PROCRIT® (epoetin alfa)
Every-Two-Week Dosing in Treating Anemia in Patients with Cancer

SUMMARY

- Initiate PROCRIT in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL, and if there is a minimum of two additional months of planned chemotherapy.[1]
- In a prospective, multicenter, noninferiority study (N=310) in patients with chemotherapy (CT)-induced anemia, initial dosing schedules of epoetin alfa (EPO) 40,000 units (U) once weekly (QW) and 80,000 U twice weekly (Q2W) resulted in similar increases in hemoglobin (Hb) from baseline (1.8 g/dL vs 1.6 g/dL, respectively). The 2 treatment groups had similar incidence and patterns of adverse events (AEs), including clinically relevant thrombotic vascular events (CRTVEs).[2]
    - Retrospective sub analyses of elderly (>65 years), breast cancer, and colorectal cancer patients from this study revealed similar changes in Hb and other efficacy endpoints across all subpopulations.[3]
- In an open-label, multicenter study (N=129) evaluating an initial regimen of EPO 60,000 U QW followed by a maintenance dosing regimen of EPO 60,000 U Q2W in anemic cancer patients receiving CT for ≥16 weeks, 68% of patients experienced a Hb increase of ≥2 g/dL from baseline or achieved a Hb level ≥12 g/dL. During the maintenance phase with Q2W dosing, 61% of patients maintained a mean Hb between 11.0 and 12.5 g/dL. AEs were consistent with underlying disease processes and CT treatment.[4]
- An open-label, pilot study (N=51) evaluating an initial regimen of EPO 60,000 U QW for 4 weeks followed by a maintenance dosing regimen of EPO 60,000 U Q2W in anemic cancer patients receiving CT demonstrated that 64.7% of patients achieved a ≥1 g/dL increase in Hb during the initial QW dosing regimen. During the maintenance phase with Q2W dosing, 17.2% of patients were withdrawn from the study due to a Hb decrease ≥2 g/dL. The most commonly reported AEs included nausea, asthenia, and fatigue.[5]
- Several retrospective studies of medical claims databases, as well as data from a prospective observational registry for erythropoiesis-stimulating agent therapies, corroborate the findings from the clinical studies described in the summary below. The claims databases and the registry support dosing of EPO beyond once weekly and show extended dosing to be common for initiation as well as maintenance therapy.[6-16]

BACKGROUND

Various studies evaluating extended or alternative dosing regimens of EPO have been conducted in both treatment of anemia in cancer patients receiving concomitant myelosuppressive CT, and in anemic cancer patients not receiving CT or radiation therapy. Extended/alternative dosing regimens of EPO may potentially offer added convenience to both health care providers and the patient.[17]

PRODUCT LABELING

Recommended Starting Dose[1]

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.

Dose Reduction[1]

- Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/dL in any 2-week period or
- Hemoglobin reaches a level needed to avoid RBC transfusion.

- Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required.

Dose Increase[1]

- After the initial 4 weeks of PROCRIT therapy, if hemoglobin increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:
  - 300 Units/kg three times per week in adults or
  - 60,000 Units weekly in adults
  - 900 Units/kg (maximum 60,000 Units) weekly in pediatric patients
- After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue PROCRIT.

CLINICAL STUDIES

Initiation: QW versus Q2W

Prospective Study

Henry et al (2006)[2] compared the safety and efficacy of EPO 80,000 U Q2W to 40,000 U QW in patients with CT-related anemia (N=310).

Study Design/Methods

- This was a prospective, randomized, open-label, multicenter, noninferiority study.
- Patients with a life expectancy of ≥6 months with a nonmyeloid malignancy scheduled to receive cyclic CT for ≥12 weeks, with a hemoglobin (Hb) ≤11 g/dL were randomized in a 1:1 ratio to receive either: EPO 80,000 U SC Q2W (n=159) or EPO 40,000 U SC QW (n=151).
- Doses were modified to maintain Hb values of approximately 12 g/dL.
- The EPO dose was increased to 60,000 U for patients in the QW group that did not achieve Hb increase ≥1 g/dL after 4 weeks.
- No dose escalations were permitted in the Q2W group.
- Patients in the Q2W group who had a decrease in Hb ≥1 g/dL were switched to the 40,000 U QW group.
- In both groups, an increase in Hb levels to >12 g/dL or >1 g/dL in a 2–week period necessitated dose reductions: EPO 80,000 U Q2W to 60,000 U Q2W; EPO 60,000 U QW to 40,000 U QW; and EPO 40,000 U QW to 30,000 U QW.
- If Hb >13 g/dL, drug was withheld until Hb ≤12 g/dL and resumed at a reduced dose.
- EPO was administered for a maximum of 12 weeks, and all patients were followed weekly until 2 weeks after the last dose of EPO or up to a maximum of 13 weeks on study.
- Oral ferrous sulfate 325 mg once daily or an equivalent formulation was administered to all patients.
- The **primary endpoint** (per-protocol population) was change in Hb from baseline to the end of the study.
- **Secondary endpoints** included the percentage of patients who achieved a Hb increase of >1 g/dL, the time to increase Hb >1 g/dL, the percentage of patients requiring packed red blood cell (pRBC) transfusion between day 29 and week 13/end of study, and the mean number of U of pRBC transfused.

Results

Patient Characteristics

- There were 72 patients in the Q2W group 76 patients in the QW group in the per-protocol population.
- There were 151 patients in the Q2W group and 144 patients in the QW group in the modified intent-to-treat (mITT) population.
- The mean baseline Hb in the mITT population was 10.1 g/dL in the Q2W group and 9.9 g/dL in the QW group.

Efficacy

- Table: Primary and Secondary Endpoints provides a summary of the study findings.
- Fewer dose reductions were required for patients enrolled in the Q2W group (41%) compared to those in the QW group (59%) (*P*=0.003).
- In the QW group, 37% (n=54) of patients required a dose increase to 60,000 U QW.
- The majority of patients in the Q2W group (87%) were able to be maintained on a Q2W regimen throughout the study.

Primary and Secondary Endpoints[2]

	EPO 40,000 U SC QW	**EPO 80,000 U Q2W**	***P*-value**
Mean cumulative dose	340,621 U	304,706 U	-
Mean treatment duration	60.6 days	58.0 days	-
Primary endpoint			
Mean change in Hb from BL to EOS	1.8 g/dL	1.6 g/dL	-
Secondary endpoints			
Patients who achieved a Hb increase of >1 g/dL	74%	76%	0.773
Time to increase Hb >1 g/dL	29.0 days	22.0 days	0.392
Patients requiring PRBC transfusion (between day 29 and week 13/EOS)	11.1%	9.6%	0.709
Mean number of U of PRBC transfused	2.5	3.4	0.056
Abbreviations: BL, baseline; EOS, end of study; Hb, hemoglobin; PRBC, packed red blood cell; QW, once weekly; Q2W once every 2 weeks; U, units.			

Safety

- The most frequently reported AEs for the QW vs the Q2W groups were diarrhea (28% vs 20%), nausea (24% vs 24%), and fatigue (20% vs 25%).
- Patients in each treatment group were withdrawn due to an AE, most of which were related to the cancer or CT (n=17).
- Nineteen patients (Q2W, n=10; QW, n=9) died during the study or within 30 days after the last dose of study drug. All deaths were considered to be unrelated to study drug.
- CRTVEs were reported in 8% of patients in each treatment group. There were 5 CRTVEs classified as life-threatening: 1 pulmonary embolism in a patient in the Q2W group and 4 cerebrovascular accidents in the QW group, 2 of which were fatal.

Retrospective Study

Henry et al (2008)[3] evaluated the results of a subset of elderly (>65 years old), breast cancer, and colorectal cancer patients included in the previously described study[2] comparing the use of EPO 80,000 U Q2W to 40,000 U QW.

Results

Patient Characteristics

- There were 84 elderly patients, 38 breast cancer patients, and 24 colorectal cancer patients randomized to the 80,000 U SC Q2W group and 63 elderly patients, 37 breast cancer patients, and 18 colorectal cancer patients randomized to the 40,000 U SC QW group.

Efficacy

- The mean cumulative dose and duration of treatment were similar between the 80,000 U Q2W and the 40,000 U QW groups for each subpopulation.
- The median time to achieve Hb ≥11 g/dL for the 80,000 U Q2W group vs the 40,000 U QW group was ≤5 weeks for both treatment regimens in all subpopulations: elderly patients: 30 days vs 29 days, respectively (*P*=0.458); breast cancer patients: 21 days for both groups (*P*=0.373); and colorectal cancer patients: 15 days vs 36 days (*P*=0.412).
- Results for the primary efficacy endpoint of mean Hb value change from baseline to the end of the study were comparable between dosing groups in all 3 subpopulations (range, 1.4-2.2 g/dL).

Safety

- The 80,000 U Q2W safety subpopulations included 80 elderly patients, 36 breast cancer patients, and 24 colorectal cancer patients. The 40,000 U QW safety subpopulations included 59 elderly patients, 37 breast cancer patients, and 18 colorectal cancer patients.
- The incidence and pattern of AEs and incidence of CRTVEs were similar between groups in each subpopulation.
- The most frequently reported AEs occurring in ≥25% of patients in either dosing group of any subpopulation included diarrhea, fatigue, nausea, and neutropenia.
- In each dosing group, 17 patients were withdrawn from the study due to an AE, most of which were related to the patient's underlying cancer or CT.
- Fewer patients in the Q2W dosing group had a Hb rate of rise ≥1.0 g/dL or ≥1.5 g/dL within a 2–week period compared with the QW group across all mITT subpopulations. In the breast cancer subpopulation, there was a significant between-dosing-group difference with respect to a Hb value rate of rise ≥1 g/dL (*P*=0.014).
- Overall, 19 patients died during the study or within 30 days of the study. Similar proportion of patients died between dosing groups in each subpopulation. All deaths were considered to be unrelated to study drug; 12 of the 19 were due to disease progression.

Initiation/Maintenance: QW Followed by Q2W

Gregory et al (2007)[4] evaluated the efficacy and safety of an initial EPO regimen of 60,000 U QW followed by a maintenance dosing regimen of EPO 60,000 U Q2W in anemic cancer patients receiving CT for at least 16 weeks (N=129).

Study Design/Methods

- This was an open-label, multicenter study.
- Patients had a Hb ≤11 g/dL and were scheduled to receive CT for a nonmyeloid malignancy, either weekly or monthly, for ≥16 weeks.
- The study consisted of 2 treatment phases.
    - During the initiation-dosing phase (IDP), patients received EPO 60,000 U SC QW to achieve a target Hb of 12 g/dL (maximum duration of 12 weeks).
    - During the extended-dosing phase (EDP), patients who achieved a Hb target of 12 g/dL in the IDP were administered EPO 60,000 U SC Q2W to maintain Hb between 11.0 g/dL and 12.5 g/dL.
- The EPO dose was withheld if Hb >13 g/dL, and the dose was reduced if the rate of Hb rise was >1.3 g/dL in a 2-week period.
- Ferrous sulfate 325 mg/day was administered as tolerated.

- The maximum study duration (IDP + EDP) was 24 weeks.
- The **primary endpoint** was the proportion of patients who achieved a hematopoietic response during the IDP, defined as an Hb increase ≥2 g/dL from baseline, or achievement of a Hb level ≥12 g/dL.
- Several **secondary endpoints** were evaluated.

Results

Patient Characteristics

- The mean baseline Hb was 10.0±0.9 g/dL.

Efficacy

- Among 45 (34.9%) of patients who only completed IDP, the average time spent in IDP was 5.2 weeks and the mean weekly EPO dose was 59,020 U.
  - A total of 6% and 11% of patients had ≥1 dose withheld or reduced, respectively. A total of 68% (84/124) of patients had a hematopoietic response.
  - The median time to achieve a hematopoietic response was 30 days (95% confidence interval: 29–37).
  - A total of 11.3% (14/124) of patients had a Hb increase from baseline of 1 g/dL to 1.9 g/dL.
  - A total of 14% (18/129) of patients received 24 pRBC transfusions (mean, 2.6 U per transfused patient).
- Among 84 patients (68%) who achieved a hematopoietic response and proceeded to the EDP, the mean treatment duration in the EDP phase was 13.2 weeks and the mean EPO Q2W dose was 49,515 U.
  - A total of 61% (51/84) of patients maintained a mean Hb between 11.0 g/dL and 12.5 g/dL.
  - A total of 70.2% (59/84) of patients withdrew early from the EDP, of which 16 patients withdrew due to Hb decrease to <11 g/dL.
  - A total of 63% and 56% of patients required ≥1 dose of EPO withheld or reduced, respectively.
  - The mean Hb level at start of EDP was 12.4±0.35 g/dL.
  - The mean Hb level of individual patients in the EDP was 12.3±0.62 g/dL.
  - A total of 88% (74/84) of patients maintained a mean Hb between 11.0 g/dL and 13.0 g/dL up to the time of withdrawal or study end.
  - The proportion of patients with Hb levels in this range by study week ranged from 69.6% to 97.5%.
  - No patient received a transfusion during the EDP.

Safety

- The most common AEs were nausea (28.7%), fatigue (20.9%), and vomiting (17.8%).
- Serious adverse events (SAEs) were reported in 50.4% (n=65) of patients.
- The most commonly reported SAEs included disease progression (6.2%), dehydration (3.9%), and vomiting (3.9%).
- During the study or within 30 days after last dose, 15 (11.6%) patients died.
- A total of 11.6% (n=15) of patients experienced CRTVE.
- During the IDP, 4.7% (6/129) of patients had 7 CRTVEs, including deep vein thrombosis (DVT; 4 occurrences), pulmonary embolism (1 occurrence), subclavian vein thrombosis (1 occurrence), and venous thrombosis (1 occurrence).
- During the EDP: 9.5% (8/84) had 9 CRTVEs, including DVT (3 occurrences), hemiparesis (2 occurrences), myocardial infarction (1 occurrence), myocardial ischemia (1 occurrence), portal vein thrombosis (1 occurrence), and transient ischemic attack (1 occurrence).
- All CRTVEs were considered to be unrelated to study drug, except the portal vein thrombosis which was considered possibly related.

- A Hb increase ≥1 g/dL within a 2-week period was observed in 12 of 14 patients (85.7%) who had a CRTVE sometime during their study participation.
- More than 1 Hb level >13 g/dL was observed in 7 of 14 patients (50%) who had a CRTVE.

Reddy et al (2006)[5] evaluated the efficacy and safety of initial administration of EPO 60,000 U QW for 4 weeks followed by EPO 60,000 U Q2W extended dosing regimen in anemic cancer patients undergoing CT (N=51).

Study Design/Methods

- This was an open-label, multicenter, single-arm pilot study.
- Patients had a Hb ≤11 g/dL and were scheduled to receive CT for a non myeloid malignancy, either weekly or monthly, for ≥16 weeks.
- The study consisted of 2 treatment phases: an IDP, when patients were administered EPO 60,000 U SC QW for 4 weeks, followed by an EDP, when EPO 60,000 U SC Q2W was initiated at week 5 and continued for up to an additional 12 weeks.
- EPO treatment was withheld when Hb levels were >13 g/dL and resumed at 40,000 U when Hb was ≤12 g/dL.
- If Hb increase was <1 g/dL during the IDP or Hb decreased ≥2 g/dL during the EDP, patients were withdrawn from the study.
- Oral ferrous sulfate 325 mg daily or an equivalent preparation was administered to all patients as tolerated.
- Transfusions were given if deemed medically necessary by the investigator.
- The **primary endpoint** was the proportion of patients achieving a hematological response, defined as ≥1 g/dL Hb increase from baseline at any time during the IDP (up to week 5).
- **Secondary endpoints** and additional outcome measures were evaluated.

Results

Patient Characteristics

- The mean baseline Hb was 10.1 g/dL±0.79 g/dL.

Efficacy

- During the IDP (n=51), 19.6% (n=10) of patients had ≥1 dose of EPO withheld for Hb >13 g/dL and 23.5% (n=12) of patients had ≥1 EPO dose reduction after a dose was withheld for Hb >13 g/dL or for a Hb rate increase >1.3 g/dL in a 2-week period.
  - The mean EPO dose was 58,268 U weekly.
  - A total of 64.7% (n=33) of patients achieved a hematological response.
  - The mean time to hematological response was 15.5±6.7 days.
- Of the patients included in the IDP, 56.9% (n=29) of patients advanced to the EDP.
  - A total of 69% (n=20) of patients had ≥1 dose withheld for Hb >13 g/dL.
  - A total of 69% (n=20) of patients had ≥1 EPO dose reduction after a dose was withheld for Hb >13 g/dL or for a Hb rate increase >1.3 g/dL in a 2-week period.
  - The mean EPO dose was 45,790 U Q2W.
  - The mean Hb level at the start of week 5 was 12.4 g/dL±0.99 g/dL.
  - A total of 41.4% (n=12) of the patients exhibited a further Hb increase.
    - A total of 6.9% (n=2) of patients had an average Hb ≥1 g/dL greater than Week 5 Hb value.
    - A total of 34.5% (n=10) of patients had an EDP average Hb 0–0.9 g/dL higher than Week 5 Hb value.
  - Overall, 17 patients did not experience a further Hb increase. Hb decreased by a mean of -1 g/dL±0.6 g/dL.
  - A total of 17.2% (n=5) of patients withdrew from the study due to a Hb decrease ≥2 g/dL.
  - The mean final Hb value was 11.7 g/dL±1.28 g/dL in the 29 patients in this phase.

- During both phases, the mean Hb level increased by 2 g/dL from baseline by week 6 and then remained stable for rest of study.
    - Four patients received 5 transfusions (weeks 1–4: n=3; weeks 5–8: n=1; weeks 9–12: n=1).

Safety

- One or more AEs were reported in 94.1% of patients. Most AEs were considered to be not related to study drug.
- The most commonly reported AEs included nausea (23.5%), asthenia (21.6%), and fatigue (21.6%).
- Overall, ≥1 SAE was reported in 25.5% (n=13) of patients.
- CRTVEs were reported in 2 patients (3.9%) who each experienced 1 CRTVE during the IDP of weekly dosing. One patient experienced DVT, and the other patient experienced chest pain. Both thrombotic vascular events were not related to study drug.
- Three (5.9%) patients died during the study due to disease progression (n=2) or sepsis (n=1).

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) was conducted on 21 August 2024.

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