ropeginterferon alfa-2b-njft (Besremi®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO257

Description

Ropeginterferon alfa-2b-njft (RIFN-α-2b; Besremi) is a long-acting, monopegylated, interferon alfa isomer which induces cellular activities related to binding specific cell-surface membrane receptors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
ropeginterferon alfa-2b-njft (Besremi)	500 µg/mL pre-filled syringe (PFS)	Polycythemia Vera (PV)	2 syringes/28 days

Initial Evaluation

I. **Ropeginterferon alfa-2b-njft (Besremi)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
   C. A diagnosis of **polycythemia vera (PV)** when the following are met:
      1. Provider attests that the member has high-risk PV and requires cytoreductive therapy; **AND**
      2. Treatment with <u>both</u> of the following has been ineffective or not tolerated, unless all are contraindicated:
         i. Hydroxyurea
         ii. Peginterferon alfa-2a (Pegasys); **AND**
      3. Ropeginterferon alfa-2b-njft (Besremi) is medically necessary for the treatment of polycythemia vera (PV) over hydroxyurea and peginterferon alfa-2a (Pegasys). (Note: preference for longer injection interval or other convenience does not meet medical necessity).

II. Ropeginterferon alfa-2b-njft (Besremi) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Myelofibrosis

B. Essential thrombocythemia
C. Chronic hepatitis infection (e.g., hepatitis B, hepatitis C)
D. Acute myeloid leukemia (AML)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited disease improvement or stability (e.g., complete hematological response (CHR), improved hematocrit ≤ 45%, platelet and WBC counts within normal range).

Supporting Evidence

I. RIFN-α-2b (Besremi) is FDA-approved for the treatment of adult patients with PV. PV is a rare, chronic, myeloproliferative disorder caused by a mutation in bone marrow stem cells resulting in blood cell overproduction. Symptoms include pruritis, fatigue, and microcirculatory disturbance. PV may progress to myelofibrosis and acute myeloid leukemia (AML).
II. PV risk stratification is based on age and comorbidities. Patients ≥ 60 years at initial diagnosis and presence of cardiovascular comorbidities or thromboembolic event history are classified as high-risk. Risk level guides treatment. For low-risk PV, periodic phlebotomy combined with low-dose aspirin remain the first-line therapy. Patients with high-risk PV may require cytoreductive therapy. Additionally, low-risk PV patients, who are symptomatic after repeated phlebotomy may be considered as potential candidates for cytoreductive therapy. This may consist of patients who experience new thrombosis, splenomegaly, progressive thrombocytosis, or disease-related major bleeding event when being managed via phlebotomy. These patients, even though classified as low-risk PV cases, are recommended to be treated similar to high-risk PV. Cytoreductive therapy may be considered medically necessary in this subgroup of patients.
III. The National Comprehensive Cancer Network (NCCN) guideline for the treatment of myeloproliferative neoplasms recommend hydroxyurea (HU) or peginterferon alfa-2a (Pegasys) as preferred cytoreductive agents. In practice, peginterferon alfa-2a (Pegasys) may be considered for younger patients, during pregnancy or where treatment with HU is contraindicated. For patients with intolerance or resistance to other cytoreductive agents, ruxolitinib (Jakafi) is a recommended subsequent-line therapy. As of March 2022, the NCCN guideline added RIFN-α-2b (Besremi) as 'other recommended regimen' (Category 2A) for the treatment of high-risk PV. Additionally, RIFN-α-2b (Besremi) may also be considered as another recommended regimen, when used adjunct to phlebotomy, for the initial treatment of low-risk

PV. This recommendation is based on lower-level evidence (Category 2B). Current clinical data for RIFN-α-2b (Besremi) does not provide a high degree of confidence for use in the initial treatment of patients with low-risk PV, and cytoreductive treatment naïve patients.

IV. FDA-approval is based on efficacy data from a single-arm, open-label Phase 1/2 clinical trial (PEGINVERA) and safety profile assessed via subsequent open-label, randomized, active-controlled Phase 3 trials (PROUD-PV, CONTINUATION-PV) in addition to PEGINVERA.

- Phase 1/2 study: patients (N=51) were newly diagnosed, had exposure to HU, any risk level disease, and refractory to phlebotomy. RIFN α-2b (Besremi) led to an overall hematological response of 75% at week 10, with 26% reported as complete response (CR). Additionally, 74% patients achieved a Hct ≤ 45% at 12 months.
- Phase 3 trials: Two concurrent randomized Phase3I trials assessed RIFN-α-2b (Besremi) versus standard therapy (HU): PROUD-PV to assess non-inferiority of RIFN-α-2b (Besremi) to HU over 12 month regimen; CONTINUATION-PV: to assess CHR and improvement in disease burden at 36 months of therapy. Primary endpoint results for these trials were not statistically significant and non-inferiority to HU was not shown. However, RIFN-α-2b (Besremi) improved long-term disease response and CHR at 36 months vs. HU.

V. Prescribing information for RIFN-α-2b (Besremi) includes a black box warning for fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations.

VI. For those with high-risk PV and require cytoreductive therapy, HU is the preferred first-line therapy given the extensive history of use, established safety profile, efficacy and cost-effectiveness. Although not FDA-approved for the treatment of PV, peginterferon alfa-2a (Pegasys) has found its place as an alternative cytoreductive agent, with supportive data from multiple clinical trials and retrospective studies. Notably, a Phase 2 open-label clinical trial assessed Pegasys for induction of CR and PR in patients with high-risk PV (n=50), where in overall response rate of 60% (22% CR) was reported. Additional Phase 3 clinical trial (N=168) also assessed efficacy of Pegasys vs. hydroxyurea and reported comparable response rates.

VII. Currently available clinical data does not conclusively establish superiority of RIFN-α-2b (Besremi) over HU. Although RIFN-α-2b (Besremi) is purported to provide better acute tolerability due to longer interval between injections (14 days) versus Pegasys (7 days), efficacy and safety of RIFN-α-2b (Besremi) has not been compared with peginterferon alfa-2a (Pegasys) in a head-to-head clinical trial. At this time, real-world safety profile and patient experience with RIFN-α-2b (Besremi) remain largely unknown. Thus, preference toward bi-weekly dosing or convenience of administration does not establish medical necessity of RIFN-α-2b (Besremi) over peginterferon alfa-2a (Pegasys). Weighing the safety, efficacy, cost, and clinical experience, HU and peginterferon alfa-2a (Pegasys) are considered standard and appropriate high-value cytoreductive treatment options for the treatment of PV.

Investigational or Not Medically Necessary Uses

I. RIFN-α-2b (Besremi) has not been FDA-approved, or sufficiently studied for the treatment of any other condition, including other myeloproliferative neoplasms (e.g., essential thrombocythemia, myelofibrosis, acute myeloid leukemia (AML)).

References

1. Gisslinger H, Zagrijtschuk O et al. Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera. Blood. 2015 Oct 8;126(15):1762-9.
2. Gisslinger H, Klade C et al. PROUD-PV Study Group. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020 Mar;7(3):e196-e208.
3. NCCN clinical practice guideline in oncology: myeloproliferative neoplasms; V2.2021; updated 08/18/2021.
4. Ropeginterferon alfa-2b-njft (Besremi). Prescribing Information. 11/ 2021. PharmaEssentia USA Corp., Burlington MA.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
peginterferon alfa-2a (Pegasys)	Polycythemia vera
	Essential thrombocythemia
	Chronic hepatitis B
	Chronic hepatitis D

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022