New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Besremi® (ropeginterferon alfa-2b-njft) [PharmaEssentia]**
Dosage Formulations:	500 mcg/mL prefilled syringe
FDA Approval Date: **FDB File Date:**	FDA: November 12, 2021 FDB: November 29, 2021
Indication:	Treatment of adults with polycythemia vera
	Interferon alfa-2b belongs to the class of type 1 interferons, which exhibit their cellular effect 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:	Patients not already on hydroxyurea: • Starting dose: 100 mcg by subcutaneous injection every two weeks • Increase 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: • Starting dose: 50 mcg by subcutaneous injection every two weeks in combination with hydroxyurea • Gradually taper off hydroxyurea by reducing the total biweekly dose by 20-40% every two weeks during weeks 3-12 • Increase Besremi dose by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized. (see above) • Discontinue hydroxyurea by week 13. Maintain the two-week dosing interval of Besremi at which hematological stability is achieved for at least 1 year. After achievement of hematological stability for at least 1 year on a stable dose, the dosing interval may be expanded to every 4 weeks. Monitor patients closely, especially during the titration phase. Perform complete blood counts (CBC) regularly, every two weeks during the titration phase and every 3 to 6 months during the maintenance phase (after the patient's optimal dose is established). Phlebotomy as rescue treatment to normalize blood hyperviscosity may be necessary during the titration phase.
Disease State Clinical Highlights:	• Polycythemia vera (PV) is the most common of the chronic myeloproliferative neoplasms (MPNs), a group of hematopoietic stem cell-derived disorders that are characterized by clonal proliferation of myeloid cells. PV differs from the other MPNs by the presence of an elevated red blood cell mass (erythrocytosis). Serious complications of PV include increased risk of blood clots and disease transformation into myelofibrosis or acute myeloid leukemia (AML). • The causes of PV are still unknown and currently being studied, however it is believed to be due to impairments in the Janus kinase 2 (*JAK2*) or tet methylcytosine dioxygenase 2 (*TET2*) genes. At least 90% of PV patients have a pathogenic variant in the *JAK2* gene.

	• PV may occur in any patient population, or age group including early adulthood as well as occasionally in children and adolescents. The median age at diagnosis is approximately 60 years. Prevalence is estimated at 44 to 57 per 100,000 people in the United States, and around 6,200 people are diagnosed with PV per year.
	• Elevated hemoglobin or hematocrit is often discovered on a routine CBC leading to diagnosis of PV. Erythrocytosis, thrombocytosis (elevated platelets), leukocytosis (elevated white blood cells), elevated leukocyte alkaline phosphatase, and low erythropoietin levels are common laboratory findings in patients with PV.
	• Physical findings include hypertension, headache, dizziness, visual disturbances, angina pectoris, gastrointestinal symptoms, splenomegaly, hepatomegaly, pruritus, erythromelalgia (burning sensation in the feet or hands), thrombosis, and hemorrhage. Pruritis occurs is roughly 68% of PV patients and is especially troublesome following a warm bath or shower. Pruritic symptoms are described as “unbearable” in 15% of patients who experience them. Erythromelalgia is associated with elevated platelet counts and responds dramatically to aspirin therapy. Arterial thrombotic complications have been reported in 16% of PV patients, while venous thrombosis has been reported in 7% of patients.
	• Diagnosis is based on the 2017 World Health Organization (WHO) criteria, which requires the presence of either all three major criteria or the first two major criteria and the minor criterion:
	  ○ Major WHO criteria:
	  ▪ Hemoglobin >16.5 g/dL in men and > 16 g/dL in women, or hematocrit > 49% in men and > 48% in women, or red cell mass > 25% above mean normal predicted value
	  ▪ 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)
	  ▪ Presence of *JAK2V617F* or *JAK2* exon 12 mutation.
	  ○ Minor WHO criterion:
	  ▪ Serum erythropoietin level below the reference range for normal

Drug Clinical Highlights:	• Besremi belongs to the class of type I interferons, which exhibit their cellular effects in PV in the bone marrow. After binding to the IFNAR receptors, Besremi initiates a downstream signaling cascade that reduces blood cell production.
	• Besremi is the first FDA-approved agent for PV that patients can utilize regardless of treatment history.
	
	<u>Contraindications</u>
	• 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
	
	<u>Warning/Precautions</u>
	• Depression and suicide
	  ○ Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including Besremi. Serious neuropsychiatric reactions have been observed in 3% of patients treated with Besremi during the clinical development program.
	  ○ Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation if such symptoms emerge.
	• Endocrine toxicity

- Endocrine toxicity has occurred in patients receiving interferon alfa product, including Besremi. This may include worsening hypothyroidism and hyperthyroidism. Eight cases of hyperthyroidism (4.5%), seven cases of hypothyroidism (3.9%), and five cases (2.8%) of autoimmune thyroiditis/thyroiditis occurred in the development program of Besremi.
  - Do not use Besremi in patients with active serious or untreated endocrine disorders associated with autoimmune disease. Evaluate thyroid function in patients who develop symptoms suggestive of thyroid disease during Besremi therapy.
- Cardiovascular toxicity
  - Cardiovascular toxicity has occurred in patients receiving interferon alfa products, including Besremi. Toxicities include cardiomyopathy, myocardial infarction, atrial fibrillation, and coronary artery ischemia.
  - Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during Besremi therapy. Avoid use in patients with severe or unstable cardiovascular disease, recent stroke, or myocardial infarction.
- Decreased peripheral blood counts
  - Decreased peripheral blood counts have occurred in patients receiving interferon alfa products, including Besremi. These include thrombocytopenia, anemia, and leukopenia. Infections occurred in 48% of Besremi-treated patients, while serious infections occurred in 8% of patients.
  - Monitor complete blood counts at baseline, during titration, and every 3 to 6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.
- Hypersensitivity Reactions
- Pancreatitis
  - Pancreatitis was reported in 2.2% of patients receiving Besremi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever.
  - Interrupt Besremi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of Besremi in patients with confirmed pancreatitis.
- Colitis
  - Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products. Symptoms may include abdominal pain, bloody diarrhea, and fever.
  - Discontinue Besremi in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.
- Pulmonary Toxicity
  - Pulmonary toxicity has occurred in patients receiving interferon alfa products, including Besremi. Some events have resulted in respiratory failure or death. Discontinue Besremi in patients who develop pulmonary infiltrates or pulmonary function impairment.
- Ophthalmologic toxicity
  - During Besremi therapy, 23% of patients were identified with an eye disorder. Eye disorders occurring in ≥ 5% included cataract (6%) and dry eye (5%).
  - Advise patients to have eye examinations before and during Besremi therapy, specifically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension.
- Hyperlipidemia
  - Hyperlipidemia, hypertriglyceridemia, or dyslipidemia occurred in 3% of patients receiving Besremi. Elevated triglycerides may result in pancreatitis.
  - Monitor serum triglycerides before Besremi treatment and intermittently during therapy and manage when elevated.
- Hepatotoxicity
  - Increases in serum ALT ≥ 3 times the upper limit of normal (ULN), AST ≥ 3 times the ULN, GGT ≥ 3 times the ULN, and bilirubin > 2 times the ULN have been

observed in patients treated with Besremi. In the clinical development program, 36 patients (20%) experienced liver enzyme elevations.
    - Monitor liver enzymes and hepatic function at baseline and during Besremi treatment. Dose reduction is warranted for patients experiencing elevated liver enzymes. Discontinue Besremi in patients who develop evidence of hepatic decompensation during treatment.
- Renal toxicity
    - During Besremi therapy, < 1% of patients were reported to develop renal impairment and < 1% of patients were reported to have toxic nephropathy.
    - Monitor serum creatinine at baseline and during therapy. Avoid use of Besremi in patients with eGFR < 30 mL/min. Discontinue if severe renal impairment develops during treatment.
- Dental and periodontal toxicity
    - Dental and periodontal toxicities may occur in patients receiving interferon alfa products, including Besremi. Toxicities may include dental and periodontal disorders, which may lead to loss of teeth.
- Dermatologic toxicity
    - Dermatologic toxicity has occurred in patients receiving interferon alfa products, including Besremi. Consider discontinuation of Besremi if clinically significant dermatologic toxicity occurs.
- Driving and operating machinery
    - Besremi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how Besremi affects their abilities. Patients who experience dizziness, somnolence, or hallucination during Besremi therapy should avoid driving or using machinery.
- Embryo-fetal toxicity
    - Based on the mechanism of action, Besremi can cause fetal harm when administered to pregnant women.
    - Pregnancy testing is recommended in females of reproductive potential, and contraception is recommended for females of reproductive potential. Contraception is to be continued for 8 weeks after final Besremi dose.

<u>Clinical Studies</u>

- PEGINVERA (N = 51) (NCT01193699): prospective, multicenter, single-arm trial lasting 7.5 years.
    - Key Inclusion Criteria:
        - Patients aged ≥ 18 years
        - Confirmed diagnosis of PV, including newly diagnosed, pre-treated, and those currently being treated with hydroxyurea who had trouble controlling hematocrit with phlebotomies or because of other symptoms were declared eligible
        - Eastern Cooperative Oncology Group performance status ≤ 2
        - Females of childbearing potential: must have negative urine pregnancy test and employ adequate birth control for the duration of the study
    - Key Exclusion Criteria:
        - Diagnosis of any other myeloproliferative disorder
        - Systemic infections (e.g., hepatitis B, hepatitis C, HIV)
        - Uncontrolled hypertension
        - Previous treatment with interferon for PV
        - Concurrent treatment with cytoreductive agents other than hydroxyurea
        - History of cancer
        - History of psychiatric disorders
        - Organ transplant, past or planned
        - Liver dysfunction
        - History of renal disease
        - Pregnant or lactating females

        - Acute or chronic infections or autoimmune diseases
    - Key Baseline Characteristics:
        - Mean age at baseline was 56 years (range 35-82 years)
        - All patients had the *JAK2V617F* pathogenic variant
        - 33% of patients were undergoing treatment with hydroxyurea
        - At baseline, the mean ± SD for:
            - Hematocrit: 45% ± 4.0%
            - Platelets: 457 x 10^9/L ± 187 x 10^9/L
            - Leukocytes: 11.8 x 10^9/L ± 5.2 x 10^9/L
        - Median spleen size was 13.2 cm, with 16 (31%) patients having splenomegaly
    - Primary outcome measure was complete hematological response (CHR) defined as:
        - Hematocrit < 45% and no phlebotomy in the preceding 2 months
        - Platelets ≤ 400 x 10^9/L
        - Leukocytes ≤ 10 x 10^9/L
        - Normal spleen size (longitudinal diameter ≤ 12 cm for females and ≤ 13 cm for males) assessed by ultrasound
        - Absence of thromboembolic events

Study Parameter	Results (N=51) n (%)
CHR	61% (31/51) (95% CI: 46, 74)
Median duration of response	14.3 months (95% CI: 5.5, 30.1)
Median time to response among patients achieving CHR	7.8 months
Hematological response based only on hematocrit, platelets, and leukocytes	80% (41/51) (95% CI: 67, 90)

    - Adverse reactions occurring in ≥ 20% of participants: influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, musculoskeletal pain, headache, diarrhea, hyperhidrosis, nausea, upper respiratory tract infection, local administration site reactions, dizziness, abdominal pain, depression, and sleep disorder.
    - Adverse reactions occurring in ≥ 10% of participants: leukopenia, decreased appetite, alopecia, edema, hypertension, muscle spasms, neutropenia, rash, transaminase elevations, urinary tract infections, thrombocytopenia, and vertigo.
    - Psychiatric adverse reactions occurred in 16 patients (31%) and treatment was permanently discontinued because of psychiatric symptoms in 2 patients.
    - Serious adverse reactions were reported in 16% of patients. The most common serious adverse reactions observed included urinary tract infection, transient ischemic attack, and depression.

- PROUD-PV/CONTINUATION-PV (N = 306) (NCT01949805, NCT02218047): randomized, phase 3, controlled, open-label trials conducted in 48 clinics in Europe. CONTINUATION-PV is an extension study of PROUD-PV and is still ongoing. Patients were randomized to receive Besremi (N = 127) subcutaneously every 2 weeks starting at 50 mcg or hydroxyurea (N = 124) orally starting at 500 mg/day.
    - Key Inclusion Criteria:
        - Participant aged ≥ 18 years
        - Diagnosis of PV with mandatory presence of *JAK2V617F* pathogenic variant
        - For patients currently treated with hydroxyurea
            - Non-responsive to therapy (as defined by the response criteria for primary endpoint)
            - Total hydroxyurea treatment duration less than 3 years
    - Key Exclusion Criteria:
        - Documented autoimmune disease at screening
        - Pulmonary infiltrates or pneumonia

- Systemic infections
- History or presence of depression requiring treatment

- Primary outcome measure:
  - PROUD-PV: noninferiority of Besremi to hydroxyurea 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 improved disease burden (IDB), defined by improvement in splenomegaly, microvascular disturbances, pruritus, and headache.
- Results:
  - PROUD-PV: 21% of patients in the Besremi arm and 28% of patients in the hydroxyurea arm met the primary endpoint. Besremi did not meet noninferiority to hydroxyurea at 12 months.
  - CONTINUATION-PV: CHR with IDB was met in 53% of patients in the Besremi arm compared to 38% of patients in the hydroxyurea arm at 36 months, p=0.044 (interim analysis, study still ongoing).

Price Per Unit (WAC):

- $6,988.00 per syringe
- $181,688.00 per year (dosed every two weeks)

Therapeutic Alternatives:

- The goals of therapy in the treatment of PV are to reduce the risk of thrombotic events, prevent bleeding events, ameliorate symptom burden, and minimize risk of evolution to myelofibrosis and AML.
- Treatment is guided by a risk-stratification approach that is based on age and history of thrombosis. Patients aged ≤ 60 years with no history of thrombosis are considered low risk, while patients > 60 years of age or those with history of thrombosis are considered high risk.
- Aspirin has been shown to be very effective in treating the refractory symptoms of PV including pruritis and erythromelalgia but should be stopped in patients experiencing bleeding.
- Phlebotomy is the initial treatment for low-risk PV patients, and is used to keep hematocrit < 45%. One standard unit phlebotomy (500 mL) should reduce hematocrit by roughly 3%.
- The National Comprehensive Cancer Network (NCCN) released updated guidelines regarding the treatment of myeloproliferative neoplasms in August 2021. For patients considered to be low-risk, treatment involves low-dose aspirin therapy and phlebotomy (to maintain hematocrit < 45%). For high-risk patients, preferred cytoreductive therapy includes hydroxyurea or peginterferon alfa-2a.

Drug	Dose	Cost per year*	Notes
Hydroxyurea	1000 – 2000 mg daily	$1,722.80	• First line agent for high-risk patients. • Cost-effective, low toxicity. • Lowers platelet count and reduces risk of thrombosis. • Shown to reduce thrombotic events compared to phlebotomy alone. • Cannot be used in pregnancy. • Approximately 10% of patients develop resistance.
Pegasys® (peginterferon alfa-2a)	Initial: 45 mcg once weekly Max: 180 mcg once weekly	$53,117.48	• First line agent for high-risk patients. • Not FDA-approved for PV, but often used in patients younger than 40 and those who may become pregnant. • Shown to provide better control of splenomegaly, thrombocytosis, pruritus, and thrombolytic/hemorrhagic

			complications compared to phlebotomy and phlebotomy plus hydroxyurea. • Has resulted in 77-95% CHR rates in studies of patients with PV. • Not as well tolerated as hydroxyurea, approximately 35% of patients discontinue therapy due to side effects.
Jakafi® (ruxolitinib)	Initial: 10 mg BID Max: 25 mg BID	$183,996.50	• Considered second or third line treatment in high-risk patients. • JAK inhibitor, approved to use in patients that are hydroxyurea-resistant or hydroxyurea-intolerant. • Usually reserved for patients with splenomegaly that do not respond to treatment with hydroxyurea, interferon, or busulfan.

*cost based on WAC price at highest recommended dose, BID = twice daily

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Approval:

- Diagnosis of polycythemia vera (D45) **AND**
- Prescribed by or in consultation with a hematologist, oncologist, or other specialist in the treated disease state **AND**
- Participant aged ≥ 18 years **AND**
- Participant lacks lifetime history of severe psychiatric disorders **AND**
- Participant lacks lifetime history of moderate to severe hepatic impairment (Child-Pugh B and C) **AND**
- Participant lacks history of Chronic Kidney Disease (CKD) Stage 4 or 5 or End-Stage Renal Disease (N18.4, N18.5, N18.6) **AND**
- Participant considered high-risk based on
  - Age > 60 years **OR**
  - Age ≤ 60 years and thrombosis history **AND**
- Patient must have resistance or intolerance to hydroxyurea defined by:
  - Need for phlebotomy to keep hematocrit < 45% after 3 months on 2 g/day of hydroxyurea **OR**
  - Platelet count >400 x 10^9/L and white blood cell count >10 x 10^9/L or hemoglobin <10 g/dL **OR**
  - Reduction of splenomegaly < 50% after 2 g/day of hydroxyurea **OR**
  - Absolute neutrophil count <1.0 x 10^9/L or platelet count <100 x 10^9/L or hemoglobin <10 g/dL **OR**
  - Presence of hydroxyurea side effects at any dose of hydroxyurea **AND**
  - Participant history demonstrates therapeutic trial of peginterferon alfa-2a (defined as 84/112 days) or documented ADE/ADR to peginterferon alfa-2a
- Initial approval period: 6 months

Continuation of therapy:

- Participant demonstrates compliance to prescribed therapeutic regimen (defined as 84/112 days)

Additional Provider Diagnostic/Monitoring criteria, if desired:

	• Monitor CBC regularly, every two weeks during the titration phase and every 3 to 6 months during the maintenance phase. Monitor patient for signs and symptoms of infection or bleeding. • Participant is not currently receiving immunosuppressive therapy for organ transplant • Monitor for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. • Monitor thyroid function in patients who develop symptoms suggestive of thyroid disease. • Monitor serum triglycerides before Besremi treatment and intermittently during therapy. • Monitor liver enzymes and hepatic function at baseline and during Besremi therapy. • Monitor serum creatinine at baseline and during Besremi therapy. • Participant should lack history or presence of active serious or untreated autoimmune disease • Participant should have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 • Participant (female of appropriate age) is utilizing a concurrent birth control method

Implication to State Medicaid Program:	• LOE: TBD
	• Besremi is currently being studied in the following disease states:
	  ○ Patients with chronic myeloid leukemia (CML) treated with bosutinib from time of diagnosis (Phase III).
	  ○ Essential thrombocythemia in patients resistant or intolerant to hydroxyurea (Phase III).
	  ○ Myelofibrosis (recruiting).
	  ○ Interferon-naïve patients with hepatitis C virus (genotype 2) infection (Phase III) and hepatitis B infection (recruiting).

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