

Dosing and Titration Guide for BESREMi



INDICATION

BESREMi is indicated for the treatment of adults with polycythemia vera

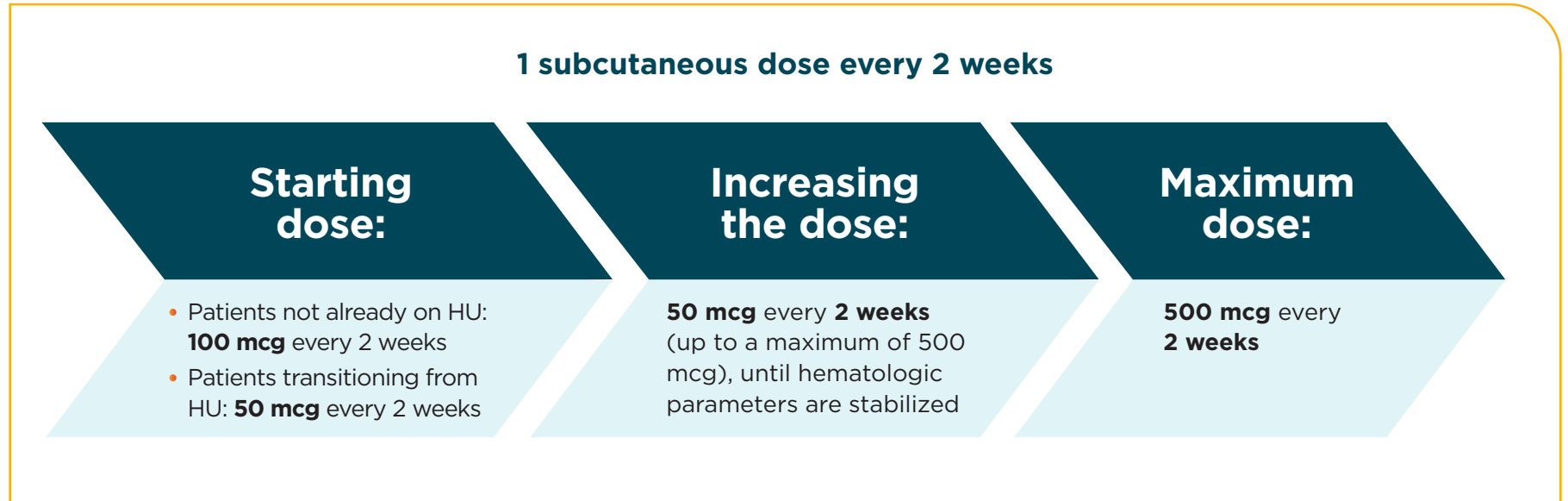
IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DISORDERS

Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

BESREMi: An innovative monopegylated interferon that provides long-term chronic dosing¹



HU, hydroxyurea.

Hematologic stability defined



Hematocrit <45%



Leukocytes <10 x 10⁹/L



Platelets <400 x 10⁹/L

IMPORTANT SAFETY INFORMATION (continued)

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.

Dose titration¹

Patients not already on HU

Increase the dose by 50 mcg every 2 weeks (up to a maximum of 500 mcg), until hematologic parameters are stabilized.

Patients transitioning from HU

Gradually taper off HU by reducing the total biweekly dose by 20% to 40% every 2 weeks during Weeks 3-12.

Increase the dose of BESREMi by 50 mcg every 2 weeks (up to a maximum of 500 mcg), until hematologic parameters are stabilized.

Discontinue HU by Week 13.

Maintain the 2-week dosing interval of BESREMi at which hematologic stability is achieved for at least 1 year. After that time, the dosing interval may be expanded to 1 dose every 4 weeks.¹

- All eligible patients in the PEGINVERA study (n=28) switched to 1 dose every 4 weeks as early as 1 year after starting BESREMi
- The mean dose of BESREMi was 237 mcg (\pm 110) during the treatment period

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS (continued)

- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

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Dose modifications¹

- Monitor complete blood counts (CBC) every 2 weeks during the titration phase and dose modification phase, and every 3-6 months during the maintenance phase (after the patient's optimal dose is established). Monitor CBC more frequently if clinically indicated
- Phlebotomy as rescue treatment to normalize blood hyperviscosity may be necessary
- If dose interruption occurs, resume dosing at previously attained levels
- If drug-related toxicities arise, reduce the dose to the next lower level or interrupt in accordance with the adjacent table
- If there is insufficient efficacy at the decreased dose following dose modification, a dose increase attempt to the next higher dose level should be considered after recovery to grade 1 toxicity

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

- Depression and Suicide: Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa-2b products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness. Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.

ADVERSE REACTION ^{1*}	SEVERITY	DOSAGE MODIFICATION
Liver enzyme elevation with concomitant bilirubin elevation, or other evidence of hepatic decompensation	Any increase above baseline	Interrupt treatment until recovery, restart at dose 50 mcg lower than the interrupted dose. If the interrupted dose is 50 mcg, refrain from treatment until recovery. Consider permanent discontinuation if toxicity persists after four dose-modifications.
	<p>Liver enzyme elevation</p> <p>>5 x the upper limit of normal (ULN) but \geq20 x ULN</p> <p>>20 x ULN</p>	<p>Decrease dose by 50 mcg; if toxicity does not improve, continue decreasing at biweekly intervals until alanine aminotransferase (ALT) and aspartate aminotransferase (AST) recover <3 x ULN if baseline was normal; 3 x baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to <2.5 x ULN if baseline was normal; 2.5 x baseline if baseline was abnormal. If the interrupted dose is 50 mcg, refrain from treatment until recovery.</p> <p>Interrupt treatment until ALT and AST recover to <3 x ULN if baseline was normal; 1.5 x baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to <2.5 x ULN if baseline was normal; 2 x baseline if baseline was abnormal. Consider permanent discontinuation if toxicity persists after four dose-modifications.</p>
Cytopenia	<p>Anemia: hemoglobin (Hgb) <8 g/dL</p> <p>Thrombocytopenia: platelet count <50,000/mm³ but \geq25,000/mm³</p> <p>Leukopenia: white blood cell count (WBC) <2,000/mm³ but \geq1,000/mm³</p>	Decrease dose by 50 mcg; if toxicity does not improve, continue decreasing at biweekly intervals until recovery of Hgb >10.0 g/dL, platelets >75,000/mm ³ , and WBC >3,000/mm ³ . If the interrupted dose is 50 mcg, refrain from treatment until recovery.
	<p>Anemia: hemoglobin levels are life threatening, or urgent intervention needed</p> <p>Thrombocytopenia: platelet count <25,000/mm³</p> <p>Leukopenia: WBC <1,000/mm³</p>	Interrupt treatment until recovery of Hgb >10.0 g/dL, platelets >75,000/mm ³ , and WBC >3,000/mm ³ . Consider permanent discontinuation if toxicity persists after four dose-modifications.
Depression	Mild, without suicidal ideation	Consider psychiatric consultation if persistent (>8 weeks).
	Moderate, without suicidal ideation	Consider dose reduction and psychiatric consultation.
	Severe, or any severity with suicidal ideation	Discontinue therapy, recommend psychiatric consultation.

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.



Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

Comprehensive training to help your patients successfully inject BESREMi



PharmaEssentia SOURCE™ Nurse Case Managers

- When patients enroll in PharmaEssentia SOURCE, Nurse Case Managers are available to walk them through the injection process step by step

To learn more, call **800-700-5053**
between 8:00 AM and 8:00 PM ET,
Monday through Friday, or visit
PharmaEssentiaSOURCE.com



In your office

- The BESREMi Demonstration Kit helps ensure that healthcare providers will be prepared to train patients how to self-inject with the single-dose BESREMi prefilled syringe
 - Speak with your PharmaEssentia representative to learn more



Specialty pharmacy

- Patients can also receive injection training through our specialty pharmacy partners—including Biologics, US Bioservices, or Onco360—upon initial fulfillment of their BESREMi prescription

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- Endocrine Toxicity: These toxicities may include worsening hypothyroidism and hyperthyroidism. 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. Discontinue BESREMi in patients who develop endocrine disorders that cannot be adequately managed during treatment with BESREMi.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Cardiovascular Toxicity:** Toxicities may 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 of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (\geq NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.
- **Decreased Peripheral Blood Counts:** These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). Monitor complete blood counts at baseline, during titration and every 3-6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.
- **Hypersensitivity Reactions:** Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.
- **Pancreatitis:** Pancreatitis has occurred in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. 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, some cases starting as early as 12 weeks after start of treatment. 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 may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.

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IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

- **Ophthalmologic Toxicity:** These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eyes disorders \geq 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. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.
- **Hyperlipidemia:** Elevated triglycerides may result in pancreatitis. Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.
- **Hepatotoxicity:** These toxicities may include increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and bilirubin. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy. Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment
- **Renal Toxicity:** Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR $<$ 30 mL/min. Discontinue BESREMi if severe renal impairment develops during treatment.
- **Dental and Periodontal Toxicity:** These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.
- **Dermatologic Toxicity:** These toxicities have included skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, and hyperhidrosis. 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 a pregnant woman. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reactions reported in > 40% of patients in the PEGINVERA study (n=51) were influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain. In the pooled safety population (n=178), the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

DRUG INTERACTIONS

Patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs. Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. Avoid use with narcotics, hypnotics or sedatives and monitor patients receiving the combination for effects of excessive CNS toxicity.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy. Advise pregnant women of the potential risk to a fetus.

- **Lactation:** There are no data on the presence of BESREMi in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from BESREMi, advise women not to breastfeed during treatment and for 8 weeks after the final dose.
- **Females of Reproductive Potential:** BESREMi may cause embryo-fetal harm when administered to a pregnant woman. Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential. Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Geriatric Use:** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.



Get your patients started on BESREMi

An innovative monopegylated interferon with PK properties that allow dosing once every 2 weeks¹

- After hematologic stability is achieved for at least 1 year, the dosing interval may be expanded to 1 dose every 4 weeks

PharmaEssentia SOURCE™ can guide your patients through the access and reimbursement process and offer personalized support throughout their BESREMi treatment

- Learn more at PharmaEssentiaSOURCE.com

PK, pharmacokinetic.

INDICATION

BESREMi is indicated for the treatment of adults with polycythemia vera



Discover more at BESREMiHCP.com

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Reference: 1. Besremi. Package insert. PharmaEssentia Corporation; 2021.

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