PHARMACY COVERAGE GUIDELINE

BESREMI® (ropeginterferon alfa-2b-njft) for subcutaneous injection Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Besremi (ropeginterferon alfa-2b-njft) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Hematologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of polycythemia vera (PV) according to the world Health Organization (WHO) criteria meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion (see Definitions section)

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Complete blood count with differential count
    b. Blood smear
    c. Testing for *JAK2* V617F in blood or *JAK2* exon 12 mutation
    d. Serum erythropoietin
    e. Eye exam in those with diabetes or hypertension
    f. Serum triglycerides
    g. Liver enzymes and hepatic function tests
    h. Serum creatinine
    i. Negative pregnancy test in females with reproductive potential

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for hydroxyurea

7. There are **NO** FDA-label contraindications such as:
    a. Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
    b. Hypersensitivity to interferons
    c. Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
    d. History or presence of active serious or untreated autoimmune disease
    e. Immunosuppressed transplant recipients

8. Will not be used in patient with significant renal impairment of eGFR less than 30mL/minute

9. Individual does not have severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Besremi (ropeginterferon alfa-2b-njft) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Hematologist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
    a. Hematocrit less than 45%
    b. Reduction in phlebotomy
    c. Platelets less than or equal to 400 x 10^9/L
    d. Reduction in spleen size

e. Absence of thromboembolic events

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use, if clinically appropriate withhold, reduce dose, or permanently discontinue based on severity, recurrence, persistence, or duration of adverse reaction as follows:
   a. Contraindications as listed in the criteria for initial therapy section
   b. Significant adverse effect such as:
      i. Development of life-threatening neuropsychiatric reaction such as severe depression, suicidal ideation, or suicide attempt
      ii. Development of endocrine disorders that cannot be adequately managed during treatment such as worsening hypothyroidism and hyperthyroidism, autoimmune thyroiditis, hyperglycemia, or new onset type 1 diabetes
      iii. Cardiovascular toxicity including cardiomyopathy, myocardial infarction, atrial fibrillation, and coronary artery ischemia
      iv. Severe anemia, leukopenia, or thrombocytopenia
      v. Urticaria, angioedema, bronchoconstriction, anaphylaxis
      vi. Pancreatitis
      vii. Ulcerative or hemorrhagic/ischemic colitis
      viii. Pulmonary toxicity including pulmonary infiltrates or pulmonary function impairment
      ix. New or worsening eye disorder such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion
      x. Hepatic decompensation characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage
      xi. Severe renal impairment

6. Individual does not have severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

PHARMACY COVERAGE GUIDELINE

BESREMI® (ropeginterferon alfa-2b-njft) for subcutaneous injection Generic Equivalent (if available)

Description:

Polycythemia vera (PV) is a chronic myeloproliferative disorder that causes the bone marrow to produce too many red blood cells. The median age at presentation is 60 years. Patients often present with either arterial or venous vascular occlusive events. The events are predominantly coronary and cerebral but can involve the skin and gastrointestinal tract. Over time PV may evolve to MF, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS). The mainstay of therapy for PV is phlebotomy which removes excess red blood cells and lowers blood viscosity. In general, the goal of phlebotomy is to keep the hematocrit below 45% in men and 42% in women. When patients remain symptomatic despite phlebotomy, other options include hydroxyurea (with or without phlebotomy), interferon alfa, ruxolitinib, thalidomide, lenalidomide, anagrelide (in certain circumstances) and rarely, chlorambucil, melphalan, or busulfan. It is estimated that 25% of PV patients remain uncontrolled despite the use of existing standard therapies.

Besremi (ropeginterferon-alfa-2b-njft) is indicated for the treatment of adults with PV. Ropeinteferon-alfa-2b-njft uses a site-specific monopegylation technology that extends half-life to 7 days. It can be dosed every 2 weeks and extended to every 4 weeks after hematologic stability is achieved for at least 1 year. Ropeginterferon-alfa-2b-njft exhibit cellular effects in PV in the bone marrow by binding to 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. The actions involved in the therapeutic effects of interferon alfa in PV are not fully elucidated.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

WHO diagnostic criteria polycythemia vera	
Major criteria:	
1.	Hemoglobin >16.5 g/dL in men
	Hemoglobin >16.o g/dL in women
	OR
	Hematocrit >49% in men
	Hematocrit >48% in women
	OR
	Increased red cell mass*
2.	Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3.	Presence of *JAK2* V617F or *JAK2* exon 12 mutation

PHARMACY COVERAGE GUIDELINE

BESREMI® (ropeginterferon alfa-2b-njft) for subcutaneous injection Generic Equivalent (if available)

Minor criteria:
1. Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion¶
* More than 25% above mean normal predicted value. ¶ Bone marrow biopsy **may not be required** in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a bone marrow biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF). MF: myelofibrosis; PV: polycythemia vera; WHO: World Health Organization

Polycythemia vera:

Low-risk patients
- Age ≤ 60 years and no history of thrombosis

High-risk patients:
- Age > 60 years
- History of thrombosis

Potential indications for cytoreductive therapy:
- New thrombosis or disease related major bleeding
- Frequent and/or persistent need for phlebotomy, but with poor tolerance for phlebotomy
- Splenomegaly
- Thrombocytosis
- Leukocytosis
- Disease related symptoms (e.g., pruritus, night sweats, fatigue)

Resources:

Besremi (ropeginterferon alfa-2b) product information, revised by PharmaEssentia USA Corporation. 04/2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 03, 2024.

Tefferi A. Clinical manifestations and diagnosis of polycythemia vera. In: UpToDate, Larsen RA and Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated November 27, 2024. Accessed February 03, 2025.

Tefferi A. Polycythemia vera and secondary polycythemia: Treatment and prognosis. In: UpToDate, Larsen RA and Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated February 27, 2024. Accessed February 03, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloproliferative Neoplasms Version 2.2024 –Updated August 08, 2024. Available at https://www.nccn.org. Accessed February 03, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

ORIGINAL EFFECTIVE DATE: 02/17/22 | ARCHIVE DATE: | LAST REVIEW DATE: 02/20/2025 | LAST CRITERIA REVISION DATE: 02/20/2025