

BESREMI[®] for durable disease control in polycythemia vera.

Dosing and dose modification guide for healthcare practitioners.

- Across the pivotal PROUD-PV study and its long-term CONTINUATION-PV extension, the complete hematological response (CHR) rate among BESREMI[®]-treated patients was 84.3%**

BESREMI[®] (ropeginterferon alfa-2b) is indicated for the treatment of adults with polycythemia vera. Please see the BESREMI[®] Product Monograph for full safety information including boxed warning, complete dosing and administration information.

BESREMI[®] (ropeginterferon alfa-2b) 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. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many cases, but not all cases, these disorders resolve after stopping interferon therapy.

* CHR defined as hematocrit <45% without phlebotomy (≥ 3 months since last phlebotomy), platelets $<400 \times 10^9/L$, and leukocytes $<10 \times 10^9/L$.

† CHR rate 84.3% (107/127; 95% CI: 76.7–90.1). CHR rates were calculated as the number of responders observed over the entire follow-up period divided by the total cohort. Best individual response defined as response achieved for at least one assessment visit over the 12-month treatment duration of PROUD-PV and 24-month treatment duration of the CONTINUATION-PV extension study. Patients lost to follow-up imputed as non-responders (if patient had not responded prior to discontinuation).

Getting patients started on BESREMI[®]

Designed for self-administration



- BESREMI[®] (ropeginterferon alfa-2b) is supplied as a single-use, pre-filled syringe.
- BESREMI[®] can be self-administered and is a subcutaneous injection with individualized dosing based on patient response and tolerability.
- Treatment consists of a titration phase followed by maintenance dosing.

BESREMI[®] offers the potential for reduced dosing frequency



Starting dose	Increasing the dose	Maintenance	Reducing frequency
 Every 2 weeks Hydroxyurea naïve patients: 100 mcg Patients transitioning from hydroxyurea: 50 mcg	 Every 2 weeks Increase the dose by 50 mcg (up to a max of 500 mcg)	 Every 2 weeks Maintain the dose at which hematological stability is achieved.	 Once a month After 1 year of stable dose and hematological parameters, the dosing interval may be expanded to every 4 weeks.

Stabilized hematological parameters are defined as:



Hematocrit
<45%



Leukocytes
<10 x 10⁹/L



Platelets
<400 x 10⁹/L

BESREMI[®] dosing overview

Titration phase

For patients not already on hydroxyurea	For patients transitioning from hydroxyurea
• Start at 100 mcg by subcutaneous injection every 2 weeks and increase the dose by 50 mcg every 2 weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematocrit less than 45%, leukocytes less than $10 \times 10^9/L$, and platelets less than $400 \times 10^9/L$).	• 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%, leukocytes less than $10 \times 10^9/L$, and platelets less than $400 \times 10^9/L$). • Discontinue hydroxyurea by Week 13.

- Phlebotomy as rescue treatment to normalize blood hyperviscosity may be necessary during the titration or modification phase.

Maintenance

- Once hematological parameters are stabilized, the dose at which hematological stability* is achieved should be maintained at a two-week administration interval for at least 1 year.

Reducing the dosing interval

- After achievement of hematological stability* for at least 1 year on a stable dose of BESREMI[®], the dosing interval may be expanded to every 4 weeks.

Dosing considerations

- BESREMI[®] is not recommended for use during pregnancy.
 - Pregnancy testing prior to treatment is recommended for women of childbearing potential.
 - Women of childbearing potential have to use effective contraception during the treatment with BESREMI[®], unless otherwise discussed with the physician.
- Treatment should be initiated under the supervision of a Health Care Provider experienced in the management of polycythemia vera.

* Hematological stability is defined as hematocrit less than 45%, leukocytes less than $10 \times 10^9/L$, and platelets less than $400 \times 10^9/L$.

Monitoring and managing BESREMI®

Dose modifications

Modifications in case of adverse reactions

- If adverse events develop during therapy, the administered dose should be reduced or treatment discontinued temporarily until adverse events abate.
- If treatment is re-initiated after experiencing drug-related toxicity, the dose should be reduced to the next lower level.
- If an increase of hematological parameters (hematocrit, platelets, and/or leukocytes) is observed, the dose and/or dosing interval needs to be adapted individually.



Adverse reaction	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.
Liver enzyme elevation	>5 x the upper limit of normal (ULN) but ≤20 x ULN	• 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 ULN baseline if baseline was abnormal, and gamma-glutamyl-transferase (GGT) recovers to <2.5 x ULN if baseline was normal; 2.5 x ULN baseline if baseline was abnormal. • If the interrupted dose is 50 mcg, refrain from treatment until recovery.

Adverse reaction	Severity	Dosage modification
Liver enzyme elevation	>20 x ULN	- Interrupt treatment until ALT and AST recover to <3 x ULN if baseline was normal; 1.5 x ULN baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to <2.5 x ULN if baseline was normal; 2 x ULN baseline if baseline was abnormal. - Consider permanent discontinuation if toxicity persists after four dose-modifications
Cytopenia	Anemia: Hemoglobin (Hgb) <8 g/dL Thrombocytopenia: platelet count <50,000/mm ³ but ≥25,000/mm ³ Leukopenia: white blood cell count (WBC) <2000/mm ³ but ≥1,000/mm ³	- 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/mm³, and WBC >3,000/mm³ - If the interrupted dose is 50 mcg, refrain from treatment until recovery.
	Anemia: Hemoglobin levels are life threatening, or urgent intervention needed Thrombocytopenia: platelet count <25,000/mm ³ Leukopenia: WBC <1000/mm ³	- Interrupt treatment until recovery of Hgb >10.0 g/dL, platelets >75,000/mm³, and WBC >3,000/mm³. - 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.

Dose adjustments for special populations

Renal impairment

- No adjustment if eGFR ≥ 30 mL/min
- Avoid use if eGFR < 30 mL/min

Hepatic impairment

- Monitor liver enzymes and hepatic function during treatment.
- No BESREMI[®] dose adjustment is required for adult patients with mild liver impairment.
- BESREMI[®] is contraindicated in patients with decompensated cirrhosis, including Child-Pugh B or C.
- Discontinue BESREMI[®] if hepatic decompensation develops during treatment.
- Increased liver enzyme levels have been observed with BESREMI[®].
- Reduce the dose if liver enzyme increases are progressive and persistent.
- Discontinue BESREMI[®] if liver enzyme increases remain progressive and clinically significant despite dose reduction.

Geriatrics

- No starting dose adjustment is required for elderly patients.

Pediatrics

- Safety and efficacy not established.

Guidance for missed doses and overdose



Missed dose

- If a dose is missed, it should be administered as soon as possible within 2 days after the missed dose.
- If more than 2 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day.



Overdose

- During the clinical study program, one accidental case of overdose has been reported with BESREMI[®].
- The patient received a 10-times higher starting dose than recommended and developed flu-like symptoms for three days which were rated as non-serious.
- The patient recovered completely after temporary discontinuation of BESREMI[®] therapy and acetaminophen administration.
- For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

Monitoring and laboratory tests



- Patients should be closely monitored, in particular, during the titration phase and during dose modification; perform complete blood counts (CBC) regularly, every 2 weeks during the titration and modification phases 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 during the titration or modification phase.



- Liver enzymes and hepatic function should be regularly monitored in patients with long-term BESREMI[®] therapy.



- Patients with pre-existing or a history of cardiovascular disorders should be closely monitored during BESREMI[®] therapy.



- Patients should be closely monitored for any symptoms of psychiatric disorders and therapeutic management should be considered by the treating physician if such symptoms emerge.



- Regardless of the starting dose or degree of renal impairment, patients should be monitored. Discontinue BESREMI[®] if severe renal impairment develops during treatment.



- Patients who develop respiratory symptoms should be monitored closely and if necessary, BESREMI[®] therapy should be discontinued.



- Patients should brush their teeth thoroughly twice daily and have regular dental examinations.



- Patients should have eye examinations before and during BESREMI[®] therapy, specifically in those patients with retinopathy associated disease such as diabetes mellitus or hypertension.

ForYOU[™] Patient Support Program



The ForYOU[™] Patient Support Program is designed to support BESREMI[®] patients and their caregivers throughout the treatment journey.

The program offers:

Reimbursement navigation and financial support

Support eligible patients in gaining access to BESREMI[®].

Treatment support

Education by a bilingual oncology nurse for patients and their caregivers related to polycythemia vera and treatment with BESREMI[®].

Ongoing support available throughout treatment with BESREMI[®] based on individual patient and caregiver needs.

Initial injection training

Personalized BESREMI[®] injection training led by nurses to help patients build confidence and learn proper injection techniques.

Personalized solutions

Connections for patients and caregivers to third-party resources, providing practical support throughout their BESREMI[®] treatment journey.

For inquiries and more information on the ForYOU[™] Patient Support Program, please call 1-833-4YOU PSP (1-833-496-8777) between 9AM-5PM ET Monday-Friday, or email besremi@foryoupsp.com.

INDICATION

BESREMI® (ropeginterferon alfa-2b) is indicated for the treatment of adults with polycythemia vera.

SERIOUS WARNINGS AND PRECAUTIONS

BESREMI® (ropeginterferon alfa-2b) 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. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many cases, but not all cases, these disorders resolve after stopping interferon therapy.

CONTRAINDICATIONS

BESREMI® is contraindicated in patients with: present or previous severe psychiatric disorders (particularly severe depression, suicidal ideation or suicide attempt); decompensated cirrhosis (Child-Pugh B or C); history of or active serious or untreated autoimmune disease; immunosuppressed transplant recipients; pre-existing uncontrolled thyroid disease; severe pre-existing cardiovascular disease, (i.e., uncontrolled hypertension, congestive heart failure [$\geq$ NYHA class 2], serious arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction; and severe/end stage renal disease (GFR <30 mL/min).

RELEVANT WARNINGS AND PRECAUTIONS

- **Monitoring/Titration:** Efficacy in reducing cardiovascular/thromboembolic risk may not be fully established during titration. Monitor CBCs (hematocrit, leukocytes, platelets) regularly; phlebotomy may be required as rescue treatment.
- **Cardiovascular:** Associated with cardiomyopathy, MI, atrial fibrillation, and ischemic coronary artery disorders. Monitor patients with pre-existing cardiovascular history closely.
- **Dental and periodontal disorders:** Loss of teeth and dry mouth associated with long-term treatment may have a damaging effect on teeth and mucous membranes of the mouth.
- **Ability to drive or use machines:** Patients who experience dizziness, somnolence or hallucination during BESREMI® therapy should be advised to avoid driving or using machines.
- **Endocrine/Metabolic:** Treat and control pre-existing thyroid disease prior to therapy. Do not initiate in patients with poorly controlled diabetes; discontinue if diabetes develops and cannot be medically managed.
- **Hepatotoxicity:** Can cause significant liver enzyme increases and hepatic decompensation. Monitor liver function regularly; discontinue if enzyme elevations are progressive/clinically significant or if decompensation occurs.
- **Other Serious Risks:** Pancreatitis, fatal/serious ulcerative or hemorrhagic/ischemic colitis, serious acute hypersensitivity reactions, and severe eye disorders (e.g., retinopathy, retinal detachment/occlusion which may cause blindness) have occurred.
- **Skin disorders:** Skin disorders such as pruritus, alopecia, rash, erythema, psoriasis, xeroderma, hyperkeratosis, hyperhidrosis, some of which may be related to the disease; discontinue treatment if these appear or worsen.
- **CNS Effects:** Depression, suicidal ideation, suicide attempts, aggression, bipolar disorder, mania, and confusion have been observed.
- **Respiratory:** Lung infiltration, pneumonitis, pneumonia, or pulmonary arterial hypertension have been reported rarely.
- **Renal:** Monitor renal function.
- **Pregnancy & Lactation:** Not recommended during pregnancy. Verify pregnancy status before initiating in women of childbearing potential; effective contraception must be used. Consult with physician prior to breastfeeding.

DOSING AND ADMINISTRATION CONSIDERATIONS

BESREMI® is administered by subcutaneous injection every 2 weeks during titration. The recommended starting dosage of BESREMI® for patients who are not already on hydroxyurea is 100 mcg. Increase dose by 50 mcg every 2 weeks (maximum of 500 mcg) until hematological parameters are stabilized. 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 until the hematological parameters are stabilized. Discontinue hydroxyurea by Week 13. After at least 1 year of hematological stability on a steady dose of BESREMI®, the dosing interval may be expanded to every 4 weeks. Monitor CBCs, every 2 weeks during titration/modification and every 3-6 months during maintenance.

FOR MORE INFORMATION

Please consult the BESREMI® Product Monograph for complete information relating to contraindications, Serious Warnings and Precautions, other relevant warnings and precautions, adverse reactions, drug interactions, dosing and administration, and conditions of clinical use. The Product Monograph is available through Health Canada's Drug Product Database, at www.besremipm.ca, or by calling FORUS Therapeutics Inc. at 1-866-542-7500.



ropeginterferon alfa-2b injection

This image shows a full page of blank, lined paper. It features approximately 20 evenly spaced horizontal grey lines across its entire width, providing a guide for handwriting or typing. The paper itself is a clean, off-white color.



ropeginterferon alfa-2b injection

This image shows a full page of blank, lined paper. It features approximately 20 evenly spaced horizontal grey lines across its entire width, providing a template for handwriting practice or general note-taking. The margins are consistent on all sides.



REFERENCE: 1. FORUS Therapeutics Inc. BESREMI[®] (ropeginterferon alfa-2b) Product Monograph. July 2, 2026

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