviews of Establishment Inspection Reports by CEB and GCP For-Cause Team)

<table>
<thead>
<tr>
<th>Name of CI Location</th>
<th>Protocol /Number of Subjects Enrolled (N)</th>
<th>Inspection Date</th>
<th>Classification* (see key from Table above)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohammed A. El-Shahawy, M.D.</td>
<td>EPOE-10-01 N=5</td>
<td>February 5 – March 19, 2015</td>
<td>OAI Untitled Letter</td>
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<tr>
<td>Academic Medical Research Institute</td>
<td>EPOE-10-13 N=14</td>
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<tr>
<td>5830 Whittier Boulevard</td>
<td>EPOE-11-04 N=8</td>
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<tr>
<td>Los Angeles, CA 90022-4302</td>
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<td></td>
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<tr>
<td>Warren B. Shapiro, M.D.</td>
<td>EPOE-10-01 N=1</td>
<td>April 28 - May 6, 2015</td>
<td>Pending Preliminary VAI</td>
</tr>
<tr>
<td>Brookdale Physicians Dialysis Associates</td>
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<tr>
<td>9701 Church Ave.</td>
<td></td>
<td></td>
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<tr>
<td>Brooklyn, NY 11212-3137</td>
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<tr>
<td>Raffi R. Minasian, M.D.</td>
<td>EPOE-10-01 N=11</td>
<td>February 5 - March 10, 2015</td>
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<td>1441 Gardena St., #6</td>
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<tr>
<td>Glendale, CA 91204</td>
<td>EPOE-11-03 N=9</td>
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<td>Paul Crawford, M.D.</td>
<td>EPOE-10-01 N=8</td>
<td>July 29 - August 18, 2014</td>
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<tr>
<td>Research by Design, LLC</td>
<td>EPOE-11-03 N=6</td>
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<tr>
<td>9730 South Western Ave., Suite 706</td>
<td></td>
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<td>Evergreen Park, IL 60805</td>
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<td>Satya Ahuja, M.D.</td>
<td>EPOE-10-13 N=12</td>
<td>July 29 - August 18, 2014</td>
<td>VAI</td>
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<td>Evergreen Park, IL 60805</td>
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<tr>
<td>Moustafa Moustafa, M.D.</td>
<td>Protocol EPOE-10-01 N=12</td>
<td>May 27 - June 6, 2012</td>
<td>NAI</td>
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<td>South Carolina Nephrology &amp; Hypertension</td>
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<td>Center, Inc.</td>
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<tr>
<td>3709 Magnolia St.</td>
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</tr>
<tr>
<td>Orangeburg, S.C. 29118</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
A. Mohammed A. El-Shahawy, M.D.
Los Angeles, CA 90022-4302

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Following review of the Form FDA 483, the EIR, and the clinical investigator’s response, it was determined that the clinical study site did not maintain adequate records with respect to temperature logs and Patient Dispensing Logs.

1. Hospira Protocols EPOE-10-01 and EPOE-10-13 required that the Unblinded Site Personnel ensure that the study drug was stored at a temperature between two and eight degrees Centigrade (between 36 and 46 degrees Fahrenheit).
   b. For Protocol EPOE-10-13, temperature logs (serial numbers) were missing from study records 0050005546 on March 14 - 17, 2013, April 19, 2013 and May 1 - 30, 2013.

2. For EPOE-11-04, investigational drugs could not be fully reconciled due to missing dispensing accountability records for seven subjects.

OSI COMMENT:
The final classification of inspection was Official Action Indicated (OAI). An OAI Untitled Letter was issued to the clinical site investigator, Dr. El-Shahawy on July 8, 2015.

Based on the inspection findings for Studies EPOE-10-01 and EPOE-10-13, OSI CEB considers the data generated at this site for these studies to be unreliable.

Based on the inspection findings for Study EPOE-11-04 at this site, OSI CEB recommends that the following subjects’ data from this site are unreliable: Subjects 21012-0016, 12012-0020, 12012-0022, 21012-0026, 21012-0109, 21012-0136, and 21012-0208.

Dr. El-Shahawy’s March 31, 2015 written response to the Form FDA 483 was evaluated by CEB and considered to be comprehensive and adequate.
In the Clinical Study Reports for EPOE-10-01 and EPOE-10-13 in the BLA submission, Hospira acknowledged that this site had been terminated from participation in both studies due to GCP violations. Although the study reports indicated that all subjects (including those enrolled at sites closed for GCP noncompliance) were included in the Intent to Treat analysis, it is not clear how all subjects from sites with GCP violations were considered for inclusion/exclusion from the Per Protocol analysis population, since only those subjects with “major” protocol deviations at the non-GCP compliant site were excluded.

B. Warren B. Shapiro, M.D.
Brooklyn, NY 11212-3137

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection related to Study EPOE-10-01 for failure to report a serious adverse event within 24 hours of becoming aware of the event as required by protocol, for not conducting the study according to the investigational plan, and for failure to maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Preliminary review of the EIR shows that for Study EPOE-10-01:

1. An SAE for Subject (osteomyelitis of fifth toe requiring amputation) was reported to the Sponsor/CRO 20 days after notification of the CI and to the IRB approximately one year after occurrence.
2. Protocol specified procedures including an ECG at Week 24 (end of treatment) and obtaining a blood sample for hemoglobin and hematocrit determination at Week 23 were not performed for Subject .
3. Failure to maintain adequate temperature records for storage of IP on multiple occasions.

OSI COMMENT:
The preliminary classification of this inspection by OSI is Voluntary Action Indicated (VAI); the classification will be finalized once the letter of correspondence is issued to the inspected entity.

Although regulatory violations were observed at Dr. Shapiro’s site the findings were isolated to a single subject and are not considered to be critical to integrity of data submitted in support of this specific study.

C. Raffi R. Minasian, M.D.
Glendale, CA 91204

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan and that investigational drug disposition records with respect to quantity and use by study subjects were inadequate.
1. The clinical study site did not conduct the study according to the investigational plan. Selected examples:
   a. For Study EPOE-10-01, Subject’s drug randomization assignment was accessible to the blinded study coordinator. The site terminated this subject from the study and reported the violation to the IRB.
   b. Subject was enrolled in Study EPOE-10-01 during a period of enrollment hold at the site due to administrative issues. The sponsor was aware of the deviation and allowed the subject to continue.
   c. Isolated laboratory assessments unrelated to the primary efficacy endpoint were not completed or repeated for 3 of 11 subjects (4 instances) in Study EPOE-10-01 and 3 of 9 subjects (3 instances) in Study EPOE-11-03.

2. Drug disposition records were inadequate with respect to quantity and use by study subjects. Specifically, for Study EPOE-10-01, records indicate a discrepancy of 10 vials of 10,000 Unit Dose/Vial dispensed to subjects and returned to sponsor (i.e. 324 vials were dispensed, but 335 vials were returned empty to the sponsor).

**OSI COMMENT:**
The preliminary classification of this inspection by OSI is Voluntary Action Indicated (VAI); the classification will be finalized once the letter of correspondence is issued to the inspected entity.

Dr. Minasian’s March 26, 2015 written response to the Form FDA 483 was considered adequate.

The above regulatory deficiencies observed at Dr. Minasian’s study site do not appear to have significant impact on data efficacy and patient safety. Notwithstanding these deficiencies, data submitted by this clinical site appear acceptable in support of this specific indication.

**D. Paul Crawford, M.D.**
Evergreen Park, IL 60805

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. See selected examples below.

1. The clinical site did not maintain adequate records with respect to temperature logs. Hospira protocol EPOE-10-01 specified that investigational study drug was to be stored between two and eight degrees Centigrade (between 36 and 46 degrees Fahrenheit).
   a. The site received six cartons of Epoetin Hospira on February 22, 2012 and two cartons of Amgen Epogen on February 23, 2012. The site did not maintain temperature records of the IP refrigerator from February
b. The site received six cartons of Epoetin Hospira on June 29, 2012. The site did not maintain temperature records of the refrigerator used to store IP for 22 days from September 5, 2012 to September 27, 2012.

2. For Study EPOE-10-01, the site failed to report an adverse event to the e-CRF, a clotted AV graft access that developed on July 3, 2013 for Subject #.

OSI COMMENT:
OSI issued a Voluntary Action Indicated (VAI) Letter to this clinical site investigator, Dr. Crawford. This letter was entered into DARRTS on July 20, 2015.

Dr. Crawford’s written response to the Form FDA 483 containing his preventive and corrective action plan, as submitted in the Establishment Inspection Report, was considered to be adequate.

The above regulatory deficiencies observed at Dr. Crawford’s study site are not critical; data submitted by this clinical site appear acceptable in support of this specific indication.

E. Satya Ahuja, M.D.
Evergreen Park, IL 60805

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. The protocol for EPOE-10-13 required that the investigational drug be stored between two and eight degrees Centigrade (between 36 and 46 degrees Fahrenheit).

On March 16, 2012, Dr. Ahuja received six cartons of the investigational drug. The site did not maintain records of the study drug refrigerator temperature from March 28 through May 1, 2012 and for 19 days from May 1, 2012 to August 31, 2012.

OSI COMMENT:
OSI issued a Voluntary Action Indicated (VAI) Letter to the clinical site investigator, Dr. Satya.

Dr. Satya’s written response to the Form FDA 483 containing his preventive and corrective action plan submitted in the Establishment Inspection Report was considered to be adequate.

The above regulatory deficiencies observed at Dr. Satya’s study site are not critical; data submitted by this clinical site appear acceptable in support of this specific indication.

F. Moustafa Moustafa, M.D.
Orangeburg, S.C. 29118
The inspection found that early discontinuations at this site were related to dosing and other errors noted in study conduct. The unblinded study coordinator was incorrectly drawing up IP, filling syringes based on a visual assessment and not differentiating between the 2,000 IU and 10,000 IU vials, resulting in underdosing of eight subjects receiving doses from the 2,000 IU vials. There were no resultant adverse events detected. Dr. Moustafa was unaware of this error because he was a blinded member of the study team. The site was closed by the sponsor on October 31, 2012.

Misdosing of subjects had previously been reported to OSI by the IRB who had accepted the clinical investigator’s corrective action plan.

OSI COMMENT:
This inspection was classified No Action Indicated (NAI) and the letter to the clinical site investigator was issued on December 17, 2014. Although this clinical investigator also participated in Study EPOE-10-13, this investigator’s conduct of this study was not subject to inspection at this time. Closure of the site for Study EPOE-10-01 reportedly resulted in early termination of all 12 enrolled subjects in Study 10-01. As previously noted for another clinical investigator, the sponsor reported the closure of the study site to the BLA and appears to have reported the underdosing of subjects as major protocol deviations in the data listings submitted to the BLA.

G. IRB:
IRB documentation regarding two clinical studies (not specified by Hospira Protocol number) was examined during a surveillance inspection of the IRB. A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for IRB meeting minutes contained documents created, reviewed, and/or approved up to four months after the date of the convened IRB meeting. This finding was attributed to meeting minute software that tracks and updates protocol related documents in files prior to the printout of a fully reviewed and signed off copy of the minutes for purposes of documentation.

OSI COMMENT:
This inspection was classified as Voluntary Action Indicated (VAI). This has no impact on data integrity or subject safety for the reviewed studies.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS (REVISED)

PDUFA-Related Inspections for BLA 125545:

Two clinical studies, EPOE-10-01 and EPOE-10-13 were inspected for this BLA. Four clinical sites covering five clinical investigators (Steven Zeig, M.D., Anant Desai, M.D., Kamal Gandhi, M.D., Mark Lee, M.D., and Susan Diamond, M.D.) and the sponsor (Hospira, Inc.) were inspected.
The final regulatory classification for Dr. Diamond is No Action Indicated (NAI). The final regulatory classification for Drs. Zeig, Dr. Desai, Dr. Gandhi, and Hospira, Inc. is Voluntary Action Indicated (VAI). The preliminary classification for Dr. Lee is VAI.

Although regulatory violations were noted at three of the clinical sites (covering four clinical investigators) inspected, the observations are unlikely to significantly impact efficacy assessment or human subject safety. Although initial interim monitoring visits by the sponsor (and/or CRO) were delayed and did not conform to the clinical management plans for the study, the sponsor monitoring process did result in identification of noncompliant sites and appropriate reporting of protocol deviations to the BLA based upon inspections of a sample of clinical sites.

**Clinical investigator/IRB inspections related to IND 100685 complaints:**

Under IND 100685, the following clinical study sites were also inspected following receipt of complaints by OSI related to GCP conduct: Mohammed El-Shahawy, M.D., Warren B. Shapiro, M.D., Raffi R. Minasian, M.D., Paul Crawford, M.D., Satya Ahuja, M.D., and Moustafa Moustafa, M.D.

The CDER regulatory classification for Dr. El-Shahawy is Official Action Indicated and an OAI-Unlited Letter has been issued. The CDER regulatory classification for the inspection of Drs. Crawford and Satya is Voluntary Action Indicated (VAI). The CDER regulatory classification for the inspection of Dr. Moustafa is No Action Indicated (NAI). The preliminary classification for Drs. Shapiro and Minasian is Voluntary Action Indicated (VAI).

With exception of the Dr. El-Shahawy site, data integrity from the other clinical study inspection sites, albeit with regulatory deficiencies, do not appear compromised.

In the Clinical Study Reports for EPOE-10-01 and EPOE-10-13, Hospira acknowledged closure of the Drs. El-Shahawy, Shapiro, and Moustafa sites due to GCP violations. Although the study reports indicated that all subjects (including those enrolled at sites closed for GCP noncompliance) were included in the Intent to Treat analysis, it is not clear how all subjects from sites with GCP violations were considered for inclusion/exclusion from the Per Protocol analysis population, since only those subjects with “major” protocol deviations at the non-GCP compliant site were excluded.

**Concluding OSI Comments:**

OSI conclusions about the data submitted to the BLA are unchanged based upon review of information obtained from inspections requested because of complaints reported to OSI and reported to IND 100685. Data from the clinical sites inspected as submitted by this sponsor appear acceptable in support of the requested indication with the exception of the Dr. Mohammed El-Shahawy site.
The sponsor reported the closure of seven and three clinical sites for Study EPOE-10-01 and Study EPOE-10-13, respectively in the clinical study reports submitted in the current BLA. The sponsor has indicated that all subjects randomized into the maintenance period of the studies were included in the intent-to-treat analysis population, however subjects with important protocol deviations (not defined) including those at sites closed for GCP compliance were excluded from the per protocol analysis. It is unclear whether important protocol deviations are consistent with “major protocol deviations” in the 16.2.2 Protocol Deviations data listings in Module 5.3.5.1 EPOE-10-01 and EPOE-10-13.

DHP may consider working with the sponsor to more clearly define the GCP deficiencies (as already identified by the sponsor) that caused closure of the clinical sites. Alternatively, additional clinical study sites could be audited upon request if the review division’s regulatory decision will be made based on the outcome of these clinical studies.

Note: The inspectional observations for Dr. Lee for the BLA 125545 submission are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR).

The inspections conducted in response to complaints received by OSI for Drs. Shapiro and Minasian have been reviewed by CEB and GCP For-Cause Team and are preliminarily classified as VAI pending completion and issuance of correspondence to the inspected entity.

{See appended electronic signature page}
Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANICE K POHLMAN
08/06/2015

KASSA AYALEW
08/07/2015
CLINICAL INSPECTION SUMMARY

DATE: July 10, 2015

TO: Beatrice Kallungal, Regulatory Project Manager
Saleh Ayache, M.D., Medical Officer
R. Angelo de Claro, M.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125545

APPLICANT: Hospira, Inc.

DRUG: Epoetin Hospira

NME: 351(k) biosimilar

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: Treatment of anemia in:
  • Patients with chronic kidney disease
  • HIV patients with anemia due to zidovudine treatment
Patients with non-myeloid malignancies
Patients with perioperative hemoglobin > 10 to < 13 g/dL at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery

CONSULTATION REQUEST DATE (signed): February 10, 2015
INSPECTION SUMMARY GOAL DATE (original): July 15, 2015
DIVISION ACTION GOAL DATE: October 15, 2015
PDUFA DATE: February 09, 2016

I. BACKGROUND:

Human erythropoietin, is a single chain, monomeric, glycosylated polypeptide that is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal interstitial cells. Erythropoietin for clinical use (originally in anemic patients with chronic kidney disease) is produced by recombinant deoxyribonucleic acid technology using mammalian cells as an expression system.

Two clinical trials submitted in support of the sponsor’s 351(k) (biosimilar) application were selected for domestic clinical site inspections. Three domestic clinical sites were selected for each study, Studies EPOE-10-01 and EPOE-10-13, based on a large number of enrolled subjects.

Study EPOE-10-01
Study EPOE-10-01 was a multicenter, randomized, active-controlled, parallel group, double-blind, Phase 3 study evaluating the efficacy and safety of IV administered Epoetin Hospira (one to three times per week) in patients with chronic renal failure requiring hemodialysis and receiving Epogen (Amgen) maintenance treatment. The primary study objective was to demonstrate therapeutic equivalence of intravenous Epoetin Hospira compared to intravenous Epogen (Amgen), based on maintenance of hemoglobin levels and study drug dose requirements. The primary efficacy endpoints were (a) the difference between treatments (Epoetin Hospira and Epogen [Amgen]) in mean weekly hemoglobin level during the last four weeks of the double-blind Treatment Period, and (b) the difference between treatments (Epoetin Hospira and Epogen [Amgen]) in mean weekly dosage per kg body weight during the last 4 weeks of the double-blind Treatment Period. The last four weeks of the Treatment Period were Week 21 through Week 24.
Study EPOE-10-13
Study EPOE-10-13 was a multicenter, randomized, active-controlled, parallel group, double-blind, Phase 3 study in patients with chronic renal failure requiring hemodialysis and receiving subcutaneous Epogen maintenance treatment. The primary study objective was to demonstrate therapeutic equivalence of subcutaneous Epoetin Hospira compared to subcutaneous Epogen (Amgen) based on maintenance of hemoglobin levels and study drug dose requirements. The primary efficacy endpoints were (a) the difference between treatments (Epoetin Hospira and Epogen [Amgen]) in mean weekly hemoglobin level during the last four weeks of the double-blind Maintenance Period, and (b) the difference between treatments (Epoetin Hospira and Epogen [Amgen]) in mean weekly dosage per kg body weight during the last four weeks of the double-blind Maintenance Period.

II. RESULTS:

<table>
<thead>
<tr>
<th>Name of CI Location</th>
<th>Study Site/Protocol /Number of Subjects Enrolled (n)</th>
<th>Inspection Date</th>
<th>Classification*</th>
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<tr>
<td>Steven Zeig, M.D. Pines Clinical Research Inc. 601 N. Foamingo Road, #104 Pembroke Pines, FL 33028</td>
<td>Site #24011 Protocol EPOE-10-13 Subjects=20</td>
<td>March 3 - 16, 2015</td>
<td>VAI</td>
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<tr>
<td>Anant J. Desai, M.D.</td>
<td>Site #24005 Protocol EPOE-10-13 Subjects=18</td>
<td>March 26-27, 2015</td>
<td>VAI</td>
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<tr>
<td>Kamal Ghandhi, M.D. Renal Consultants Medical Group 16907 Devonshire Street Granada Hills, CA 91344</td>
<td>Site #14011 Protocol EPOE-10-01 Subjects=28</td>
<td>March 24-27, 2015</td>
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<td>Susan Adele Diamond, M.D. San Antonio Kidney Disease Center Physicians Group, PLLC 8042 Wurzbach Road, Suite 500 San Antonio, TX 78229</td>
<td>Site #11003 Protocol EPOE-10-01 Subjects=29</td>
<td>April 20 –May 1, 2015</td>
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<td>Site #21001 Protocol EPOE 10-13 Subjects=9</td>
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**Clinical Study Site Investigator**

1. Steven Zeig, M.D., Site #24011, Protocol EPOE-10-13
   Pembroke Hills, Fl

   **a. What was inspected:**
   The inspection was conducted from March 3 to 16, 2015.

   A total of 37 subjects were screened, and 20 subjects were enrolled. Seventeen subjects completed the treatment period phase of the study. An audit of 9 enrolled subjects’ records was conducted.

   The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

   **b. General observations/commentary:**
   Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

   A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. For example:

   (a) Subject [reference_id: 3790802] had platelet count of $81 \times 10^9/L$ at screening visit (below the cutoff inclusion criteria of $100 \times 10^9/L$), but was randomized on February 12, 2013. The subject had a subsequent SAE of gastrointestinal bleed and died.

   (b) (6)
(b) Subject had multiple drug allergies per September 14, 2011 consultation records, at screening, but was not excluded from Study EPOE-10-13.

(c) Subject showed two post-dialysis treatment blood pressure out-of-range excursions (>170/110 mm Hg) two weeks prior to screening. Patient was not excluded from Study EPOE-10-13.

(d) Subject study medication was placed on hold by the CI on March 30, 2013, and was to re-start on April 30, 2013, at a 25% reduced dose. However, this subject was dosed erroneously, with standard of care Epogen, dispensed by dialysis nurses who were new to the dialysis facility and not familiar with the study protocol during Weeks #10 - #12 (4/20 – 5/2/2013) of the Maintenance Period.

OSI Comment:
Wide blood pressure excursions are expected in subjects with chronic renal failure, on hemodialysis, such as in the case of Subject. Further, despite the multiple drug allergies history, Subject did not have episodes of critical hypersensitivity drug reactions and completed this study. Thus, for Subjects, the observations listed above at Dr. Zeig’s study site were unlikely to have an impact on safety or efficacy.

Although the protocol did not specify rescreening procedures, Subject had a platelet count of 112 x 10^9/L on the day of randomization and treatment. Subsequent platelet counts on March 14 and April 11, 2013 were < 100 x 10^9/L. Based upon the CI’s written follow-up dated March 31, 2015, the low platelet counts were attributed to platelets adhering to the dialysis instrument membrane. At the time of hospitalization the subject was also suffering from diabetic ketoacidosis and angina, as well as gastrointestinal bleeding for gastrointestinal bleeding and the subject’s platelet count was 141 x 10^9/L. This case was discussed with DHP who noted the subject’s platelet count at the time of occurrence of SAEs and attributed events to be due to the underlying chronic kidney disease and multiple co-morbidities.

The CI had appropriately ordered study medication to be held for Subject, however during the period the study medication was on hold, new employees at the dialysis center (not aware of the protocol) administered Epogen to the subject. During this time period the subject’s hemoglobin trended downward from 12.2 g/dL (value at time of study medication hold) to 10.9 to 11.3 g/dL. Although Epogen was administered according to standard of care, it did not have an impact on efficacy (due to timing of efficacy assessment) or safety for this subject.

Dr. Zeig responded adequately in a letter dated March 31, 2015.

c. Assessment of data integrity:
Despite the above minor regulatory deficiencies, data submitted by this clinical site appear acceptable in support of this specific indication.

2. Anant J. Desai, M.D., Site #24005, Protocol EPOE-10-13
Granada Hills, CA
a. **What was inspected:**
The inspection was conducted from March 26 to 27, 2015.

A total of 31 subjects were screened, and 18 subjects were enrolled. Fifteen subjects completed the treatment period phase of the study. An audit of 18 enrolled subjects’ records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. **General observations/commentary:**
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. Subject - was randomized to Study EPOE-10-13, despite not meeting the hemoglobin 9.0 and 11 g/dL inclusion criteria, four weeks prior to randomization.

Dr. Desai’s April 2, 2015 written response to the Form FDA 483 was adequate.

c. **Assessment of data integrity:**
Despite the above isolated deficiency, data submitted by this clinical site appear acceptable in support of this specific indication.

3. **Kamal Ghandhi, M.D./ Site #14011, Protocol EPOE-10-01**
Granada Hills, CA

a. **What was inspected:**
The inspection was conducted from March 24 to 27, 2015.

A total of 39 subjects were screened, and 28 subjects were enrolled. Twenty five subjects completed the treatment period phase of the study. An audit of 25 enrolled subjects’ records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.
b. General observations/commentary:
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. Subject # had a screening transferrin saturation (TSAT) of 16% (October 23, 2012) and randomized with a value of 16% on October 30, 2012. This subject did not meet the adequate iron stores criteria of ferritin > 100 ug/L and transferrin saturation (TSAT) > 20% prior to randomization.

Dr. Gandhi’s March 31, 2015 written response to the Form FDA 483 was adequate.

c. Assessment of data integrity:
Despite the above isolated deficiency, data submitted by this clinical site appear acceptable in support of this specific indication.

4. Mark C. Lee, M.D., Site #11015, Protocol EPOE-10-01
Whittier, CA

a. What was inspected:
The inspection was conducted from June 23 to 30, 2015.

A total of 47 subjects were screened, and 30 subjects were enrolled. Twenty nine subjects completed the treatment period phase of the study. An audit of 15 enrolled subjects’ records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. Subject # had a screening transferrin saturation (TSAT) of 16% (October 23, 2012) and randomized with a value of 16% on October 30, 2012. This subject did not meet the adequate iron stores criteria of ferritin > 100 ug/L and transferrin saturation (TSAT) > 20% prior to randomization.
OSI Comment:
While Subject did not meet the criteria for iron stores adequacy, this was considered as an isolated occurrence at this clinical study site.

c. Assessment of data integrity:
Despite the above isolated deficiencies, data submitted by this clinical site appear acceptable in support of this specific indication.

5. Susan Diamond, M.D./ Site #11003, Protocol EPOE-10-01 & Site #21001, Protocol EPOE 10-13
San Antonio, TX

a. What was inspected:
The inspection was conducted from April 20 – May 1, 2015.

For Study EPOE-10-01, a total of 32 subjects were screened, and 29 subjects were enrolled. Twenty six subjects completed the study. An audit of 29 enrolled subjects’ records was conducted. For Study EPOE-10-03, a total of 11 subjects were screened, and 9 subjects were enrolled. Six subjects completed the study. An audit of 9 enrolled subjects’ records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR
6. Hospira, Inc.
Lake Forest, IL
a. What was inspected:
The inspection was conducted from March 25 – April 13, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:
Monitoring deficiencies, in terms of initiating interim monitoring visits within a timely manner were identified. However, when noncompliance with good clinical practices was observed at sites, the sponsor closed noncompliant clinical sites. There was no evidence of under-reporting of adverse events.
A Form FDA 483 was issued at the end of the sponsor inspection for (1) failure to ensure proper monitoring of the study and (2) failure to adequately transfer obligations to a Contract Research Organization for the conduct of any clinical study.

1. Failure to ensure proper monitoring of the study. Specifically,

   A. Clinical Management Plans specified that Interim Monitoring Visits (IMVs) were to begin approximately two weeks after the first randomization at each site, to ensure subject safety, data accuracy, protocol adherence, and adherence to FDA regulations.

Interim Monitoring Visit Records were reviewed for seven (of 95) enrolling clinical sites for Study EPOE-10-01 and three (of 68) enrolling clinical sites for Study EPOE-10-03. For Study EPOE-10-01, the median number of days between initial Blinded and Un-blinded IMVs was 37 and 36, respectively (averages 42 and 36 days, respectively). For Study EPOE-10-13, the median number of days between initial Blinded and Un-blinded IMVs was 28 days for both (averages 38 days).

For example for Study EPOE-10-01:

   i. Site 11100 randomized Subject on October 11, 2012. However, the first Blinded IMV began 61 days and Un-blinded IMV began 18 days after the first subject randomization.

   ii. Site 14015 randomized Subject on August 7, 2012. However, the first blinded IMV began 37 days and un-blinded IMV began 71 days after the first subject randomization.

Both Site 11100 and 14015 were subsequently closed for non-compliance with good clinical practices including source documentation inconsistencies, drug accountability deficiencies, protocol deviations, and lack of principal investigator oversight.
B. The Clinical Management Plans for EPOE-10-01 specified that all sites were to have Site Initiation Visits (SIVs) prior to subject enrollment. This was to ensure that all CIs and site personnel were ready to participate in the study and had appropriate equipment to conduct the study. However, the sponsor did not conduct adequate monitoring procedures as outlined in their plans at the study sites.

Specifically, for Study EPOE-10-01, a CI listed two sites (Sites 11002-a and 11003) on a Form FDA 1572. A SIV was held at these sites February 29 to March 1, 2012. The CI subsequently added a third site (Site 11116) on April 25, 2012, but an SIV was not performed. Subsequently the first Interim Monitoring Visit Reports showed dosing-related protocol deviations at this site.

C. The Clinical Management Plan for EPOE-10-13 specified that Blinded and Un-blinded Interim Monitoring Visits be conducted separately and routinely, each with different objectives, schedules and associated study staff. However, the sponsor did not conduct adequate monitoring procedures at the study sites.

For example, a CI had two sites (Sites 24010-a and 24011) listed on a Form FDA 1572. All subjects were enrolled at Site 24011 (Site 24010-a indicated that this was an administrative site for Site 24011). All 18 blinded Interim Monitoring Visits for Site 24011 showed that the blinded monitor visited Site 24010-a exclusively throughout the study. There was no evidence that the blinded monitor visited Site 24011 at any point during the study.

2. Failure to notify FDA in a timely fashion regarding transfer of obligations for a study including site monitoring, including clinical and safety management to a contract research organization for site management including the conduct of any clinical study. Specifically, the sponsor failed to report to FDA the contracting to (a CRO) parts of the clinical study until March 29, 2012. Transfer of obligations was also reported later on January 21, 2013.

OSI Comments:
Monitoring deficiencies, in terms of timing of initial interim monitoring visits, were identified during inspection. These delays in monitoring, in addition to the medical complexities of the study population (subjects with chronic kidney disease) and administration of study treatment at hemodialysis centers distinct from sites (i.e. physician medical offices) where study documents were maintained may have contributed to the relatively large number of protocol deviations reported in the clinical study reports, especially for Study EPOE-10-01 (22.9% of Epoetin Hospira and 26.1% of Epogen treatment groups). Some of these protocol deviations included violations of inclusion/exclusion criteria observed at OSI clinical site inspections as described above.
The field investigator communicated to OSI that these studies in dialysis patients had multi-layered complexities to operationalize and execute. The studies involved separate administrative sites distinct from the dialysis or satellite site. The sponsor defined administrative and satellite sites used in EPOE-10-01 and EPOE-10-13. A satellite site was where the investigational drug product was present and where subject enrollment and medical management was performed, generally dialysis clinics. An administrative site, designated by the “-a” suffix, was where no investigational product was present and no study subject enrollment was performed. This administrative site was used by the clinical site staff to manage study-specific documentation such as regulatory documents and facilitate study conduct. Due to lack of sufficient space at the satellite site, patient medical records at the satellite site were copied for review at the administrative site.

Hospira provided a written response to the Form FDA 483 on May 1, 2015. Their responses appeared adequate.

c. **Assessment of data integrity:**
Despite the regulatory deficiencies described above, based upon inspection findings at the selected clinical sites described above, the sponsor adequately reported protocol deviations to the BLA. Therefore, data submitted by this sponsor appear acceptable in support of the requested indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Two clinical studies, EPOE-10-01 and EPOE-10-13 were inspected for this BLA. Four domestic clinical study sites covering five clinical investigators (Steven Zeig, M.D., Anant Desai, M.D. and Kamal Gandhi, M.D. Mark Lee, M.D., and Susan Diamond, M.D.) were inspected. The sponsor (Hospira, Inc.) was also audited.

The regulatory classification for Dr. Diamond is No Action Indicated (NAI). The regulatory classification for Drs. Zeig, Dr. Desai, and Dr. Gandhi is Voluntary Action Indicated (VAI). The preliminary classification for Dr. Lee is VAI.

Although regulatory violations were noted at three clinical sites (covering four clinical investigators), the protocol deviations observed were unlikely to significantly impact efficacy assessment or human subject safety. Although initial interim monitoring visits by the sponsor (and/or CRO) were delayed and did not conform to the clinical management plans for the study, the sponsor monitoring process did result in identification of noncompliant sites and appropriate reporting of protocol deviations to the BLA based upon inspections of a sample of clinical sites.

**Note:** The inspectional observations for the sponsor and Dr. Lee, are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.
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/s/

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07/10/2015

JANICE K POHLMAN  
07/10/2015

KASSA AYALEW  
07/10/2015
DATE: May 5, 2015

TO: Sharon Hertz, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction Products
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THROUGH: Charles Bonapace, Pharm.D.
Acting Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
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SUBJECT: Review of Establishment Inspection Report (EIR) covering Study EPOE-12-02 and BLA 125545 (Retacrit Epoetin, sponsored by Hospira, Inc.)

Summary and Recommendations:

At the request of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and the Division of Hematology Products (DHP), the Office of Study Integrity and Surveillance (OSIS) performed an inspection of the analytical portions of Studies EPOE-12-02 and EPOE-14-01 (BLA 125545) conducted at In addition, several additional studies conducted
and BLA 125545 (Retacrit Epoetin Sponsored by Hospira, Inc.)

at after 2012 were selected and reviewed to assess the firm’s overall bioanalytical operations and quality performance.

The inspection was conducted by OSIS Pharmacologists Seongeun (Julia) Cho, Ph.D. and Srinivas Chennamaneni (Staff Fellow), Ph.D. from April . The audit included a thorough review of the study records, electronic and paper documentation and audit trails, sample receipt and handling, examination of facilities and equipment, employee training, and interviews and discussions with the firm’s management and staff.

Based on the inspectional outcome and an overall site performance assessment, OSIS recommends that the bioanalytical portions of the Studies for NDA and EPOE-12-02 and EPOE-14-01 for BLA 125545 are acceptable for further Agency review.
II. **BLA 125545 (Retacrit Epoetin)**

At the request of the Division of Hematology Products (DHP), the OSIS conducted an inspection of the analytical portions of the following bioequivalence studies.

**Study Number:** EPOE-12-02  
**Study Title:** A phase I, randomized, single-dose, crossover study evaluating the pharmacokinetics and pharmacodynamics of Epoetin Hospira compared to Epogen (Amgen) following subcutaneous administration to healthy male volunteers  
**Sample analysis:** September 18, 2013 – October 15, 2013

**Study Number:** EPOE-14-01  
**Study Title:** A randomized, open-label, multiple-dose, parallel group study evaluating the pharmacodynamics and pharmacokinetics of Epoetin Hospira compared to Epogen (Amgen) following subcutaneous administration to healthy male volunteers
Sample analysis: August 13, 2014 – September 12, 2014

The inspection covered erythropoietin pharmacokinetic sample analysis for the above clinical studies. Review of inspections covering analysis of anti-drug antibodies and neutralizing antibodies and other clinical measurements will be provided in a separate memo.

The concentrations of Hospira Epoetin and Amgen Epogen in human serum from the above studies were measured using WHO rh-EPO (erythropoietin) as a reference standard. In the study report, concentrations in study samples were reported as milli-international units per milli-liter (mIU/mL). However, the assay was conducted using R&D systems Quantikine ELISA kit and as such, the measurement represents the mass of the analyte rather than its biological activities or effects. (b) (4) acknowledged that their assay indeed did not measure the bioactivity of erythropoietin in subject samples and the correct unit should be based on the conversion of mIU/mL to the concentration of the WHO reference standard. While this error affects the absolute values of the subject sample data presented in the study report, we determined that because the unit conversion would apply to all the study samples, the final study outcome would remain unchanged from that in the original report.

Please note that the inspections of the clinical sites (PPD Phase I Clinic, Austin, TX and Sea View Research, Miami, FL) for studies EPOE-12-02 and EPOE-14-01 will be scheduled. A review memo for these inspections will be provided soon after completion of the inspections.

III. Surveillance

As part of a global assessment of the bioanalytical operations and quality performance, the inspectors requested a list of all bioanalytical studies and method validations conducted since 2012. From the list, several key study components and institutional procedures that represent the firm’s bioanalytical operations were reviewed using a surveillance approach. No significant anomalies or systemic deficiencies that would have an impact on the study integrity were observed.

At the conclusion of the inspection, no Form FDA 483 was issued.
Conclusion:

Based on the inspectional outcome, the bioanalytical portions of the studies and EPOE-12-02 and EPOE-14-01 (BLA 125545) are acceptable for further Agency review.

Seongeun (Julia) Cho, Ph.D.
DNDBE, OSIS

Srinivas R. Chennamaneni, Ph.D.
DNDBE, OSIS

Final Classification:

NAI: 

Attachment:

Attachment 1: 

CC:
OTS/OSIS/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Cho/Chennamaneni
OTS/OSIS/Fenty-Stewart/Nkah/Dejernett/Johnson/Kavavil
CDER/OND/DAAAP/Hertz/Basham
CDER/OND/DHP/Farrell/Kallungal

Draft: SJC 4/21/2015, CSR 04/22/2015
Edit: CRB 5/4/2015
OSI: BLA 125545 = BE 6827
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice_Compliance/INSPECTIONS/BE Program/Analytical Sites/
FACTS: (BLA 125545)
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/s/

SRINIVAS RAO N CHENNAMANENI
05/07/2015

SEONGEUN CHO
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