NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: Post-Authorisation Safety Cohort Observation of Retacrit and Silapo (epoetin zeta) Administered Subcutaneously for the Treatment of Renal Anaemia (PASCO II)

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Rationale and background: Epoetin-associated pure red call aplasia (PRCA) is characterised by severe anaemia, low reticulocyte count, absence of erythroblasts, neutralising antibodies against erythropoietin and, as a consequence of nonresponse to therapeutically administered epoetin. Between 1999 and 2004, an increased rate of PRCA was observed in patients with epoetin-associated PRCA across Australia, Canada, certain European countries and Asia. The majority of these cases (95%) were observed in haemodialysis patients who had received several months of treatment with epoetin alfa (Eprex) administered SC, and SC use was identified as a risk factor and patients with renal anaemia as an at risk population. Changes in the formulation of the product, along with pharmacovigilance efforts and safety guidance, resulted in a >95% decrease in the number of new cases of epoetin-associated PRCA. Since then, antibody mediated PRCA is regarded as a rare class related toxicity that occurs after extended periods of subcutaneous administration of epoetins to chronic renal failure patients. This non-interventional study (NIS) was designed as a Post Authorisation Safety Study (PASS), to be followed up to approximately 3 years of treatment per patient with epoetin zeta. Hospira and STADA conducted separate observational studies with the same product, epoetin zeta, but different trade names Retacrit and Silapo.

Research question and objectives: The primary objective was to estimate the incidence rates for adverse events of special interest (AESIs) (PRCA, neutralizing antibodies, lack of efficacy and thromboembolic events) under treatment with Retacrit or Silapo administered SC in patients with renal anaemia. The secondary objective was to obtain information on adverse drug reactions (ADRs) associated with Retacrit or Silapo, use of Retacrit or Silapo during pregnancy and lactation and long-term use.

Study design: PASCO II was a non-interventional, longitudinal, multicentre, prospective cohort study of patients with renal anaemia treated with epoetin zeta. A minimum of 6206 patients were each to be followed for up to 3 years of treatment with epoetin zeta.

Setting: The administration and dosage for individual patients being treated with epoetin zeta SC, was determined as per the current Summary of Product Characteristics (SmPC) for Retacrit and Silapo. Patient observation was conducted between July 2010 and May 2020 at nephrologists' practices and dialysis centres treating patients with renal disease in 12 European countries.

Subjects and study size, including dropouts: The observation had initially planned to enrol up to 6700 patients. Following consultation with the PRAC in June 2019 and based on the observed PRCA incidence rate at that time, it was agreed that the planned sample size for the study could be reduced to a minimum of 6206.

A total of 6346 patients (4501 Retacrit, 1845 Silapo) were finally enrolled in the study. Of these, 6337 patients (4496 Retacrit, 1841 Silapo) received epoetin zeta and were included in the safety set. Overall, 3763 (59.3%) patients discontinued from the study prior to completing the observation period.

Variables and data sources: AESIs and ADRs (other than AESIs) were documented in the patient case report form (CRF). All detailed information for these events was reported to the safety database. All the steps related to the selection, enrolment and treatment of the patients were carried out in accordance with standard medical care.

Results:

The overall incidence rates for predefined AESIs and ADRs among 6337 patients of the safety set were:

- AESIs overall: 527 events in 418 (6.60%) patients.
    - PRCA: 1 (0.02%) patient (in the Retacrit group), and the same patient tested positive for neutralising antibodies,
    - Lack of efficacy: 34 (0.54%) patients,
    - Thomboembolic events: 389 (6.14%) patients.
- Other ADRs: 41 events in 28 (0.44%) patients.

Discussion:

A single event of PRCA was observed in 1 out of 6337 patients included in the safety set for this observational study. The exposure-adjusted incidence rate of PRCA was 0.84

per 10,000 patient years, which is substantially below the incidence rate of 4.5 per 10000 patient years observed in 2002 for innovator's reference product (Eprex).

The overall percentage of patients with other AESIs were low with lack of efficacy and thromboembolic events observed for 0.54% and 6.14% of patients, respectively. For thromboembolic events, the frequency category in the current European Union (EU) SmPC is "Common" (>1/100 to <1/10, ie, >1% to <10%), which is consistent with the observed frequency in PASCO II (6.14%).

Based on the observed incidence rate in this study, there is no immunogenicity concern over the SC use of the biosimilar product epoetin zeta in patients with renal anaemia. In addition, results for other AESIs and ADRs did not identify new safety concerns. No pregnant or lactating women were exposed to epoetin zeta during the study.

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