NEW DRUG APPROVAL

Brand Name	Besremi®
Generic Name	ropeginterferon alfa-2b-njf
Drug Manufacturer	PharmaEssentia Corporation

New Drug Approval

FDA Approval Date: November 12, 2021
Review Designation: N/A
Type of Review: Orphan, Biologics License Application (BLA): 761166
Dispensing Restriction: Specialty Only, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Polycythemia vera is a rare, chronic disorder involving the overproduction of blood cells in the bone marrow (myeloproliferation). The overproduction of red blood cells is most dramatic, but the production of white blood cells and platelets are also elevated in most cases. Since red blood cells are overproduced in the marrow, this leads to abnormally high numbers of circulating red blood cells (red blood mass) within the blood. Consequently, the blood thickens and increases in volume, a condition called hyperviscosity. Thickened blood may not flow through smaller blood vessels properly. A variety of symptoms can occur in individuals with polycythemia vera including nonspecific symptoms such as headaches, fatigue, weakness, dizziness or itchy skin; an enlarged spleen (splenomegaly); a variety of gastrointestinal issues; and the risk of blood clot formation, which may prevent blood flow to vital organs. More than 90 percent of individuals with polycythemia vera have a variation (mutation) in the JAK2 gene. The exact role that this variation plays in the development of polycythemia vera is not yet known.

The disease epidemiology covered in the report provides historical as well as forecasted epidemiology segmented by Total Prevalent Population of Polycythemia Vera (PV), Prevalence Population of PV Based on Symptoms, Gender-specific Symptomatic Prevalence of PV, Age-specific Symptomatic Prevalence of PV, Prevalence of PV Based on Risk, and Prevalence of PV by Gene Mutation scenario of PV covering the United States from 2017 to 2030.

- The estimates show the highest prevalence of PV in the United States with 157,290 cases in 2017.
- The epidemiology model for PV estimates that out of the total population of 157,290 cases in the US for PV, 62,916 cases and 94,374 cases were contributed by asymptomatic and symptomatic, respectively.
- Out of the total symptomatic population in the US for PV, 61,060 cases and 33,314 cases were contributed by males and females in 2017.
- It has been also observed that PV in the US is mostly prevalent in the age group of >75 years.
- A total of 94,374 diagnosed (symptomatic) prevalent population of PV was assessed in 2017. Out of these cases, ~87,881 cases of PV were calculated for patients with JAK2 V617F, thereby accounting for the highest number of cases with gene mutation with ~97% of total PV cases with JAK2 mutation.
- Around 23% of patients accounted for low-risk categories, and 77% accounted for high-risk cases in 2017 in the United States.

Efficacy

Phase 1/2 Trials: The efficacy and safety of Besremi were evaluated in the PEGINVERA study, a Phase 1/2 prospective, multicenter, single arm trial that lasted 7.5 years. Besremi®'s effectiveness was assessed by looking at the number of patients who achieved complete hematological response (CHR), defined as a red blood cell

volume of less than 45% without a recent phlebotomy, normal white cell counts and platelet counts, a normal spleen size, and no blood clots. Overall, 61% of patients who received Besremi had a CHR.

Table 1. PEGINVERA (NCT01193699): Study Design Summary

Study Design	• Prospective, open-label, multicenter Phase 1/2 dose-escalation study
Study Population	• 51 adults with PV; all had *JAK2V617F* mutation ○ 25 patients enrolled in Phase 1 ○ An additional 26 patients enrolled in Phase 2 • Mean age at baseline: 56 years (range, 35–82 years) o 39% female; 61% male • 16 patients (31%) had splenomegaly (length >12 cm) ○ Median spleen size: 13.1 cm (range, 8–22 cm)
Interventions	• **Phase 1** (N = 25): 8 dose levels (range, 50 mcg to 540 mcg) of Besremi® administered every 2 weeks over 13 months using a 3 + 3 dose-escalation design to determine MTD • **Phase 2** (N = 51): Besremi® administered once every 2 weeks; dosing was adjusted based on efficacy rather than tolerability ○ Mean administered dose in study: 237 mcg (± 110) every 14 days ○ Median duration of treatment exposure: 61 months
Endpoints	• **Phase 1:** Define MTD • **Phase 2:** Evaluate optimal dosing and efficacy
Efficacy and Safety Results	• No dose-limiting toxicities occurred within dose range (50 mcg–540 mcg) • CHR during treatment period: 61% (31/51) (95% CI: 46, 74) • Median time to response among treated patients who achieved CHR: 7.8 months • Hematological response based only on hematocrit, platelets, and leukocytes was achieved in 80% of patients treated with Besremi® (41/51) (95% CI: 67, 90)
Adverse Events	• In total, 744 AEs were noted; 330 of these were drug-related • **AEs observed in >20% of patients:** pruritus, arthralgia, fatigue, headache, diarrhea, influenza like illness, vertigo • **AEs observed in >10% of patients:** nasopharyngitis and rhinitis, nausea, decreased appetite, pyrexia, myalgia, alopecia, chills, deterioration of general physical health, injection site reactions, leukopenia, thrombocytopenia, increase of γ-glutamyltransferase, pain in extremity, hyperhidrosis, night sweats • **Psychiatric AEs*** occurred in 16 patients (31%); treatment was permanently discontinued because of psychiatric symptoms in 2 patients (4%); the majority of these symptoms (70%) were of mild intensity, and in 77% of patients, psychiatric symptoms completely resolved during the study

Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; HU, hydroxyurea; MTD, maximum tolerated dose; PV, polycythemia vera; SD, standard deviation; TEAEs, treatment-emergent adverse events; WBC, white blood cells.

*Psychiatric AEs included acute stress disorder, aggression, apathy, depression, depressive symptoms, hallucination, insomnia, listlessness, altered mood, nervousness, sleep disorder, stress, and anxiety.

Phase 3 Trials

Table 2. PROUD-PV/CONTINUATION-PV (NCT01949805/NCT02218047): Study Design Summary	
Study Design	PROUD-PV and its extension study, CONTINUATION-PV, were Phase 3, randomized, controlled, open-label trials conducted in 48 clinics in Europe. The CONTINUATION-PV trial is ongoing.
Study Population (N = 306)	**Key inclusion criteria:** • ≥18 years of age • Early-stage PV (no history of cytoreductive treatment or less than 3 years of previous HU treatment), diagnosed by 2008 WHO criteria
Interventions	**PROUD-PV:** 257 patients were randomly assigned 1:1 to receive: • Besremi® (n = 127) SC every 2 weeks, starting at 50 mcg or • HU (n = 124) orally, starting at 500 mg/day After 1 year, 171 patients elected to roll over to CONTINUATION-PV.
Endpoints	• **PROUD-PV:** Primary endpoint was noninferiority of Besremi® vs. HU regarding CHR with normal spleen size (≤12 cm for women and ≤13 cm for men) at 12 months • **CONTINUATION-PV:** Coprimary endpoints were CHR with normal spleen size and with IDB
Efficacy and Safety Results	• **PROUD-PV:** 21% of patients in the Besremi® group and 28% of patients in the HU group met the composite primary endpoint* ○ CHR without spleen criterion: 43% Besremi® vs. 46% HU (*P* = 0.63 at 12 months) • **CONTINUATION-PV:** CHR with IDB was met in 53% of patients in the Besremi® group vs. 38% of patients in the HU group (*P* = 0.044 at 36 months) ○ CHR without spleen criterion: 71% Besremi® vs. 51% HU (*P* = 0.012 at 36 months)
Adverse Events	• The most frequently reported grade 3 and grade 4 TRAEs were: ○ Besremi group: increased γ-glutamyltransferase (6%) and increased alanine aminotransferase (3%) ○ HU group: leukopenia (5%) and thrombocytopenia (4%) • Treatment-related SAEs occurred in 2% of patients in the Besremi® group and 4% of patients in the HU group • 1 treatment-related death (acute leukemia) was reported in the HU group

Abbreviations: CHR, complete hematological response; HU, hydroxyurea; IDB, improved disease burden; SAEs, serious adverse events; ST, standard therapy; TRAEs, treatment-related adverse events; WHO, World Health Organization.

*The study did not meet noninferiority.

Safety

ADVERSE EVENTS

The most common adverse reactions reported in > 40% of patients were influenza-like illness, arthralgia, fatigue, pruritus, nasopharyngitis, and musculoskeletal pain.

WARNINGS & PRECAUTIONS

Patients exhibiting the following events should be closely monitored and may require dose reduction or discontinuation of therapy: depression and suicide, endocrine toxicity, cardiovascular toxicity, decreased peripheral blood counts, hypersensitivity reactions, pancreatitis, colitis, pulmonary toxicity, ophthalmologic toxicity, hyperlipidemia, hepatotoxicity, renal toxicity, dental and periodontal toxicity, dermatologic toxicity.

CONTRAINDICATIONS

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt.
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of Besremi®.
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.
- History or presence of active serious or untreated autoimmune disease.
- Immunosuppressed transplant recipients.

Clinical Pharmacology

MECHANISMS OF ACTION

Interferon alfa belongs to the class of type I interferons, which exhibit their cellular effects in polycythemia vera in the bone marrow by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through the activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. The actions involved in the therapeutic effects of interferon alfa in polycythemia vera are not fully elucidated.

Dose & Administration

ADULTS

- **Patients Not Already on Hydroxyurea**

The recommended Besremi® starting dosage for patients not on hydroxyurea is 100 mcg by subcutaneous injection every two weeks. Increase the dose by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9 /L, and leukocytes less than 10 x 10^9 /L).

- **Patients Transitioning from Hydroxyurea**

When transitioning to Besremi® from hydroxyurea, start Besremi® at 50 mcg by subcutaneous injection every two weeks in combination with hydroxyurea. Gradually taper off the hydroxyurea by reducing the total biweekly dose by 20-40% every two weeks during Weeks 3-12. Increase the dose of Besremi® by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9 /L, and leukocytes less than 10 x 10^9 /L). Discontinue hydroxyurea by Week 13.

PEDIATRICS

Safety and effectiveness in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

- Estimated glomerular filtration rate (eGFR) of 30 mL/min or higher: No dosage adjustment is necessary.
- eGFR less than 30 mL/min: Avoid use.

HEPATIC IMPAIRMENT

- Mild hepatic impairment (Child-Pugh class A) at baseline*:* Specific guidelines for dosage adjustments in mild hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment at baseline*:* Use is contraindicated.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 500 mcg/mL solution in a single-dose prefilled syringe