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NCCN Guidelines Panel: Cancer and Chemotherapy Induced Anemia



Dear NCCN Cancer and CIA panel members,

On behalf of Pfizer, I respectfully request the NCCN Guideline Panel for Cancer and Chemotherapy Induced Anemia (CIA) to review the enclosed information for inclusion of RETACRIT™ (epoetin alfa-epbx), a biosimilar to Epogen® and Procrit® (epoetin alfa), for the treatment of patients with chemotherapy induced anemia.

**Specific Changes Requested:** Recommend the addition of RETACRIT as a treatment option for patients with chemotherapy induced anemia, similar to Procrit/Epogen.

**FDA Clearance:** On May 15<sup>th</sup> 2018, FDA approved RETACRIT, a biosimilar to Procrit/Epogen, for the treatment of patients with chemotherapy induced anemia (CIA).

**Rationale:** Based on the totality of evidence, the FDA approved RETACRIT as the first and only biosimilar ESA to Procrit/Epogen. In addition to analytical biosimilarity assessments, the registration clinical trials included PK/PD studies in healthy volunteers (EPO 12-02 & EPOE 14-01) and clinical confirmatory studies in patients with chronic kidney disease (EPOE 10-13, 10-01).

Assessment of biosimilarity is based on the totality of evidence from the RETACRIT registration program, and according to the FDA 351(k) pathway.

#### Analytical Tests and Non-clinical studies

Thirty-three state of the art analytical methods were developed to comparatively examine product attributes related to primary structure, secondary and tertiary structure, post-translational modification, product-related substances and impurities, drug product characteristics and the functional activity of the epoetin protein present in the RETACRIT and Procrit/Epogen. Structure and function of RETACRIT was demonstrated to be highly similar to Epogen/Procrit in analytical studies.

#### Clinical Pharmacology

Two clinical pharmacology studies (EPOE 12-01 & EPOE 14-01) in healthy male volunteers demonstrated PK/PD biosimilarity between RETACRIT and Procrit/Epogen.

In EPOE 12-02 (single dose cross-over study), for PK, 90% CI of the geometric mean ratios (GMR) for both AUC (101 – 111%) and C<sub>max</sub> (101 – 118%) were completely contained within the pre-specified acceptance limits (80- 125%) consistent with FDA guidance for industry regarding clinical pharmacology data for biosimilars. For PD, 90% CI of the GMR for reticulocyte count for AUEC (98 – 105%) and Emax (98 – 105%) were completely contained within the pre-specified acceptance limits (80 – 125%).

In EPOE 14-01 (multiple dose parallel study), for PK, 90% CI for the GMR for AUC (89.6 – 105.9%) and Cmax (83.9 – 104.9%) were both entirely contained within the pre-defined 80-125% equivalence margin. For PD, 90% CI of the GMR for AUEC for hemoglobin (99.8 – 101.5%) were completely contained within the pre-specified acceptance limits (96.5 – 103.5%).

#### Clinical Studies

Two clinical studies in patients with anemia due to chronic kidney disease on dialysis (EPOE 10-13 & EPOE 10-01) supported the demonstration of clinical biosimilarity for RETACRIT to Procrit/Epogen.

In EPOE 10-13 (comparative SC efficacy and safety) the 90% CI for the co-primary endpoints were entirely contained within the pre-specified limits. The 90% CI for mean weekly Hb (g/dL) during last 4 weeks maintenance was -0.13 to 0.21 (pre-specified equivalent limit  $\pm 0.5$  g/dL/week). The 90% CI for mean weekly dose (U/kg/week) during last 4 weeks maintenance was -12.54 to 7.85 (pre-specified equivalence limits  $\pm 45$  U/kg/week).

In EPOE 10-01 (comparative IV efficacy and safety), the 90% CI for the co-primary endpoints were entirely contained within the pre-specified limits. The 90% CI for mean weekly Hb (g/dL) during last 4 weeks maintenance was -0.22 to -0.01 (pre-specified equivalent limit  $\pm 0.5$  g/dL/week). The 90% CI mean weekly dose (U/kg/week) during last 4 weeks maintenance was -8.67 to 9.40 (pre-specified equivalence limits  $\pm 45$  U/kg/week).

The clinical data also support consistent and well characterized safety and immunogenicity profiles between RETACRIT and Procrit/Epogen. Similar rates of adverse events, serious adverse events and adverse events of special interest (hypertension, thromboembolism, myocardial infarction, cerebrovascular events, allergic reactions and seizures) were found in the 2 products. There were a similar number of patients with detectable anti-drug antibodies (ADA) results between RETACRIT and Procrit/Epogen. In all cases, patients remained clinically stable throughout treatment. No neutralizing antibodies were detected in any patient and no cases of PRCA were reported.

#### Extrapolation

The demonstration of biosimilarity coupled with the well-characterized nature of the reference product together support extrapolation across all conditions of use for the reference product.

The consistent MoA and PK, as well as the well-established safety and immunogenicity profile of the reference product, Epogen/Procrit, for all approved indications, including chemotherapy induced anemia, combined with the totality of data supporting biosimilarity justifies extrapolation across all indications granted by FDA.

The development and manufacturing of RETACRIT was based on our highly-related epoetin product in Europe, called Retacrit epoetin zeta. This was approved as a biosimilar in Europe in December 2007, and has been in the market for over 10 years with more than 400,000 patient years of treatment administered. The drug substance, also known as the active ingredient, for RETACRIT originated from the development of our biosimilar approved in Europe and utilizes the same cell line, growth medium and purification manufacturing processes. However, due to differences in the protein content and manufacturing scale between epoetin zeta and US RETACRIT a specific US development program was required for RETACRIT. Therefore, the efficacy and safety of epoetin zeta cannot be directly inferred to RETACRIT epoetin alfa-epbx.

The following resources are submitted in support of this requested change:

1. Retacrit Prescribing Information
2. FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Guidance for Industry)
3. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting May 25, 2017. BLA 125545 "Epoetin Hospira", a proposed biosimilar to Epogen/Procrit (epoetin alfa). Applicant: Hospira Inc., a Pfizer Company
4. Losem et al (2016)
5. Michallet et al, (2014)
6. Tzekova et al (2009)
7. Scotte et al (2016)

We appreciate the Panel's thorough consideration of Pfizer's submission for RETACRIT for the treatment of chemotherapy induced anemia. We welcome any questions that you may have.

Sincerely,



Dr. Selwyn Fung  
Medical Director Biosimilars Oncology  
Pfizer Inc.