HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BESREMi safely and effectively. See full prescribing information for BESREMi.

BESREMi (ropeginterferon alfa-2b-njft) injection, for subcutaneous use
Initial U.S. Approval: 2021

WARNING: RISK OF SERIOUS DISORDERS

See full prescribing information for complete boxed warning.

Risk of Serious Disorders: Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders. ***(5.1, 5.2, 5.3, 5.4)***

----------RECENT MAJOR CHANGES----------

Indications and Usage, Essential Thrombocythemia (1.1)	08/2026
Dosage and Administration (2.2, 2.3)	08/2026
Dosage and Administration (2.4)	06/2026
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.9, 5.10, 5.11)	08/2026

----------INDICATIONS AND USAGE----------

BESREMi is an interferon alfa-2b indicated for:

- The treatment of adults with essential thrombocythemia. (1.1)
- The treatment of adults with polycythemia vera. (1.2)

----------DOSAGE AND ADMINISTRATION----------

Essential thrombocythemia:

- The recommended dose of BESREMi is: a starting dose of 250 mcg by subcutaneous injection, at 2 weeks, increase the dose to 350 mcg by subcutaneous injection, at 4 weeks, increase to the maintenance dosage of 500 mcg by subcutaneous injection every 2 weeks. Maintain an every 2-week schedule throughout treatment unless dose modification is required for safety or tolerability. Consider dose re-escalation in case of prior dose reduction, recovery, and lack of hematologic response. (2.2, 2.3, 5)

Polycythemia vera:

- The recommended dose of BESREMi is: a starting dosage of 100 mcg by subcutaneous injection every 2 weeks (50 mcg if receiving hydroxyurea). Increase the dose by 50 mcg every 2 weeks (up to a maximum of 500 mcg) until hematological parameters are stabilized (2.1). Interrupt or discontinue dosing if certain adverse reactions occur. Dose re-increase to be considered in case of prior dose reduction, recovery, and lack of hematologic response. (2.2, 2.3, 5)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 500 mcg/mL solution in a single-dose prefilled syringe (3)
- Injection: 500 mcg/0.5 mL solution in a single-dose prefilled pen injector (3)

----------CONTRAINDICATIONS----------

BESREMi is contraindicated in patients with:

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt (4)
- Hypersensitivity to interferons or to any of the inactive ingredients in BESREMi (4)
- Hepatic impairment (Child-Pugh B or C) (4)
- History or presence of active serious or untreated autoimmune disease (4)
- Immunosuppressed transplant recipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Depression and Suicide: Monitor for symptoms and need for treatment. (5.1)
- Endocrine Toxicity: Discontinue if endocrine disorders occur that cannot be medically managed. (5.2)
- Cardiovascular Toxicity: Avoid use in patients with severe or unstable cardiovascular disease. Monitor patients with history of cardiovascular disorders more frequently. (5.3)
- Hematologic and Hemorrhagic Disorders: Perform blood counts at baseline, every 2 weeks during titration, and at least every 3-6 months during maintenance treatment. (5.4)
- Hypersensitivity Reactions: Stop treatment and immediately manage reaction. (5.5)
- Pancreatitis: Consider discontinuation if confirmed pancreatitis. (5.6)
- Colitis: Discontinue if signs or symptoms of colitis. (5.7)
- Pulmonary Toxicity: Discontinue if pulmonary infiltrates or pulmonary function impairment. (5.8)
- Ophthalmologic Toxicity: Monitor for ocular toxicity. Promptly evaluate eye symptoms and discontinue if new or worsening eye disorders. (5.9)
- Hyperlipidemia: Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. (5.10)
- Hepatotoxicity: Monitor liver enzymes and hepatic function at baseline and during treatment. Reduce dose or discontinue depending on severity. (5.11)
- Renal Toxicity: Monitor serum creatinine at baseline and during therapy. Discontinue if severe renal impairment develops. (5.12)
- Dental and Periodontal Toxicity: Advise on good oral hygiene and regular dental examinations. (5.13)
- Dermatologic Toxicity: Consider discontinuing if clinically significant dermatologic toxicity. (5.14)
- Driving and Operating Machinery: Advise patients to avoid driving or using machinery if they experience dizziness, somnolence, or hallucination. (5.15)
- Embryo-Fetal Toxicity: Can cause fetal harm. (5.16)

----------ADVERSE REACTIONS----------

- Essential thrombocythemia: The most common adverse reactions reported in >20% of patients were transaminase elevations, anemia, pyrexia, beta 2 microglobulin urine increased, bacterial infection, pruritus, and weight decreased. (6)
- Polycythemia vera: The most common adverse reactions reported in >40% of patients were influenza-like illness, arthralgia, fatigue, pruritus, nasopharyngitis, and musculoskeletal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact PharmaEssentia at 1-800-999-2449 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Monitor patients taking CYP450 substrates with a narrow therapeutic index for adverse reactions to inform the need for dose adjustment of the concomitant drug. (7.1)
- Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. (7.2)
- Avoid use with narcotics, hypnotics or sedatives. Monitor patients receiving the combination for excessive central nervous system toxicity. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (8.1, 8.3)
- Lactation: Breastfeeding not recommended. (8.2)
- Renal Impairment: Avoid use in patients with eGFR <30 mL/min. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

[*Sections or subsections omitted from the full prescribing information are not listed]

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS

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 *[see Warnings and Precautions (5.1, 5,2, 5.3, 5.4) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Essential Thrombocythemia

BESREMi is indicated for the treatment of adults with essential thrombocythemia.

1.2 Polycythemia Vera

BESREMi is indicated for the treatment of adults with polycythemia vera.

2 DOSAGE AND ADMINISTRATION

2.1 Pre-Treatment Testing

Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with BESREMi *[see Use in Specific Populations (8.3)]*.

2.2 Recommended Dosage

Essential Thrombocythemia:

- The recommended dose of BESREMi is:
  - A starting dose of 250 mcg by subcutaneous injection.
  - At 2 weeks, increase the dose to 350 mcg by subcutaneous injection.
  - At 4 weeks, increase to the maintenance dosage of 500 mcg by subcutaneous injection every 2 weeks.
- Maintain an every 2-week schedule throughout treatment unless dose modification is required for safety or tolerability.
- Consider dose re-escalation in case of prior dose reduction, recovery, and lack of hematologic response (platelets less than 400×10^9/L and leukocytes less than 10×10^9/L).
- Monitor complete blood counts every 2 weeks during titration and every 3 to 6 months during maintenance.

Polycythemia Vera:

Patients Not Already on Hydroxyurea

- The recommended BESREMi starting dosage for patients not on hydroxyurea is 100 mcg by subcutaneous injection every two weeks.
- Increase the dose by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematologic response: hematocrit less than 45%, platelets less than 400×10^9/L, and leukocytes less than 10×10^9/L).
- Consider dose re-escalation in case of prior dose reduction, recovery, and lack of hematologic response.

Patients Transitioning from Hydroxyurea

- 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%, platelets less than 400×10^9/L, and leukocytes less than 10×10^9/L).
- 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 of BESREMi, 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 2 weeks during the titration 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 during the titration phase *[see Clinical Pharmacology (12.2)]*.

2.3 Dose Modifications

Essential Thrombocythemia:

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 tables below (Table 1 and Table 2).

Table 1 Dose Modifications for BESREMi Adverse Reactions in Patients with Essential Thrombocythemia

Severity[1]	Recommended Dosage Modification[2]
Grade 3 or 4 toxicity (except neutropenia)	Interrupt treatment until recovery to Grade ≤1. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters).
Grade 3 or 4 neutropenia (ANC <0.5 × 10^9/L)	Interrupt treatment until ANC >0.5 × 10^9/L. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters).
Grade 2 toxicity (except neutropenia)	Reduce to the next lower dose level (see Table 2). Treatment interruption may be considered until recovery to Grade ≤1. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters).
Grade 2 neutropenia (ANC <0.75 × 10^9/L but ≥0.5 × 10^9/L)	Reduce to the next lower dose level (see Table 2). Treatment interruption is not required. Continued monitoring of the patient is advised; re-escalation to the previous dose level may be considered. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters).

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
[2] If toxicity or neutropenia occurs at the lowest recommended dose (100 mcg), withhold treatment until resolution to baseline or Grade ≤1, then resume at the same dose level at the discretion of the treating healthcare provider.

Table 2 Dose Reduction Sequence for BESREMi Adverse Reactions in Patients with Essential Thrombocythemia

Dose Level	Dosage
Maintenance dose	500 mcg every 2 weeks
First dose reduction	350 mcg every 2 weeks
Second dose reduction	250 mcg every 2 weeks
Third dose reduction	200 mcg every 2 weeks
Fourth dose reduction	150 mcg every 2 weeks
Fifth dose reduction	100 mcg every 2 weeks

Polycythemia Vera:

Monitor CBC every 2 weeks during the titration phase and dose modification phase. Phlebotomy as rescue treatment to normalize blood hyperviscosity may be necessary *[see Clinical Pharmacology (12.2)]*.

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 table below (Table 3). 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.

Table 3 Dose Modifications for BESREMi Adverse Reactions in Patients with Polycythemia Vera

Adverse Reaction[a]	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 reductions.
Liver enzyme elevation	>5 × the upper limit of normal (ULN) but ≤20 × ULN	Decrease dose by 50 mcg; if toxicity does not improve, continue decreasing by 50 mcg at biweekly intervals until alanine aminotransferase (ALT) and aspartate aminotransferase (AST) recover <3 × ULN if baseline was normal; 3 × baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to <2.5 × ULN if baseline was normal; 2.5 × baseline if baseline was abnormal. If the interrupted dose is 50 mcg, refrain from treatment until recovery.
	>20 × ULN	Interrupt treatment until ALT and AST recover to <3 × ULN if baseline was normal; 1.5 × baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to <2.5 × ULN if baseline was normal; 2 × baseline if baseline was abnormal. Continued monitoring of the patient is advised; re-escalation to the previous dose level may be considered. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters). Consider permanent discontinuation if toxicity persists after four dose reductions.
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) <2,000/mm^3 but ≥1,000/mm^3	Decrease dose by 50 mcg; if toxicity does not improve, continue decreasing by 50 mcg at bi-weekly 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. Continued monitoring of the patient is advised; re-escalation to the previous dose level may be considered. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters).

	Anemia: Hemoglobin levels are life threatening, or urgent intervention needed Thrombocytopenia: platelet count <25,000/mm^3 Leukopenia: WBC <1,000/mm^3	Interrupt treatment until recovery of Hgb >10.0 g/dL, platelets >75,000/mm^3, and WBC >3,000/mm^3. Re-escalate the dose to the previous dose level if recovered to Grade ≤1, and if patient is a non-responder (hematological parameters). Consider permanent discontinuation if toxicity persists after four dose reductions.
Depression	Mild, without suicidal ideation	Consider psychiatric consultation if persistent (>8 weeks).
	Moderate, without suicidal ideation	Consider dose reduction to 50 mcg and psychiatric consultation is recommended.
	Severe, or any severity with suicidal ideation	Discontinue therapy, recommend psychiatric consultation.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

2.4 Preparation and Administration

Read the INSTRUCTIONS FOR USE before administering the single-dose BESREMi prefilled syringe or prefilled pen injector. BESREMi is for subcutaneous injection only and may be administered by either a healthcare professional, a patient or a caregiver. Before a decision is made to allow BESREMi to be administered by a patient or caregiver, ensure that the patient is an appropriate candidate for self-administration or administration by a caregiver. Proper training on storage, preparation and administration technique should be provided. If a patient or caregiver is not an appropriate candidate for any reason, then BESREMi should be administered by a healthcare professional.

Before each injection, remove the carton that contains the BESREMi prefilled syringe or prefilled pen injector from the refrigerator. Keep the prefilled syringe or prefilled pen injector in the carton and lay it flat on a clean work surface for 15-30 minutes to allow the prefilled syringe or prefilled pen injector to reach room temperature [59˚F to 77˚F (15˚C to 25˚C)].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit (do not use if the solution in the syringe or pen injector is cloudy, discolored, contains particulate matter or if the syringe or pen injector shows any sign of damage).

Prefilled Syringe Preparation
- Remove the prefilled syringe cap by unscrewing it counterclockwise.
- Attach the covered needle to the prefilled syringe by firmly pushing it onto the collar of the syringe and then screwing (turn clockwise) it on until it feels securely attached.
- Choose one of the following injection sites: Lower stomach (abdomen) area, at least 2 inches away from the belly button, or top of thighs. Rotate (change) the injection site for each injection. Do not inject into skin that is irritated, red, bruised, infected, or scarred; clean the chosen injection site with an alcohol swab and let air dry.
- Uncap needle and move air bubbles to top. Pull the pink needle shield back and hold the syringe from the syringe body. Remove the clear needle cap by pulling it straight off. Throw away the needle cap into the trash. Hold the prefilled syringe with the needle pointing up. Tap on the body of the prefilled syringe to move any air bubbles to the top.

Set Injection Dose
- The dose markings on the prefilled syringe are in 50 mcg increments.
- Depending on the prescribed dose, the amount of dose in the syringe may need to be adjusted by discarding some of the medication.
- Hold the prefilled syringe at eye level with the needle pointing straight up over a paper towel, sink, or trash can. Check that you can see the dose lines and number markings on the prefilled syringe.
- Pinch the end of the plunger and slowly push up to remove liquid medicine until the top edge of the gray stopper lines up with the marking for the prescribed dose.

Inject BESREMi
- Pinch the chosen injection site. While pinching the skin, insert needle at a 45- to 90-degree angle into the pinched skin, then release the pinched skin.
- Inject BESREMi by slowly pressing on the plunger all the way until it stops. After all the liquid medicine is injected, remove the needle from the skin.

Dispose of Used Prefilled Syringe
- Carefully push the pink needle shield over the needle until it snaps into place and covers the needle. Do not recap the needle using the needle cap; only use the pink needle shield to cover the needle.
- Throw away the used prefilled syringe with the needle still attached, into an FDA-cleared sharps disposal container.

Prefilled Pen Injector Preparation
- The prefilled pen injector delivers BESREMi in 50 mcg increments.
- Remove the prefilled pen injector cap by pulling it straight off.
- Choose one of the following injection sites: Lower stomach (abdomen) area, at least 2 inches away from the belly button, or top of thighs. Rotate (change) the injection site for each injection. Do not inject into skin that is irritated, red, bruised, infected, or scarred; clean the chosen injection site with an alcohol swab and let air dry.
- Clean the rubber stopper on the tip of the prefilled pen injector with an alcohol swab. Peel off the protective seal from the needle. Attach the capped needle by pushing it straight onto the prefilled pen injector until you feel or hear it snap into place. Turn or rotate the needle until it "clicks" into place. The needle is attached when it no longer turns or rotates freely.
- Remove the needle cover by pulling off the needle cover and throw it away.

Remove Air/Flow Check
- Turn the dose selector knob until the drop symbol is centered in the dose window. Hold the prefilled pen injector with the needle pointing up and press the injection button all the way in until it stops and the dose window returns to "0". Repeat these steps 3 more times for a total of 4 cycles.
- Look for liquid medicine at the tip of the needle. If you do not see liquid at the tip of the needle, repeat these steps up to 3 more times for a total of 7 cycles or until you see liquid medicine at the tip of the needle.

Inject BESREMi
- Set your dose by turning the dose selector clockwise until the prescribed dose is centered in the dose window. Check the number in the dose window to make sure you have dialed the correct prescribed dose before giving the injection.
- If you accidentally dial past the prescribed dose, dial the dose selector back to the correct dose.
- Hold the prefilled pen injector straight (90 degrees) over the cleaned injection site.
- Push the prefilled pen injector down to fully insert the needle without touching the injection button.
- Press and hold the injection button all the way until it stops. The number in the dose window will go back to "0".
- Keep holding the injection button down after the dose window returns to "0" and count to 5 to make sure the full dose is delivered.
- Note: There may still be liquid remaining in the prefilled pen injector after the injection. This is normal.
- Remove the needle from the skin by lifting straight up.

Dispose of Used Prefilled Pen Injector
- Do not recap the needle or attempt to remove it. Throw away the used prefilled pen injector with the needle still attached into a sharps disposal container.

3 DOSAGE FORMS AND STRENGTHS

BESREMi is a clear and colorless to slightly yellowish solution available as:
- Prefilled Syringe
  Injection: 500 mcg/mL in a single-dose prefilled syringe
- Prefilled Pen Injector
  Injection: 500 mcg/0.5 mL in a single-dose prefilled pen injector

4 CONTRAINDICATIONS

BESREMi is contraindicated in patients with:
- 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.

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicide

Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness. Psychiatric reactions have been observed in 10% of BESREMi-treated patients with essential thrombocythemia including depression, adjustment disorder with depressed mood, and depressed mood. Serious neuropsychiatric reactions have been observed in 3% of BESREMi-treated patients with polycythemia vera,

including depression, depressive symptoms, depressed mood, and listlessness. Of these cases, 3.4% of the patients recovered with temporary drug interruption and 2.8% stopped BESREMi treatment.

Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. BESREMi is contraindicated in patients with a history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt *[see Contraindications (4)]*.

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.

5.2 Endocrine Toxicity

Endocrine toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include worsening hypothyroidism and hyperthyroidism. Autoimmune thyroiditis and hyperglycemia, including new onset type 1 diabetes, have been reported in patients receiving interferon alfa-2b products. Endocrine toxicities included hyperthyroidism (1.1%), hypothyroidism (1.1%), autoimmune thyroiditis (0.5%), and thyroiditis (0.5%) in BESREMi-treated patients with essential thrombocythemia. Endocrine toxicities included hyperthyroidism (4.5%), hypothyroidism (3.9%), and autoimmune thyroiditis/thyroiditis (2.8%) in BESREMi-treated patients with polycythemia vera.

Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease *[see Contraindications (4)]*. 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.

5.3 Cardiovascular Toxicity

Cardiovascular toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Toxicities may include cardiomyopathy, myocardial infarction, atrial fibrillation, coronary artery ischemia, and acute coronary syndrome *[see Adverse Reactions (6.1)]*. Three thrombotic events of transient ischemic attack (grade 2, 1 patient), pulmonary embolism (grade 3, 1 patient), and peripheral vein thrombosis (grade 2, 1 patient) occurred in the essential thrombocythemia Phase 3 SURPASS ET study. Patients with a history of cardiovascular disorders and/or thrombotic events should be closely monitored for cardiovascular toxicity and/or thrombotic events during BESREMi therapy. Avoid use of BESREMi in patients with 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.

5.4 Hematologic and Hemorrhagic Disorders

Decreased peripheral blood counts have occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). In BESREMi-treated patients with essential thrombocythemia, anemia of grade 3 or greater occurred in 1% of patients. Leukopenia of grade 3 or greater occurred in 2% of patients. Infection occurred in 45% of patients, while serious infections occurred in 4% of patients. Essential thrombocythemia-related hemorrhagic cases occurred in 6% of patients and included gingival bleeding, tongue hemorrhage, epistaxis, purpura, and retinal hemorrhage. In BESREMi-treated patients with polycythemia vera, thrombocytopenia of grade 3 (platelet counts <50,000 – 25,000/mm^3) or greater occurred in 2% of patients. Anemia of grade 3 (Hgb <8 g/dL) or greater occurred in 1% of patients. Leukopenia of grade 3 (WBC counts <2,000 – 1,000/mm^3) or greater occurred in 2% of patients. Infection occurred in 48% of patients, while serious infections occurred in 8% of patients. 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.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. BESREMi is contraindicated in patients with hypersensitivity reactions to interferon products or any of the inactive ingredients in BESREMi *[see Contraindications (4)]*. Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis, drug eruption). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.

5.6 Pancreatitis

Pancreatitis has occurred in patients receiving interferon alfa products, including BESREMi. Pancreatitis was reported in 2.2% of patients receiving BESREMi for polycythemia vera. 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.

5.7 Colitis

Serious and, in very rare cases potentially life-threatening ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases occurring 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.

5.8 Pulmonary Toxicity

Pulmonary toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Pulmonary toxicity may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, pleural effusion, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.

5.9 Ophthalmologic Toxicity

Ophthalmologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. 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 in patients with essential thrombocythemia, 23% of patients were identified with eye disorders. Eye disorders in ≥5% of patients included vision blurred (8%) and dry eye (7%). During BESREMi therapy in patients with polycythemia vera, 23% of patients were identified with an eye disorder. Eyes disorders ≥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.

5.10 Hyperlipidemia

Hyperlipidemia has occurred in patients treated with interferon alfa products, including BESREMi. Hypertriglyceridemia occurred in 9% of patients, hyperlipidemia occurred in 2% of patients, and dyslipidemia occurred in 0.5% of patients receiving BESREMi for essential thrombocythemia. Hyperlipidemia, hypertriglyceridemia, or dyslipidemia occurred in 3% of patients receiving BESREMi for polycythemia vera. Elevated triglycerides may result in pancreatitis *[see Warnings and Precautions (5.6)]*. 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.

5.11 Hepatotoxicity

Hepatotoxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT, and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Contraindications (4)]*.

Increases in serum ALT ≥3 × the upper limit of normal (ULN), AST ≥3 × the ULN, GGT ≥3 × ULN, and bilirubin >2 × ULN have been observed in patients treated with BESREMi.

In BESREMi-treated patients with essential thrombocythemia, 4% of patients experienced Grade ≥3 liver enzyme elevations including alanine aminotransferase increased in 2.7% of patients, aspartate aminotransferase increased in 1.1% of patients, and blood bilirubin increased in 0.5% of patients. There were 20% of patients with alanine aminotransferase levels ≥3 × ULN and 9% of patients with aspartate aminotransferase levels ≥3 × ULN. A single Grade 4 adverse reaction of hepatitis was reported in an open-label single arm study of BESREMi in patients with essential thrombocythemia, with a time to recovery of 11 days.

In BESREMi-treated patients with polycythemia vera, 36 patients (20%) experienced liver enzyme elevations, 33 of whom had elevations of 1.25-5 × ULN. Patients were able to resume BESREMi upon resolution of liver enzyme elevations. 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. For dose modifications see Table 1 for patients with essential thrombocythemia and see Table 3 for patients with polycythemia vera *[see Dosage and Administration (2.3)]*.

Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment *[see Use in Specific Populations (8.7)]*.

5.12 Renal Toxicity

Renal toxicity has occurred in patients receiving interferon alfa products, including BESREMi. During BESREMi therapy in patients with polycythemia vera, <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 BESREMi if severe renal impairment develops during treatment *[see Use in Specific Populations (8.6)]*.

5.13 Dental and Periodontal Toxicity

Dental and periodontal toxicities may occur in patients receiving interferon alfa products, including BESREMi. 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 oral mucous membranes during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.

5.14 Dermatologic Toxicity

Dermatologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. 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.

5.15 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.

5.16 Embryo-Fetal Toxicity

Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.1)]*. Obtain a pregnancy test in females of reproductive potential prior to initiating 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 *[see Dosage and Administration (2.1) and Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Depression and Suicide *[see Warnings and Precautions (5.1)]*
- Endocrine Toxicity *[see Warnings and Precautions (5.2)]*
- Cardiovascular Toxicity *[see Warnings and Precautions (5.3)]*
- Hematologic and Hemorrhagic Disorders *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Pancreatitis *[see Warnings and Precautions (5.6)]*
- Colitis *[see Warnings and Precautions (5.7)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.8)]*
- Ophthalmologic Toxicity *[see Warnings and Precautions (5.9)]*
- Hyperlipidemia *[see Warnings and Precautions (5.10)]*
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*
- Renal Toxicity *[see Warnings and Precautions (5.12)]*
- Dental and Periodontal Toxicity *[see Warnings and Precautions (5.13)]*
- Dermatologic Toxicity *[see Warnings and Precautions (5.14)]*
- Driving and Operating Machinery *[see Warnings and Precautions (5.15)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Essential Thrombocythemia

The pooled safety population described in the Warnings and Precautions section reflects exposure to BESREMi as monotherapy for the treatment of essential thrombocythemia dosed every 2 weeks in 182 patients in an open-label trial [P1101 ET, SURPASS ET] and a single-arm trial [A22-301, EXCEED ET]. The mean age was 56 years (range: 21 to 84 years). There were 104 (57%) women, 78 (43%) men, and 93 (51%) Asian, 76 (42%) Caucasian, 5 (2.7%) Black or African American, 5 (2.7%) Other, and 3 (1.6%) Hispanic patients were included in the studies. Among 182 patients who received BESREMi, 70 (39%) patients were exposed for >56 weeks (>14 months). The mean (SD) dose of BESREMi was 394.9 (98.4) mcg during the treatment period. In this pooled safety population, the most common adverse reactions in ≥10% of BESREMi-treated patients were aspartate aminotransferase increased (44%), alanine aminotransferase increased (43%), fatigue (31%), anemia (24%), white blood cell count decreased (23%), neutrophil count decreased (22%), pruritus (17%), gamma-glutamyltransferase increased (16%), alopecia (16%), headache (15%), diarrhea (13%), nausea (13%), beta 2 microglobulin

urine increased (12%), influenza like illness (11%), and myalgia (11%).

The safety findings described below reflect exposure to BESREMi as monotherapy for the treatment of essential thrombocythemia in 91 patients in the SURPASS ET study *[see Clinical Studies (14)]*. Among the 91 patients receiving BESREMi, 55% were exposed for 9 to 13 months and 36% were exposed for more than 13 months.

Serious adverse reactions were reported in 2.2% of patients treated with BESREMi in the SURPASS ET study and included vascular headache and drug eruption.

Adverse reactions requiring permanent discontinuation of patients treated with BESREMi occurred in 1.1% patient each and included aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, pneumonitis, pulmonary hypertension, thyroiditis, dry eye, and erythema.

The most common adverse reactions reported in ≥10% of patients in the SURPASS ET study are listed in Table 4.

Table 4 Adverse Reactions in ≥10% of Patients with Essential Thrombocythemia in the SURPASS ET Study Over 13 Months.

	BESREMi N=91		**Anagrelide N=80**	
Term	***All Grade*** **n (%)**	***Grade ≥3*** **n (%)**	***All Grade*** **n (%)**	***Grade ≥3*** **n (%)**
Transaminase elevations[1]	49 (54)	3 (3)	11 (14)	0
Anemia	25 (28)	0	24 (30)	3 (4)
Pyrexia	24 (26)	0	7 (9)	0
Beta 2 microglobulin urine increased	23 (25)	0	3 (4)	0
Bacterial infection[2]	22 (24)	5 (5)	18 (23)	2 (3)
Pruritus	20 (22)	1 (1.1)	15 (19)	0
Weight decreased	19 (21)	1 (1)	5 (6)	0
Leukopenia[2]	17 (19)	1 (1)	2 (3)	1 (1)
Fatigue	16 (18)	0	10 (13)	0
Hemorrhage[2]	15 (17)	0	30 (38)	3 (4)
Alopecia	14 (15)	0	1 (1)	0
Headache	14 (15)	0	25 (31)	0
Diarrhea	13 (14)	0	19 (24)	0
Gamma-glutamyl transferase increased	12 (13)	0	9 (11)	0
Nasopharyngitis[2]	12 (13)	0	14 (18)	0
Abdominal pain[2]	11 (12)	0	11 (14)	0
Neutrophil count decreased	11 (12)	1 (1)	0	0
Arthralgia	10 (11)	0	7 (9)	0
Cough	10 (11)	0	5 (6)	0
Rash[3]	10 (11)	0	4 (5)	0
Dizziness	10 (11)	0	16 (20)	1 (1)
Malaise	10 (11)	0	3 (4)	0
Myalgia	10 (11)	0	7 (9)	0
Back pain[2]	10 (11)	0	5 (6)	0

*Adverse Reactions defined as all treatment-emergent adverse events

[1] Transaminase elevations include: Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic function abnormal, and Liver function test increased

[2] Grouped related terms

[3] Rash includes: Rash, Rash maculo-papular, and Rash pruritic

Polycythemia Vera

The pooled safety population described in the Warnings and Precautions section reflects exposure to BESREMi as monotherapy for the treatment of polycythemia vera dosed every two to four weeks in 178 patients in two open-label trials [PEGINVERA, PROUD-PV/CONTINUATION-PV]. The mean age at baseline was 58.6 years (range 30-85 years), 88 (49%) women, 90 (51%) men, 177 (99%) Caucasian and 1 (1%) Asian. Among 178 patients who received BESREMi, 80% were exposed for 12 months or longer. The mean dose of BESREMi was 334 mcg SD ± 121 during the treatment period. In this pooled safety population, 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%).

The safety findings described below reflect exposure to BESREMi as monotherapy for the treatment of polycythemia vera in 51 patients in the PEGINVERA study *[see Clinical Studies (14)]*. Among the 51 patients receiving BESREMi, 71% were exposed for 12 months or longer, 63% were exposed for three years or longer, and 53% were exposed for greater than five years.
Serious adverse reactions were reported in 16% of patients in the PEGINVERA study. The most common serious adverse reactions observed during the study (≥4%) included urinary tract infection (8%), transient ischemic attack (6%) and depression (4%).

Adverse reactions requiring permanent discontinuation in >2% of patients who received BESREMi included depression (8%), arthralgia (4%), fatigue (4%), and general physical health deterioration (4%). In the PEGINVERA study, patients were not pre-screened for depression or anxiety disorders.

The most common adverse reactions reported in ≥10% of patients in the PEGINVERA study are listed in Table 5.

Table 5 Adverse Reactions in >10% of Patients with Polycythemia Vera in the PEGINVERA Study Over 7.5 Years.

Adverse Reactions*	BESREMi N=51 %
Influenza-like illness [a]	59
Arthralgia	47
Fatigue [b]	47
Pruritus	45
Nasopharyngitis [c]	43
Musculoskeletal pain [d]	41
Headache [e]	39
Diarrhea	33
Hyperhidrosis [f]	29
Nausea	28
Upper respiratory tract infection [g]	27
Local administration site reactions	26
Dizziness	22
Abdominal pain [h]	20
Depression	20
Sleep disorder [i]	20
Leukopenia	18
Decreased appetite	18
Alopecia	16
Edema [j]	16
Hypertension [k]	16
Muscle spasms	16
Neutropenia	16
Rash [l]	16
Transaminase elevations [m]	16
Urinary tract infection	16
Thrombocytopenia	12
Vertigo	12

*Adverse Reactions defined as all treatment emergent adverse events

Grouped Term Definitions
[a] Includes pyrexia, chills, and influenza-like illness.
[b] Includes asthenia, malaise, and fatigue.
[c] Includes pharyngitis and nasopharyngitis.
[d] Includes musculoskeletal pain, back pain, pain in extremity, bone pain, flank pain, and spinal pain.
[e] Includes headache, migraine, and head pain.
[f] Includes night sweats and hyperhidrosis.
[g] Includes upper respiratory tract infection, rhinitis, bronchitis, and respiratory tract infection.
[h] Includes abdominal pain upper, abdominal pain lower, and abdominal pain.
[i] Includes insomnia, sleep disorder, and abnormal dreams.
[j] Includes peripheral edema and generalized edema.
[k] Includes hypertension and hypertensive crisis.
[l] Includes rash, maculopapular rash, and pruritic rash.
[m] Includes transaminase increase, hepatic enzyme increase, GGT increase, AST increase, and ALT increase.

Clinically relevant adverse reactions in <10% of patients include:
Cardiovascular System: Atrial fibrillation

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

Certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates *[see Clinical Pharmacology (12.3)]*. Therefore, patients on BESREMi who are receiving concomitant drugs that are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.

7.2 Myelosuppressive Agents

Concomitant use of BESREMi and myelosuppressive agents can produce additive myelosuppression. Avoid use and monitor patients receiving the combination for effects of excessive myelosuppression *[see Warnings and Precautions (5.4)]*.

7.3 Narcotics, Hypnotics or Sedatives

Concomitant use of BESREMi and narcotics, hypnotics or sedatives can produce additive neuropsychiatric side effects. Avoid use and monitor patients receiving the combination for effects of excessive CNS toxicity *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Available human data with BESREMi use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. An abortifacient effect was reported in cynomolgus monkeys receiving ropeginterferon alfa-2b (see Data). Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi can 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 *(see Clinical Considerations)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study, pregnant cynomolgus monkeys received subcutaneous injection of ropeginterferon alfa-2b twice weekly during the period of organogenesis (Gestation Days 20-48). Maternal toxicity, characterized by a significant decline in food consumption and transient body weight loss, occurred at all dose levels and ropeginterferon alfa-2b was abortifacient and caused embryonic death at exposures 275-times (C_{max}) and 64-times (AUC) the human exposure at the maximum recommended human dose of 500 mcg. There were no effects on fetal developmental parameters or abnormalities in the surviving fetuses (GD 100) where the ropeginterferon alfa-2b exposures achieved in pregnant cynomolgus monkeys during the first trimester were 961-times (C_{max}) and 224-times (AUC) the human exposure at the maximum recommended human dose of 500 mcg.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Untreated polycythemia vera during pregnancy is associated with adverse maternal outcomes such as thrombosis and hemorrhage. Adverse pregnancy outcomes associated with polycythemia vera include increased risk for miscarriage.

8.2 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.

8.3 Females and Males of Reproductive Potential

BESREMi can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential.

Contraception
Females

Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

Infertility

Females

Based on its mechanism of action, BESREMi can cause disruption of the menstrual cycle *[see Clinical Pharmacology (12.1)]*. No animal fertility studies have been conducted with BESREMi.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of BESREMi-treated patients in the essential thrombocythemia studies, 65 (36%) were 65 years of age and older, while 15 (8%) were 75 years of age and older *[see Clinical Studies (14)]*. Of the total number of BESREMi-treated patients in the polycythemia studies, 17 (33%) were 65 years of age and older, while 5 (10%) were 75 years of age and older. Clinical studies of BESREMi did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Renal Impairment

No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min *[see Clinical Pharmacology (12.3)]*. Avoid use of BESREMi in patients with eGFR <30 mL/min *[see Warnings and Precautions (5.12)]*.

8.7 Hepatic Impairment

BESREMi is contraindicated in patients with hepatic impairment (Child-Pugh B or C) *[see Contraindications (4)]*.

Increased liver enzyme levels have been observed in patients treated with BESREMi. When the increase in liver enzyme levels is progressive and persistent, reduce the dose of BESREMi. If the increase in liver enzymes is progressive and clinically significant despite dose-reduction, or if there is evidence of hepatic impairment (Child-Pugh B or C), discontinue BESREMi *[see Dosage and Administration (2.2) and Warnings and Precautions (5.11)]*.

10 OVERDOSAGE

Overdosage of BESREMi may result in influenza-like symptoms or other adverse reactions. There is no antidote to BESREMi overdosage. In case of an overdose, frequently monitor signs and symptoms for adverse reactions. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Ropeginterferon alfa-2b-njft, an interferon alfa-2b, is an N-terminal monopegylated covalent conjugate of proline interferon alfa-2b, produced in *Escherichia coli* cells by recombinant DNA technology, with a methoxy polyethylene glycol (mPEG) moiety. Ropeginterferon alfa-2b-njft has an approximate molecular weight of 60 kDa and the approximate molecular weight of the PEG portion of the molecule is 40 kDa.

BESREMi (ropeginterferon alfa-2b-njft) injection is a sterile, clear and colorless to slightly yellowish solution for subcutaneous use supplied in a single-dose prefilled syringe or in a single-dose prefilled pen injector.

Each prefilled syringe delivers 1 mL of solution containing 500 mcg of ropeginterferon alfa-2b-njft and benzyl alcohol (10 mg), glacial acetic acid (0.05 mg), polysorbate 80 (0.05 mg), sodium acetate (1.58 mg), sodium chloride (8 mg), and Water for Injection, USP. The pH is approximately 6.

Each prefilled pen injector delivers 0.5 mL of solution containing 500 mcg of ropeginterferon alfa-2b-njft and benzyl alcohol (5 mg), glacial acetic acid (0.025 mg), polysorbate 80 (0.025 mg), sodium acetate (0.79 mg), sodium chloride (4 mg), and Water for Injection, USP. The pH is approximately 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Interferon alfa belongs to the class of type I interferons, which exhibit their cellular effects in polycythemia vera and essential thrombocythemia 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 and essential thrombocythemia are not fully elucidated.

12.2 Pharmacodynamics

The efficacy of ropeginterferon alfa-2b-njft is dependent on the stabilization of hematological parameters (hematocrit <45%, platelets $<400 \times 10^9$/L and leukocytes $<10 \times 10^9$/L). Pharmacokinetic-pharmacodynamic analyses have demonstrated that the reduction in the individual hematological parameters is dependent on ropeginterferon alfa-2b-njft concentrations. Complete hematological response (CHR, defined as a patient achieving hematocrit <45% without phlebotomy [at least 2 months since last phlebotomy], platelets $\leq 400 \times 10^9$/L and leukocytes $\leq 10 \times 10^9$/L) increased with increasing ropeginterferon alfa-2b-njft concentration over time. Based on the exposure-response (E-R) analyses using data from the PEGINVERA study in patients with polycythemia vera, the predicted probability of CHR (95% Prediction Intervals) was 22% (11% – 34%) before treatment, 50% (38% – 62%) at week 20 (end of titration), 64% (47% – 78%) at week 52, and 70% (55% – 88%) at week 104. The E-R analyses show that the maximum probability of CHR is reached after 2 years of continuous treatment.

12.3 Pharmacokinetics

In patients with essential thrombocythemia, following subcutaneous administration of BESREMi, peak serum concentrations (C_{max}) were reached between 62 to 123 hours post-dose (T_{max}). Exposure appeared generally dose-proportional following repeated subcutaneous doses of 250 to 500 mcg at Week 12.

In patients with polycythemia vera, the estimated steady state C_{max}, C_{min} and area under the curve (AUC) after a two-week dosing interval of BESREMi over a dose range of 100 mcg to 500 mcg ranged from 4.4 – 31 ng/mL, 1.4 – 12 ng/mL, and 1,011 – 7,809 ng × h/mL, respectively. The estimated steady state C_{max} occurs between 2 to 5 days.

Absorption
The estimated geometric mean (CV%) of the absorption rate constant of BESREMi is 0.12 day^{-1} (27%) in patients with polycythemia vera.

Distribution
The estimated geometric mean (CV%) of apparent volume of distribution of BESREMi is 4.8 L (21%) in patients with polycythemia vera.

Elimination

BESREMi undergoes receptor independent degradation/excretion and receptor binding and subsequent degradation of the drug-receptor complex. The half-life of BESREMi is approximately 7 days and the clearance is approximately 1.7-2.5 L/h in patients with polycythemia vera over a dose range of 100 mcg to 500 mcg, respectively.

In patients with essential thrombocythemia, the median terminal phase half-life ($t_{1/2,\lambda z}$) is 122 hours following a single subcutaneous dose. Following repeated subcutaneous dosing, the median $t_{1/2,\lambda z}$ ranged from 210 to 251 hours across doses of 250 mcg to 500 mcg at Week 12.

Specific Populations
No clinically significant differences in the pharmacokinetics of BESREMi were observed based on age, sex, body surface area, and JAK2V617F mutation.

Drug Interactions
Clinical Studies
No clinical studies evaluating the drug interaction potential of BESREMi have been conducted.

In Vitro Studies
In vitro studies indicate that BESREMi exhibited time-dependent inhibitory potential on CYP2A6. BESREMi did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in human liver microsomes. BESREMi is not expected to induce CYP enzymes. However, interferon may influence CYP450 through modulating transcription factors and altering protein expression and/or structure. As this mechanism requires more time to exert effect, it cannot be evaluated by in vitro assays.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ropeginterferon alfa-2b-njft or of other ropeginterferon alfa-2b products.

The immunogenicity of BESREMi was evaluated in adult patients with essential thrombocythemia in two clinical studies (SURPASS ET and EXCEED ET). In the SURPASS ET study, among 91 evaluable patients treated with BESREMi, 7% (6/91) developed treatment-induced anti-ropeginterferon alfa-2b antibodies. In the EXCEED ET study, among 88 evaluable patients, 13% (11/88) developed treatment-induced anti-ropeginterferon alfa-2b antibodies. These antibody responses were transient and of low titer. No neutralizing antibodies against ropeginterferon alfa-2b were detected in patients from either study. The presence of anti-ropeginterferon alfa-2b-njft antibodies was not associated with a clinically meaningful impact on the pharmacokinetics, safety, or efficacy of BESREMi.

In three studies in patients with polycythemia vera (PEGINVERA, PROUD-PV/CONTINUATION-PV), from a total of 146 subjects who have been followed up to 362 weeks, the incidence of confirmed anti-drug antibodies was 1.4% (2/146). No neutralizing antibodies were detected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ropeginterferon alfa-2b-njft has not been tested for its carcinogenic potential. Neither ropeginterferon alfa-2b-njft nor its components, interferon or methoxypolyethylene glycol, caused damage to DNA when tested in the standard battery of mutagenesis assays. Ropeginterferon alfa-2b-njft effects on fertility have not been assessed *[see Use in Specific Populations (8.1, 8.2, 8.3)]*.

14 CLINICAL STUDIES

14.1 Essential Thrombocythemia

SURPASS ET:

The SURPASS ET study was a randomized, open-label, multicenter, active-controlled study to assess pharmacokinetics, efficacy, safety, and tolerability of BESREMi compared to anagrelide as second line therapy after 12 months of treatment. The study included 174 adults with essential thrombocythemia and documented resistance/intolerance to hydroxyurea, of which, 91 patients received BESREMi and 83 patients received anagrelide. The median age at baseline was 62.5 years (range 20-83 years), with 52% females and 48% males, and 96% Asian and 4% Caucasian patients. There were 79% of patients with an ECOG Grade 0 and patients had a mean (SD) TSS of 12.5 (14) at baseline. Hydroxyurea was previously used by all patients, with an overall mean (SD) duration of use of 27.9 (59.7) months; the mean (SD) prior duration of use was 22 (39.9) months for patients who received BESREMi and 35.2 (80) months for patients who received anagrelide. There were 82% of patients with a JAK2V617F mutation at baseline, with a mean (SD) allelic burden of 44 (30)%. There were 12% of patients with a CALR mutation at baseline, with a mean (SD) allelic burden of 25 (18)%. One percent of patients had an MPL mutation at baseline, with a mean (SD) allelic burden of 29 (4.1)%. At baseline, mean (SD) platelets and white blood cells were $1,024.5 \times 10^9$/L (439.1) and 14.2×10^9/L (7.7), respectively. The spleen was palpable in 14% of patients at baseline, with a median spleen size of 13.9 cm. Two percent of patients had splenomegaly at baseline (defined as a longitudinal diameter of >17 cm). There were 35% of patients with a history of thrombosis, 35% of patients with a history of hemorrhage, 85% of patients with a JAK-2 mutation history, 9% of patients with a CALR mutation history, and 2% of patients with an MPL mutation history.

BESREMi was administered subcutaneously every 2 weeks at the starting dose of 250 mcg (Week 0), then 350 mcg (Week 2), and 500 mcg (Week 4), and then remained fixed at 500 mcg for the remaining Treatment Period. Anagrelide was administered orally; the starting dose, maintenance dose, and any dose adjustment was according to the local country product label and treatment practices. Low-dose aspirin (75 to 150 mg/day per local practice) was given to subjects in both arms during the 12 months of study treatment, unless contraindicated.

The median duration of treatment exposure was 11.9 months; 55% of patients completed at least 12 months of treatment and 36% of patients completed more than 12 months of treatment. Overall, 74% of patients completed the study, with 10% of patients discontinuing due to a study drug related treatment-emergent adverse event. The mean (SD) dose of BESREMi was 10,174.2 (3,120.3) mcg during the treatment period.

The efficacy of BESREMi was evaluated in the SURPASS ET study by assessing durable Modified European Leukemia Net (ELN)

response rates at Months 9 and 12. The modified ELN response criteria involved the following: peripheral blood count remission (platelets ≤400 × 10^9 and white blood cells <9.5 × 10^9/L) AND improvement or non-progression in disease-related signs (splenomegaly) AND absence of hemorrhagic or thrombotic events. The modified ELN response differs from the 2013 ELN response criteria as it excludes components for bone marrow histological remission and the requirement for durable resolution of disease-related signs and large symptoms improvement, and uses a lower white blood cell threshold. Additional evaluations for efficacy included durable response at Months 3 and 6, longitudinal rate of change in the ELN response rates over 12 months, change from baseline in JAK2V617F allelic burden from baseline over time (by 2013 ELN criteria), and thromboembolic events. Other evaluations for efficacy included response rates based on peripheral blood count remission, no signs of progressive disease, and absence of any hemorrhagic or thrombotic events at 3, 6, 9, and 12 months, and time to first peripheral blood count remission response.

In the SURPASS ET study, the BESREMi treatment demonstrated a statistically significantly higher response rate compared with anagrelide for the durable modified ELN response rate at both Months 9 and 12. Table 6 summarizes the efficacy results for SURPASS ET.

Table 6 Efficacy Results for SURPASS ET Study

Endpoint	**BESREMi (N = 91)**	**Anagrelide (N = 83)**	**Difference Between Arms, % (95% CI)[1]**
Durable Modified ELN Response[2] at Months 9 and 12, n (%) (95% CI)[3]	34 (37.4) (27.4, 48.1)	3 (3.6) (0.8, 10.2)	33.9 (23.5, 44.4)
Occurrence of Thromboembolic Events Over 12 Months, n/N[C]	1/82	10/51	
Durable Modified ELN Response[2] at Months 3 and 6, n (%) (95% CI)[3]	28 (30.8) (21.5, 41.3)	3 (3.6) (0.8, 10.2)	26.8 (16.5, 37.0)

Abbreviations: ELN = European Leukemia Net; CI = confidence interval; SD = standard deviation
The p-values of the efficacy endpoints met the significant levels via a Graphical Chain Procedure.
For a composite approach, all patients who early withdrew or who took any prohibited medications were classified as non-responders.
n represents the number of patients contributing to a summary statistic; percentages are based on N or N^C (completers of the study).

1 The 95% CIs for the differences between treatment arms were calculated using the normal approximation method.

2 Included peripheral blood count remission (platelets ≤400 × 10^9 and white blood cells <9.5 × 10^9/L), improvement or non-progression in disease related signs (splenomegaly), and an absence of hemorrhagic or thrombotic events. Excluded large symptom improvement or maintain non-progression of symptoms component due to open-label trial design.

3 The 95% CIs were calculated using the Clopper-Pearson (exact) method.

14.2 Polycythemia Vera

The efficacy and safety of BESREMi were evaluated in the PEGINVERA study, a prospective, multicenter, single-arm trial of 7.5 years duration. The study included 51 adults with polycythemia vera. The mean age at baseline was 56 years (range 35-82 years) with 20 (39%) women and 31 (61%) men. All patients had the JAK2V617F mutation with 16% of subjects being newly diagnosed; 84% had known disease with a median duration of 2.2 years. One-third (33%) of patients were undergoing treatment with hydroxyurea (HU) upon study entry. At baseline, the mean ± SD hematocrit, platelets, and leukocytes were 45% ± 4.0%, 457 × 10^9/L ± 187 × 10^9/L and 11.8 × 10^9/L ± 5.2 × 10^9/L, respectively. Median spleen size was 13.2 cm with 16 (31%) having splenomegaly (defined as a longitudinal diameter of >12 cm for women and >13 cm for men). Eleven patients (22%) had a prior history of a major cardiovascular event including pulmonary embolism (6), stroke (2), myocardial infarction (2) and portal vein thrombosis (1).

In stage I, the maximum tolerated dose, defined as the highest administered dose without dose-limiting toxicities was determined to be 540 mcg. In stage II, an intra-patient dose escalation began at 150 mcg, or 100 mcg if titrating from hydroxyurea, or at the highest dose achieved in those patients enrolled during stage I. Titration with BESREMi occurred every two-weeks at doses of 225 mcg, 300 mcg, 400 mcg, and 450 mcg with dose escalation stopping when hematological parameters were stabilized. For patients transitioning from hydroxyurea, the hydroxyurea dose was tapered off over the first 12 weeks of treatment to avoid toxicity. After at least one year on therapy and at a median time of 21.5 months, 28 eligible patients in the PEGINVERA study increased the dosing interval to once every 4 weeks. Because of formulation changes, the recommended starting dose, titration amounts, and maximum dose of BESREMi differ slightly from those used in the trial *[see Dosage and Administration (2)]*.

The median duration of treatment exposure was 61 months and 53% of patients completed at least 60 months of treatment. Thirty-six patients completed one year of treatment with eleven patients discontinuing after one year of treatment mainly due to treatment emergent adverse events. The mean dose of BESREMi was 237 mcg (± 110) during the treatment period.

The efficacy of BESREMi was evaluated in the PEGINVERA study by assessing complete hematological response (CHR) defined as hematocrit <45% and no phlebotomy in the preceding 2 months, platelets ≤400 × 10^9/L and leukocytes ≤10 × 10^9/L, normal spleen size (longitudinal diameter ≤12 cm for females and ≤13 cm for males) assessed by ultrasound and absence of thromboembolic events.

The CHR in the treated population during the treatment period was 61% (31/51) (95% CI: 46, 74). The median duration of response was 14.3 months (95% CI: 5.5, 30.1).

Among the patients in the treated population who achieved a CHR, the median time to response was 7.8 months of treatment with BESREMi. It required 1.2 years of treatment with BESREMi for 50% of patients (hydroxyurea-naïve) to achieve a CHR and 1.4 years for 50% of patients with prior hydroxyurea use to achieve a CHR.

A hematological response based only on hematocrit, platelets, and leukocytes was achieved among 80% of patients treated with BESREMi (41/51) (95% CI: 67, 90). The median duration of this response was 20.8 months (95% CI: 13.0, 43.8).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- **Prefilled syringe – 500 mcg/mL**

BESREMi (ropeginterferon alfa-2b-njft) injection is a sterile, clear and colorless to slightly yellowish solution for subcutaneous administration in a single-dose prefilled syringe. Each carton contains one 500 mcg/mL prefilled syringe with a 30 gauge, ½ inch safety hypodermic needle (NDC 73536-500-01).

- **BESREMi Pen – 500 mcg/0.5 mL**

BESREMi Pen (ropeginterferon alfa-2b-njft) injection is a sterile, clear and colorless to slightly yellowish solution for subcutaneous administration in a single-dose prefilled pen injector. Each carton contains one 500 mcg/0.5 mL prefilled pen injector with a 30 gauge, 8 mm needle (NDC 73536-511-01).

Storage and Handling
Store in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Depression and Suicide
Inform patients, their caregivers, and family members that suicidal ideation and behavior, as well as new onset or worsening depression have been reported in patients treated with BESREMi. Advise them to be aware of any unusual changes in mood or behavior, new onset or worsening of depression, or the emergence of suicidal thoughts or behavior. Instruct patients, caregivers, and family members to report signs or symptoms of depression to their healthcare provider right away, but to discontinue BESREMi immediately and seek immediate medical attention if suicidal ideation or attempts occur *[see Warnings and Precautions (5.1)]*.

Endocrine Toxicity
Advise patients to report any signs or symptoms of diabetes or thyroid dysfunction *[see Warnings and Precautions (5.2)]*.

Cardiovascular Toxicity
Advise patients to report signs or symptoms of cardiovascular toxicity to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Hematologic and Hemorrhagic Disorders
Advise patients to seek prompt medical attention if they experience weakness/fatigue, fever, easy bruising, or frequent nose bleeds *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions
Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.5)]*.

Pancreatitis
Advise patients to report signs or symptoms of pancreatitis *[see Warnings and Precautions (5.6)]*.

Colitis
Advise patients to report signs or symptoms of colitis *[see Warnings and Precautions (5.7)]*.

Pulmonary Toxicity

Advise patients to report signs or symptoms of pulmonary toxicity *[see Warnings and Precautions (5.8)]*.

Ophthalmologic Toxicity
Advise patients to report visual changes and to have eye examinations before and during treatment *[see Warnings and Precautions (5.9)]*.

Hyperlipidemia
Advise patients that BESREMi may increase blood triglycerides and that they will need blood testing to monitor for this toxicity *[see Warnings and Precautions (5.10)]*.

Hepatotoxicity
Advise patients to report signs or symptoms of hepatic toxicity to their healthcare provider *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.7)]*.

Renal Toxicity
Advise patients to report signs or symptoms of kidney disease *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.6)]*.

Dental and Periodontal Toxicity
Advise patients to maintain good oral hygiene and to have regular dental examinations *[see Warnings and Precautions (5.13)]*.

Dermatologic Toxicity
Advise patients to seek medical attention if significant pruritus, alopecia, rash and/or other dermatological toxicities occur *[see Warnings and Precautions (5.14)]*.

Hazardous Occupations/Operating Machinery
Advise patients to refrain from engaging in operating heavy or potentially dangerous machinery until they know how BESREMi will affect their abilities. Advise patients who experience dizziness, somnolence, and hallucinations not to drive or use heavy machinery *[see Warnings and Precautions (5.15)]*.

Pregnancy and Contraception
Advise women about the need to use an effective method of contraception while taking BESREMi and for at least 8 weeks after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation
Advise women not to breastfeed during treatment and for 8 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Instruction on Injection Technique
Instruct patients on proper storage, preparation and administration techniques for BESREMi. Instruct patients who are self-administering to inject the prescribed dose of BESREMi *[see Dosage and Administration (2.4)]*.

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Nangang District, Taipei 115, Taiwan
U.S. License number 2155

Distributed by:
PharmaEssentia USA Corporation
35 Corporate Dr, Suite 325, Burlington, MA 01803, USA

Medication Guide
BESREMi® (bez-reh-me)
ropeginterferon alfa-2b-njft
injection, for subcutaneous use

What is the most important information I should know about BESREMi?

BESREMi can cause serious side effects that may cause death, be life threatening, or worsen certain serious conditions that you may already have.

Tell your healthcare provider right away if you get any of the problems listed below during treatment with BESREMi.

- **Mental health problems, including depression and suicide.** BESREMi may cause you to develop mood or behavior problems that may get worse during treatment with BESREMi or after your last dose. Your healthcare provider should closely monitor you for new or worsening depression and any unusual changes in mood or behavior during treatment with BESREMi. **If you have thoughts of hurting yourself or thoughts of suicide, stop using BESREMi right away. You, your caregiver, or family member should tell your healthcare provider or get medical help right away** if you develop any of the following signs or symptoms, especially if they are new, worse, or worry you:
  - thoughts about suicide or dying
  - new or worse depression
  - feeling very agitated or restless
  - trouble sleeping (insomnia)
  - acting aggressive, being angry, or violent
  - an extreme increase in activity or talking (mania)
  - suicide attempts
  - new or worse anxiety
  - panic attacks
  - new or worse irritability
  - acting on dangerous impulses
  - other unusual changes in behavior or mood
- **New or worsening autoimmune problems.** BESREMi may cause autoimmune problems (a condition where the body's immune cells attack other cells or organs in the body), including thyroid problems, increased blood sugar (hyperglycemia), and type I diabetes. In some people who already have an autoimmune problem, it may get worse during your treatment with BESREMi. Tell your healthcare provider if you get any of the following symptoms:
  - tiredness
  - urinating more often than normal
  - very thirsty
  - increase in appetite
  - problems concentrating
  - sensitivity to heat or cold temperature
  - weight changes
  - skin changes
- **Heart and blood vessel (cardiovascular) problems.** BESREMi may cause heart problems, including problems with your heart muscle (cardiomyopathy), heart attack, abnormal heart rhythm (atrial fibrillation), and decreased or sudden loss of blood flow to your heart. BESREMi may also cause blood clots (thrombotic events) in your brain, lungs, arms, and legs. Your healthcare provider should closely monitor you during treatment with BESREMi if you have a history of heart problems or blood clots. **You should not use BESREMi if you have:**
  - high blood pressure that is not controlled
  - congestive heart failure
  - a serious abnormal heart rhythm
  - narrowing of the arteries to your heart
  - certain types of chest pain (angina)
  - a recent stroke or heart attack

  Tell your healthcare provider right away if you develop any of the following signs and symptoms during treatment with BESREMi:
  - fast heart rate or abnormal heart beat
  - trouble breathing or chest pain
  - pain, swelling, or redness in the arms, legs, ankles, or feet
  - tiredness
  - sudden confusion
  - numbness or weakness
  - loss of coordination
  - trouble speaking clearly
  - sudden vision changes

If symptoms get worse, or become severe and do not go away, your healthcare provider may tell you to stop using BESREMi permanently. For some people, these symptoms may go away after they stop using BESREMi.

See **"What are the possible side effects of BESREMi?"** for more information about side effects.

What is BESREMi?

BESREMi is a prescription medicine that is used to treat adults with:

- essential thrombocythemia.
- polycythemia vera.

It is not known if BESREMi is safe and effective in children.

Who should not use BESREMi?

Do not use BESREMi if you:

- have or had severe mental health problems, especially severe depression, thoughts of suicide, or attempted suicide
- are allergic to another interferon product, including interferon alfa-2b, or to any of the ingredients in BESREMi. See the end of this Medication Guide for a complete list of ingredients in BESREMi. Ask your healthcare provider if you are not sure.
- have certain types of liver problems
- have or had a serious or untreated autoimmune disease
- have received an organ or stem cell transplant and take immunosuppressive medicines

Talk to your healthcare provider before taking BESREMi if you have any of these conditions.

Before using BESREMi, tell your healthcare provider about all of your medical conditions, including if you:

- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and have had thoughts of hurting yourself or others.
- have thyroid problems
- have diabetes
- have a condition that suppresses your immune system, such as cancer
- have or ever had any problems with your heart, including heart attack or high blood pressure
- have or ever had bleeding problems or a blood clot
- have liver problems
- have kidney problems
- are pregnant or plan to become pregnant. BESREMi can harm your unborn baby and can cause loss of your pregnancy (miscarriage).

  Females who can become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with BESREMi.
  - Use effective birth control (contraception) during treatment and for at least 8 weeks after your final dose of BESREMi. Talk to your healthcare provider about birth control choices for you during treatment with BESREMi.
  - BESREMi can affect your menstrual cycles and may cause your menstrual periods to stop.
  - Tell your healthcare provider if you become pregnant during treatment with BESREMi.
- are breastfeeding or plan to breastfeed. It is not known if BESREMi passes into your breast milk. **Do not** breastfeed during treatment and for 8 weeks after your final dose of BESREMi.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

BESREMi and certain other medicines may affect each other and cause side effects. Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use BESREMi?

Read the Instructions for Use that comes with BESREMi for detailed instructions on how to prepare and inject a dose of BESREMi.

- Use BESREMi exactly as your healthcare provider tells you to use it. Your healthcare provider will tell you how much BESREMi to inject and when to inject it. **Do not** inject more than your prescribed dose.
- **Do not** inject more than 1 dose of BESREMi every 2 weeks without talking to your healthcare provider.
- BESREMi comes in a single-dose prefilled syringe and in a single-dose prefilled pen injector.
- BESREMi is given as an injection under your skin (subcutaneous injection).
- BESREMi can be given by yourself, a caregiver, or healthcare provider. If your healthcare provider decides that you or a caregiver may give your injections of BESREMi at home, you should receive training on the right way to prepare and inject BESREMi. **Do not** try to inject BESREMi yourself until your healthcare provider has shown you how to give BESREMi the right way.

- **Do not** reuse the BESREMi single-dose prefilled syringe or the single-dose prefilled pen injector. They are for one time use only.
- Your healthcare provider will do blood tests before you start BESREMi, and regularly during treatment to monitor your essential thrombocythemia or polycythemia vera, and to check you for side effects.
- If you inject too much BESREMi, call the Poison Help Line at 1-800-222-1222 or your healthcare provider right away.

What should I avoid during treatment with BESREMi?

BESREMi may cause neurologic symptoms including dizziness, sleepiness, and hallucinations. Avoid driving or using heavy machinery if you develop any of these neurologic symptoms during treatment with BESREMi.

What are the possible side effects of BESREMi?

BESREMi can cause serious side effects including:

- See **"What is the most important information I should know about BESREMi?"**
- **Decreased blood cell counts and bleeding problems.** BESREMi can cause decreased blood cell counts, including decreased platelets, red blood cells, or white blood cells, that can sometimes be severe. If your blood cell counts are low, you can develop anemia, serious infections, or have problems with bleeding or bruising. Your healthcare provider will monitor you for signs or symptoms of infection or bleeding.

  Tell your healthcare provider or get medical help right away if you develop any of the following symptoms:
  - weakness and tiredness
  - bruising easily
  - you have nose bleeds often
  - fever
  - gum or tongue bleeding
  - chills
  - burning and painful urination
  - urinating often
  - coughing up yellow or pink mucus (phlegm)
  - bleeding in the eye
- **Serious allergic reactions and skin reactions. BESREMi can cause serious, sudden allergic reactions.** Stop using BESREMi and get medical help right away if you get any of the following symptoms:
  - skin rash or hives
  - itching swelling of your face, eyes, lips tongue, or throat
  - trouble breathing
  - chest pain
  - feeling dizzy or faint
- **Inflammation of the pancreas (pancreatitis).** Tell your healthcare provider if you develop signs and symptoms of pancreatitis, including:
  - nausea
  - vomiting
  - upper stomach area (abdomen) pain
  - bloating
  - fever
- **Inflammation of the intestine (colitis).** BESREMi can cause serious and possibly life-threatening colitis. This can lead to open sores, bleeding, or reduced blood flow to the intestine. Tell your healthcare provider if you develop any signs or symptoms of colitis, including:
  - stomach area (abdomen) pain
  - bloody diarrhea or blood in your stool
  - fever
- **Lung problems.** BESREMi can cause serious and life-threatening lung problems that can lead to breathing problems (respiratory failure) or death. Tell your healthcare provider if you develop any signs or symptoms of a lung problem, including:
  - shortness of breath
  - cough
  - difficulty breathing
- **Eye problems.** BESREMi can cause severe eye problems with your retinas that can lead to vision loss or blindness. You should have an eye exam before and during treatment with BESREMi, if you have diabetes or high blood pressure. Your healthcare provider may stop BESREMi if you develop new or worsening eye problems during treatment with BESREMi. Tell your healthcare provider if you develop any new or worsening eye symptoms or vision changes during treatment with BESREMi, including:
  - blurred vision
  - dry eyes
  - seeing floaters or flashes of light
  - sudden loss of vision
  - eye pain or redness
- **High cholesterol and triglycerides (fats in the blood).** BESREMi can cause high levels of cholesterol and fats (triglyceride) in your blood. High triglyceride levels may lead to inflammation of the pancreas (pancreatitis). Your healthcare provider may treat high cholesterol or triglyceride levels.

- **Liver problems**. BESREMi can cause increases in liver enzymes and liver damage. Tell your healthcare provider if you develop any signs and symptoms of a liver problem, including:
  - yellowing of your skin or the white part of your eyes
  - swelling of your stomach area (abdomen)
  - stomach area (abdomen) pain or discomfort
  - confusion
  - sleepiness
  - nausea
  - loss of appetite
  - tiredness
  - diarrhea
  - bleeding more easily than normal
- **Kidney problems.** Tell your healthcare provider if you develop any signs or symptoms of a kidney problem, including:
  - changes in the amount or color of your urine
  - blood in your urine
  - swelling in your ankles
  - loss of appetite
- **Tooth and gum (periodontal) problems.** BESREMi can cause tooth and gum problems which can lead to tooth loss. BESREMi can also cause problems with dry mouth that can damage your teeth and the lining of the mouth during long-term treatment. Brush and floss your teeth well and get regular dental examinations during treatment with BESREMI.
- **Skin problems.** Get medical help if you develop any signs and symptoms of a skin problem during treatment with BESREMi including:
  - itching
  - hair loss
  - rash
  - redness
  - dry skin
  - a skin condition causing red, scaly patches (psoriasis)
  - acne
  - thickening of the skin
  - excessive sweating

The most common side effects of BESREMi in adults with essential thrombocythemia include:

- increased liver function tests
- low red blood cell counts (anemia)
- fever
- increased protein in the urine
- bacterial infection
- itching
- weight loss

The most common side effects of BESREMi in adults with polycythemia vera include:

- flu-like symptoms
- joint pain
- tiredness
- itching
- runny or stuffy nose, cough, or sore throat
- muscle and bone pain

Your healthcare provider may reduce your dose, temporarily stop, or permanently stop your treatment with BESREMi if you develop side effects.

These are not all of the possible side effects of BESREMi.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BESREMi?

- Store BESREMi in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC).
- Keep BESREMi in the original carton to protect it from light.
- **Do not** freeze BESREMi.

Keep BESREMi and all medicines out of the reach of children.

General information about the safe and effective use of BESREMi.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BESREMi for a condition for which it was not prescribed. Do not give BESREMi to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BESREMi that is written for health professionals.

What are the ingredients in BESREMi?

Active ingredient: ropeginterferon alfa-2b-njft

Inactive ingredients: benzyl alcohol, glacial acetic acid, polysorbate 80, sodium acetate, sodium chloride, and Water for Injection.

Manufactured by: PharmaEssentia Corporation 13F, No. 3, Park Street, Nangang District, Taipei 115, Taiwan
U.S. License number: 2155
Distributed by: PharmaEssentia USA Corporation, 35 Corporate Dr, Suite 325, Burlington, MA 01803, USA

For more information, go to www.BESREMi.com or call 1-800-999-2449

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 08/2026

Doc. No. 1634LPN-Vf-3008-1-E0, Ver. 0, 2025-10-07

Verifine® Snap-Fit

Safety Pen Needles Instructions for Use

INDICATIONS FOR USE/INTENDED USE

The device are disposable, sterile needles intended for use with a pen injector device for the subcutaneous injection of Ropeginterferon alfa-2b-njft. After injection and withdrawal from the body, the safety shield automatically covers the needle to minimize the risk of accidental needle sticks.

FEATURES

The device are sterile, non-pyrogenic, for single use only and may be usedwith most universal threading pen injector devices.

Compatible Pens

PharmaEssentia	BESREMI Pen

PRECAUTIONS

- Safety pen needles are for self-injection and professional use.
- Safety pen needles are single use only. Always use a new, sterile safety pen needle. Do not reuse to avoid cross-contamination.
- Store safety pen needles in a cool and dry place.
- Do not use the safety pen needles if the cover is missing or loose.
- Avoid contaminating the safety pen needle with hand lotion, oils, dirt, or debris.
- Safety pen needles should be disposed of in an appropriate sharps container.
- Do not use the safety pen needles past the expiration date noted on the seal or carton.

IMPORTANT SAFETY INFORMATION

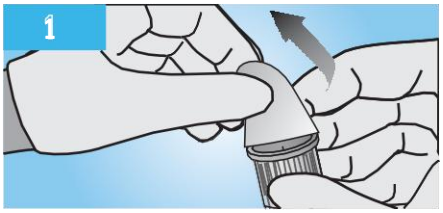
- Before injection, consult the pen injector device manual.
- Do not use if the protective seal is missing or loose, or the needle is bent or damaged.

INSTRUCTIONS FOR USE

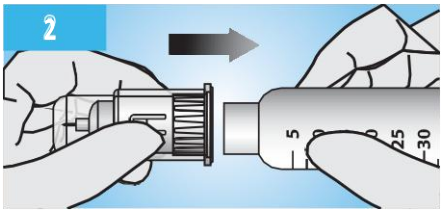
Before injection, consult the pen injector device manual.

If you are using for the first time and have questions, please contact your physician or healthcare professional.

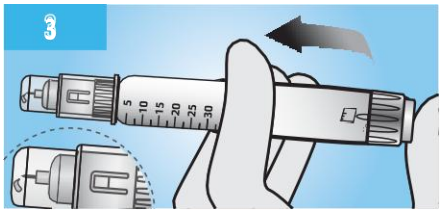
Reference ID: 5880158



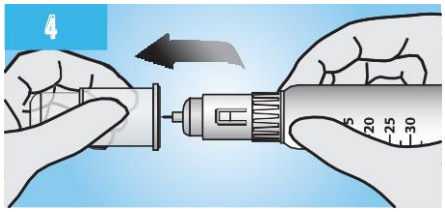
Remove the seal from the safety pen needle.



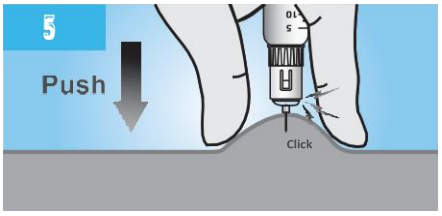
Attach the safety pen needle securely to the pen injector device by twisting clockwise until it stops.



Prime the pen injector device according to the pen injector device instructions for use.

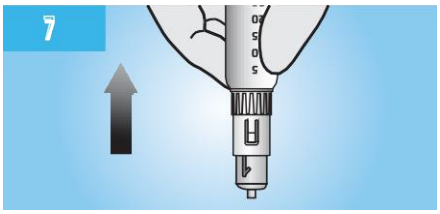


Remove the cover from the safety pen needle to expose the needle.

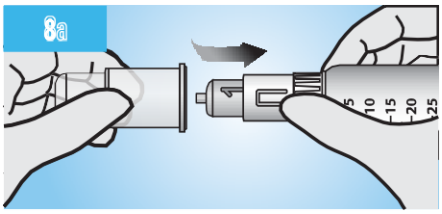


Inject into the skin as recommended by your physician with or without a skin lift.

Hold the injection for 5 to 10 seconds before withdrawal as recommended by your physician to ensure delivery of the full dose and to prevent leakage of medication.



Remove the safety pen needle by lifting straight up from the injection site.



Attach the cover securely by pushing cover over the used needle being careful to avoid a needlestick.

SYMBOLS GLOSSARY

▪ SYMBOL	▪ STANDARD REFERENCE	▪ STANDARD TITLE	▪ SYMBOL TITLE	▪ EXPLANATORY TEXT
LOT	ISO 15223-1: 2021 Reference no. 5.1.5. (ISO 7000-2492)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Batch code	Indicates the manufacturer's batch code so that the batch or lot can be identified. Synonyms for “batch code” are “lot number”, “lot code” and “batch number”.
	ISO 15223-1: 2021 Reference no. 5.1.3. (ISO 7000-2497)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Date of manufacture	Indicates the date when the medical device was manufactured

▪ SYMBOL	▪ STANDARD REFERENCE	▪ STANDARD TITLE	▪ SYMBOL TITLE	▪ EXPLANATORY TEXT
	ISO 15223-1: 2021 Reference no. 5.1.6 (ISO 7000-2493)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Catalogue number / Catalog number	Indicates the manufacturer's catalog number so that the medical device can be identified
	ISO 7000, ISO 7886-3	Graphical symbols for use on equipment	Re-use prevention	A feature that allows one use and prevents further uses.
	ISO 15223-1: 2021 Reference no. 5.1.4. (ISO 7000-2607)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Use-by date Use by date	Indicates the date after which the medical device is not to be used iso_15223 Use-by date iso_grs_7000_2607 Use by date
	ISO15223-1: 2021 Reference no. 5.7.10	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Unique device identifier	Indicates a carrier that contains unique device identifier information
	ISO 15223-1: 2021 Reference no. 5.4.4. (ISO 7000-0434A)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Caution	To indicate that caution is necessary when operating the device or control close to where the symbol is placed, or to indicate that the current situation needs operator awareness or operator action in order to avoid undesirable consequences
	ISO 15223-1:2021 Reference no. 5.2.3. (ISO 7000-2501)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Sterilized using ethylene oxide	Indicates a medical device that has been sterilized using ethylene oxide.
	ISO/DIS 15223- 1:2021 Reference no. 5.2.11. (ISO 7000-3707)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Single sterile barrier system	Indicates a single sterile barrier system
	ISO 15223-1:2021 Reference no. 5.4.2. (ISO 7000- 1051)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Do not re-use	Indicates a medical device that is intended for one single use only NOTE: Synonyms for “Do not reuse” are “single use” and “use only once”.
	ISO 15223-1: 2021 Reference no. 5.2.8. (ISO 7000-2606)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Do not use if package is damaged and consult instructions for use	Indicates a medical device that should not be used if the package has been damaged or opened and that the user should consult the instructions for use for additional information

▪ SYMBOL	▪ STANDARD REFERENCE	▪ STANDARD TITLE	▪ SYMBOL TITLE	▪ EXPLANATORY TEXT
	ISO/DIS 15223- 1:2021 Reference no. 5.7.7	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Medical device	Indicates the item is a medical device
	ISO 15223-1:2021 Reference no. 5.2.6. (ISO 7000- 2608)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Do not resterilize	Indicates a medical device that isnot to be resterilized
	ISO 15223-1:2021 Reference no. 5.4.3. (ISO 7000-1641)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Consult instructions for use or consult electronic instructions for use	Indicates the need for the user to consult the instructions for use iso_15223 Consult instructions for useiso_grs_7000_1641 Operator's manual;operating instructions
	ISO 15223-1: 2021 Reference no. 5.6.3. (ISO 7000-2724)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Non-pyrogenic	Indicates a medical device that isnon-pyrogenic
	/	/	Federal (U.S.A) law restricts this device to sale by or on the order of a physician	N/A
	ISO 7000 Reference no. 0623	Graphical symbols for use on equipment - registered symbols	This way up	N/A
	ISO 15223-1: 2021 Reference no. 5.3.4. (ISO 7000-0626)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Keep dry Keep away from rain	Indicates a medical device that needs protection from moisture ISO 15223 Keep dry ISO 7000 Keep away from rain
	ISO 15223-1: 2021 Reference no. 5.3.2. (ISO 7000-0624)	Medical devices — Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements.	Keep away from sunlight	Indicates a medical device that needs protection from light sources

Explanation of other terms

- **Not made with natural rubber latex**– natural rubber latex was not used as material in the manufacture of the device.
- **Meets ISO 10993** (Cytotoxicity, Skin Irritation, Skin Sensitivity, Acute Systematic Toxicity, Hemolysis and Pyrogenicity)

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www.promisemed-global.com

INSTRUCTIONS FOR USE

BESREMi Pen **[bez-reh-me p-eh-n]**

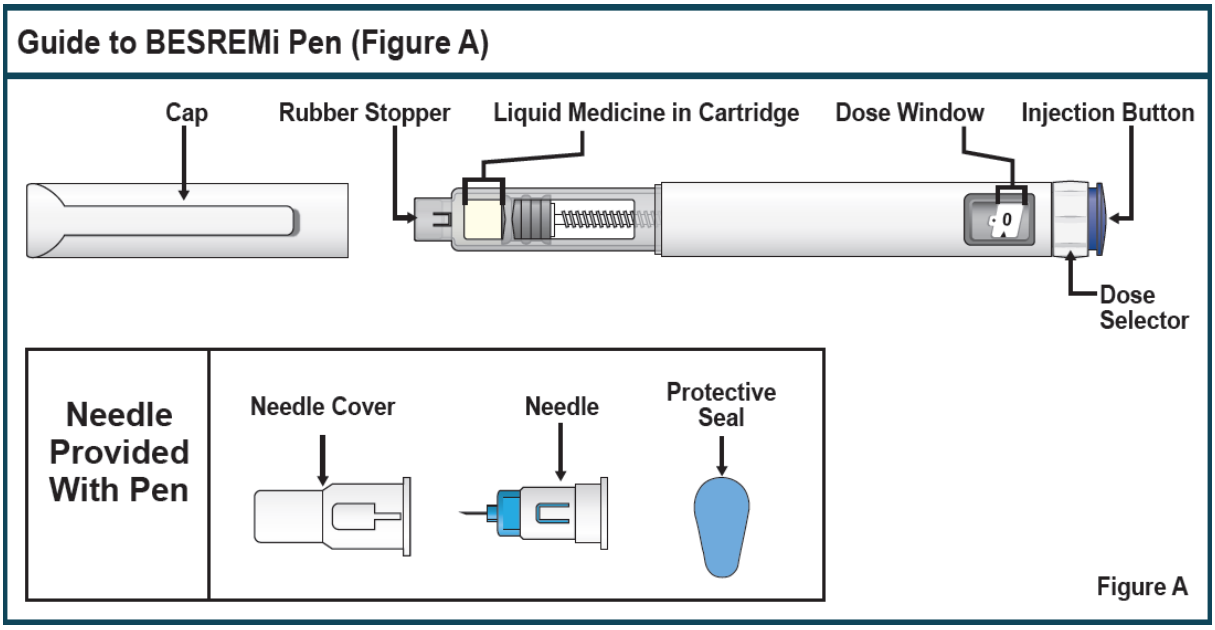
(ropeginterferon alfa-2b-njft)

injection, for subcutaneous use

Single-dose prefilled pen injector

This Instructions for Use contains information on how to prepare and inject BESREMi under your skin (subcutaneous injection) using the single-dose prefilled pen injector.

Guide to BESREMi Pen (Figure A)



Important Information You Need to Know Before Injecting BESREMi Pen

Read this Instructions for Use before using your single-dose BESREMi Pen and each time you get a new prescription. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment. Ask your healthcare provider about the right way to prepare and give your BESREMi injection.

- Your healthcare provider will tell you the prescribed dose that you should take using BESREMi. Each time you inject, be sure that you know the prescribed dose of BESREMi to inject. Your dose may change over time.
- **BESREMi Pens are for one-time use only. A single-use safety needle is provided with the pen and cannot be removed from the pen after attaching. Do not reuse the pen or needle.**
- BESREMi is for subcutaneous (under the skin) injection only. **Do not** inject into a vein.

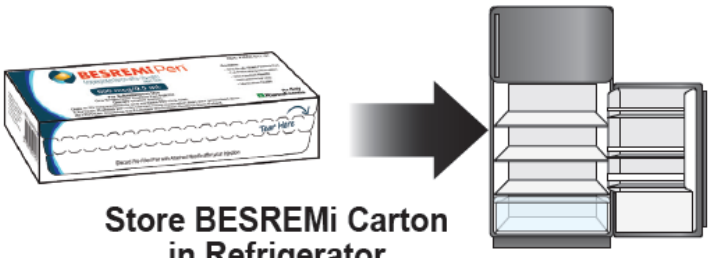
- **Do not** use BESREMi Pen if: it is **damaged or broken**, the **expiration date has passed**, or the **liquid is cloudy, discolored, or contains particles.**
- Contact your pharmacist for a replacement pen or needles.
- Inject BESREMi into the lower stomach (abdomen) area or top of the thighs. **Do not** inject BESREMi into any other area of the body. See Step 5 for injection site information.
- Throw away (dispose of) the BESREMi Pen with the needle attached into a sharps disposal container right away after use, even if there is still medicine in the pen. See Step 14 for disposal instructions.

Storing BESREMi Pen

Store the BESREMi Pen carton in the refrigerator between 36°F to 46°F (2°C to 8°C) (Figure B).

Keep the BESREMi Pen in the original carton to protect it from light (Figure B).

Do not freeze the BESREMi Pen. **Keep the BESREMi Pen, needles, and all medicines out of the reach of children.**



Store BESREMi Carton in Refrigerator

Figure B

Prepare to Inject BESREMi Pen

1 Prepare BESREMi Pen

1.1 Take the BESREMi Pen carton out of the refrigerator (Figure C).

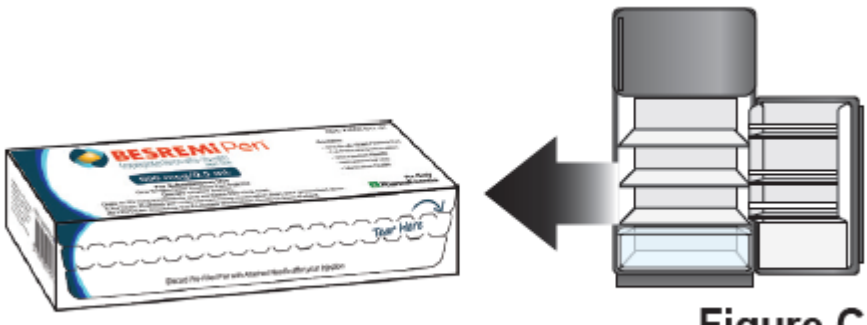
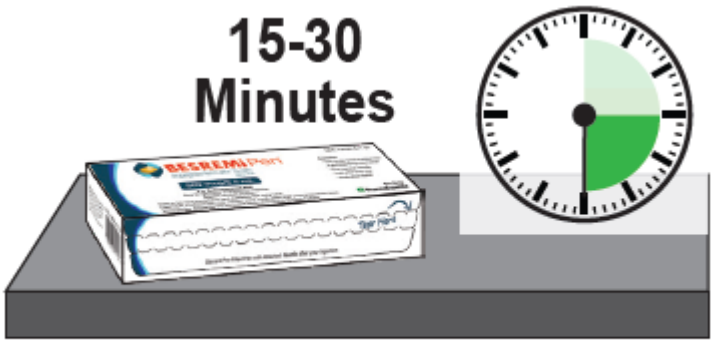
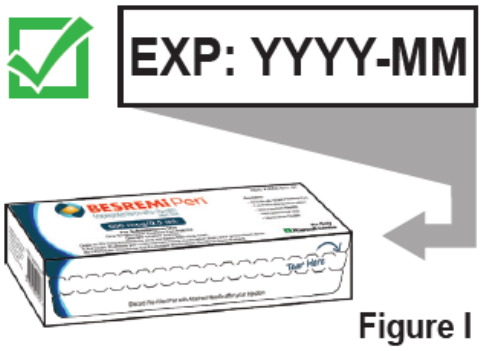
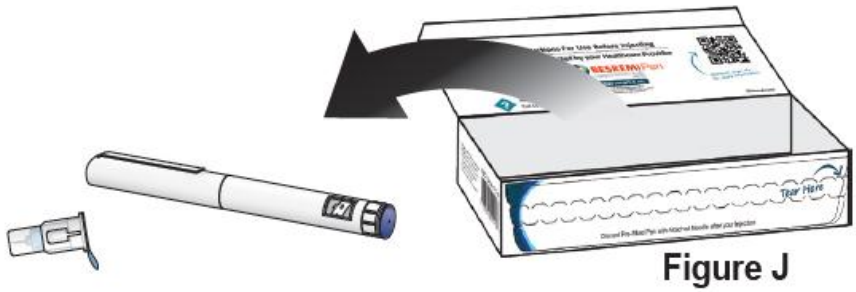
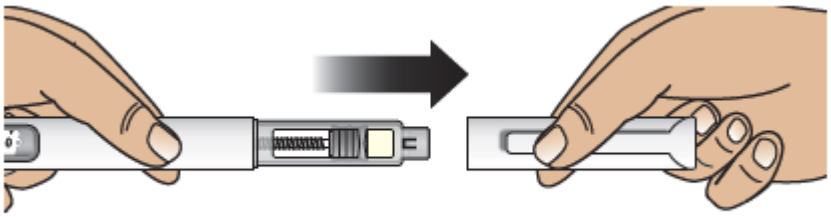
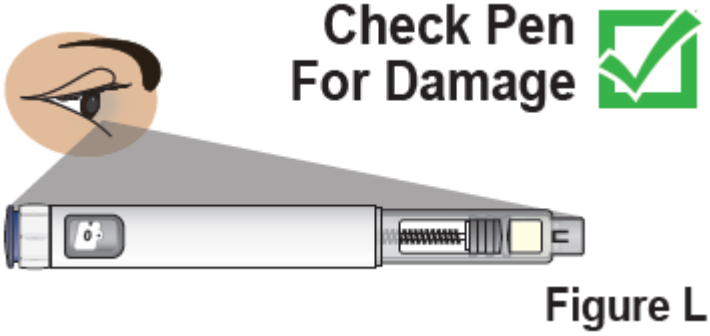


Figure C

1.2 Let the carton containing the BESREMi Pen sit on a flat, clean work surface for **15 to 30 minutes to allow it to come to room temperature between 59˚F to 77 ˚F (15 ˚C to 25 ˚C).** (Figure D). **Do not** warm the BESREMi Pen any other way.	 Figure D
2 Gather supplies for injection	

2.1 After allowing the BESREMi Pen to come to room temperature, **gather the following additional supplies** not provided in the BESREMi Pen carton (Figure E, Figure F, and Figure G).	• **Alcohol**  **Figure E** • **Sharps Disposal Container**  **Figure F** • **Optional Items:** Gauze or Cotton Ball and a Small Adhesive  **Figure G**
3. Wash hands, check expiration date, and remove BESREMi Pen from carton	
3.1 Wash your hands with soap and water, then dry your hands (Figure H).	 **Figure H**
3.2 Check the expiration date (EXP) on the carton to make sure it has not passed (Figure I).	

Do not use the BESREMi Pen if the expiration date has passed.	 Figure I
3.3 Open the carton and **remove the BESREMi Pen and needle** (Figure J).	 Figure J
4 Remove the pen cap, check BESREMi Pen, and check liquid medicine	
4.1 Remove the pen cap by pulling it straight off the BESREMi Pen (Figure K) and throw away.	 Figure K
4.2 Check the BESREMi Pen to see if it is damaged or broken (Figure L). **Do not** use the BESREMi Pen if it shows any signs of damage or breakage.	 Figure L

4.3 Check the liquid medicine in the BESREMi Pen (Figure M). The liquid should appear clear and colorless to slightly yellow in color.

Do not use the BESREMi Pen if the liquid is cloudy, discolored, or contains particles.

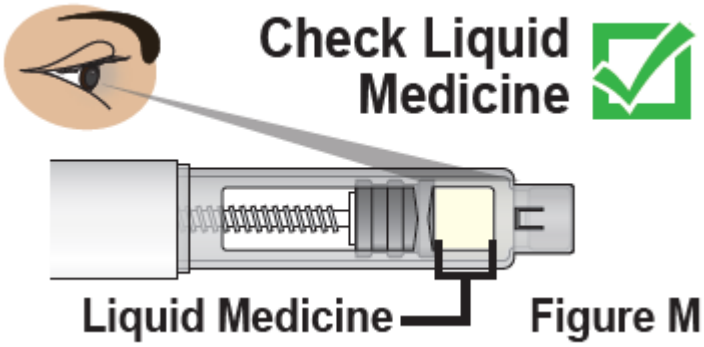


Figure M

5 Choose and clean injection site

5.1 Choose one of the following injection sites (Figure N):

- **Lower stomach (abdomen)** area, at least 2 inches away from the belly button, or
- **Top of thighs.**

Rotate (change) the injection site for each injection.

Do not inject into skin that is irritated, red, bruised, infected, or scarred.

Do not inject into a vein. BESREMi Pen is for subcutaneous (under the skin) injection only.

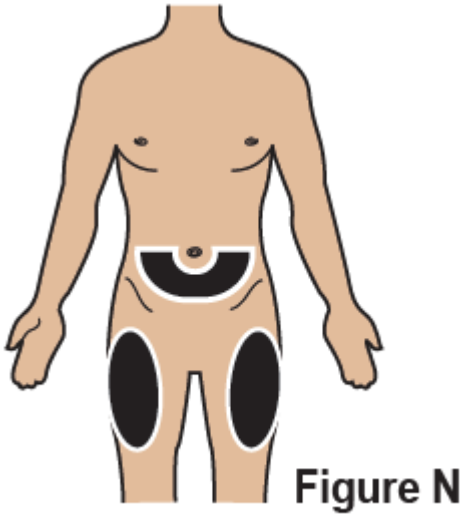
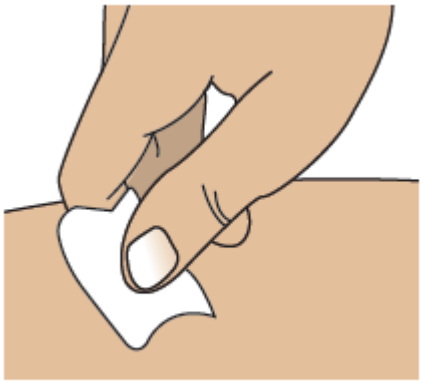
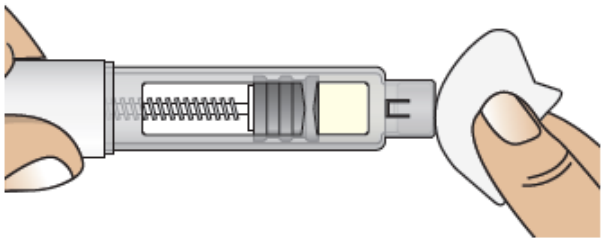
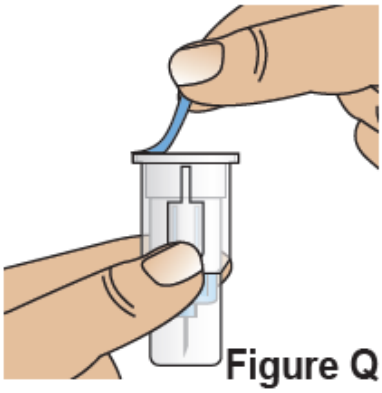
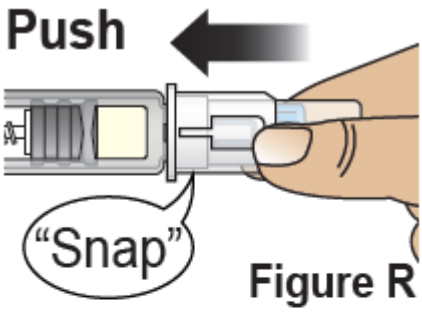
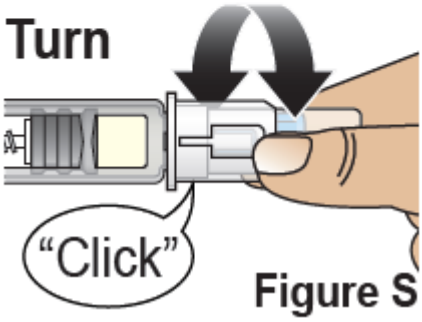
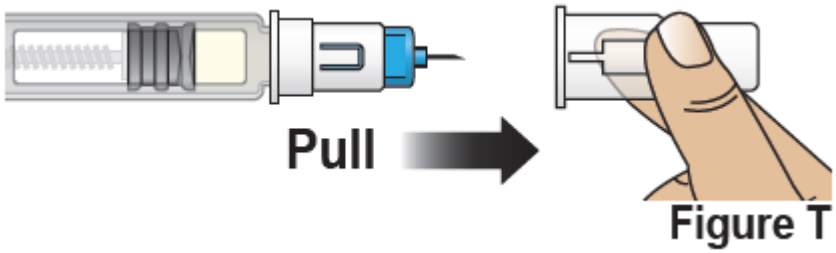
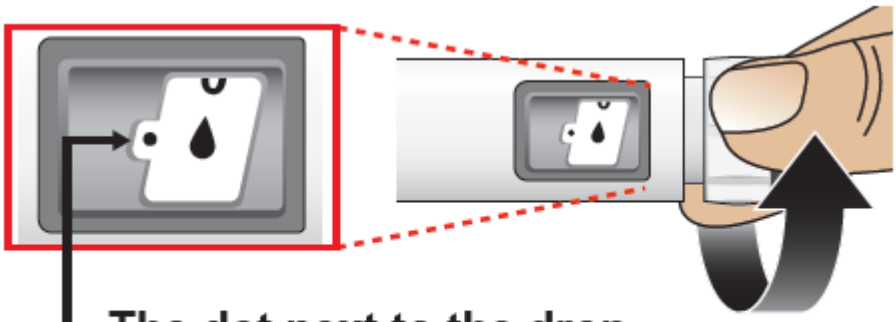
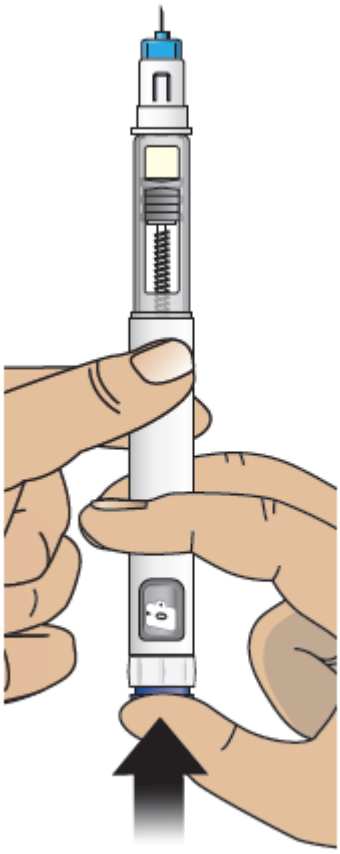


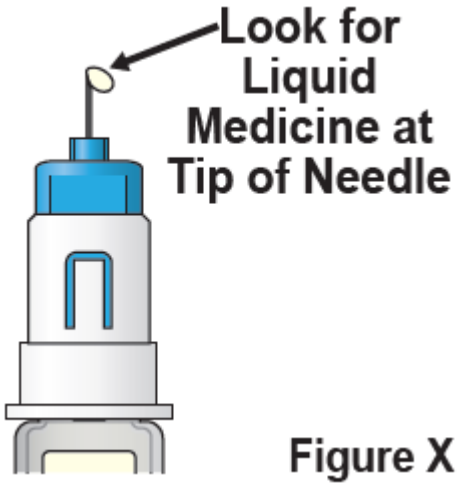
Figure N

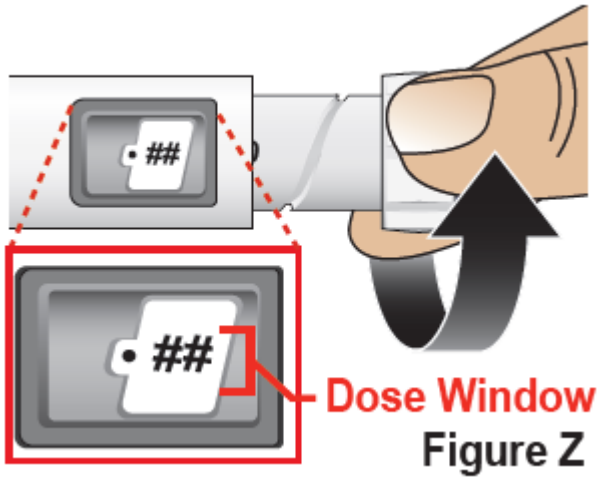
5.2 Clean the chosen injection site with an alcohol swab and let it air dry (Figure O). Throw away the alcohol swab after use. **Do not** blow on or touch the cleaned injection site.	 Figure O

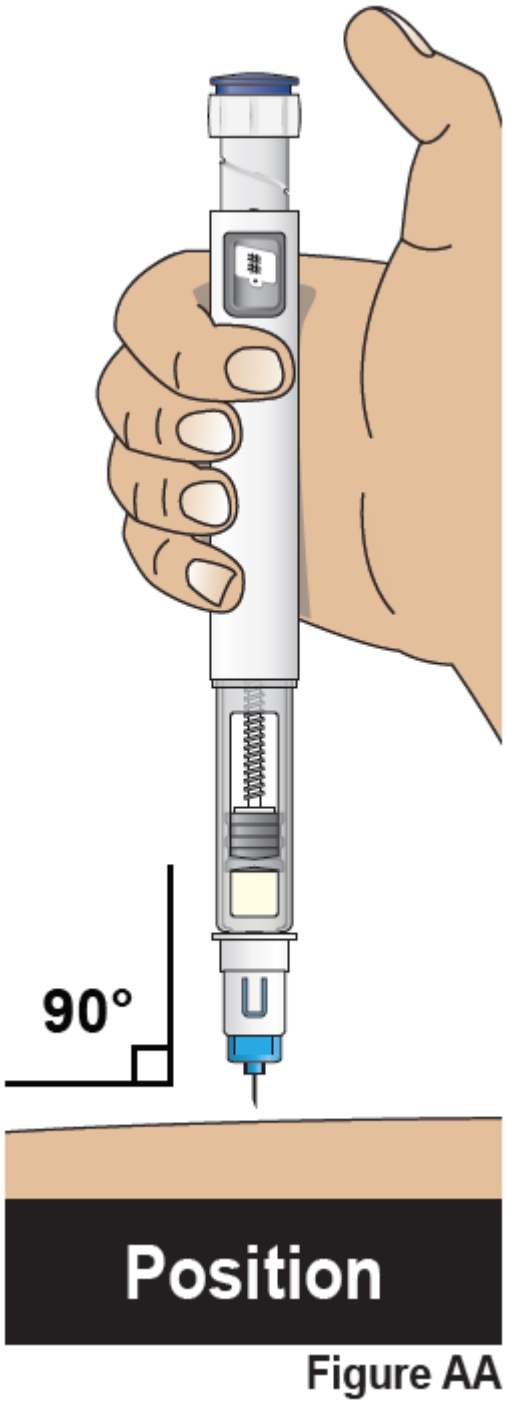
6 Clean the rubber stopper and peel off needle seal	
6.1 Clean the rubber stopper on the tip of the pen with a new alcohol swab (Figure P). Throw away the alcohol swab after use.	 Figure P
6.2 Peel off the protective seal from the needle and throw it away (Figure Q).	 Figure Q
7 Attach the needle to the BESREMi Pen and remove the needle cover	
7.1 Attach the capped needle by pushing it straight onto the BESREMi Pen **until you feel or hear it "snap"** into place (Figure R). **Turn or rotate** the needle in either direction **until it "clicks"** into place (Figure S). The needle is attached when it no longer turns or rotates freely.	 Figure R  Figure S

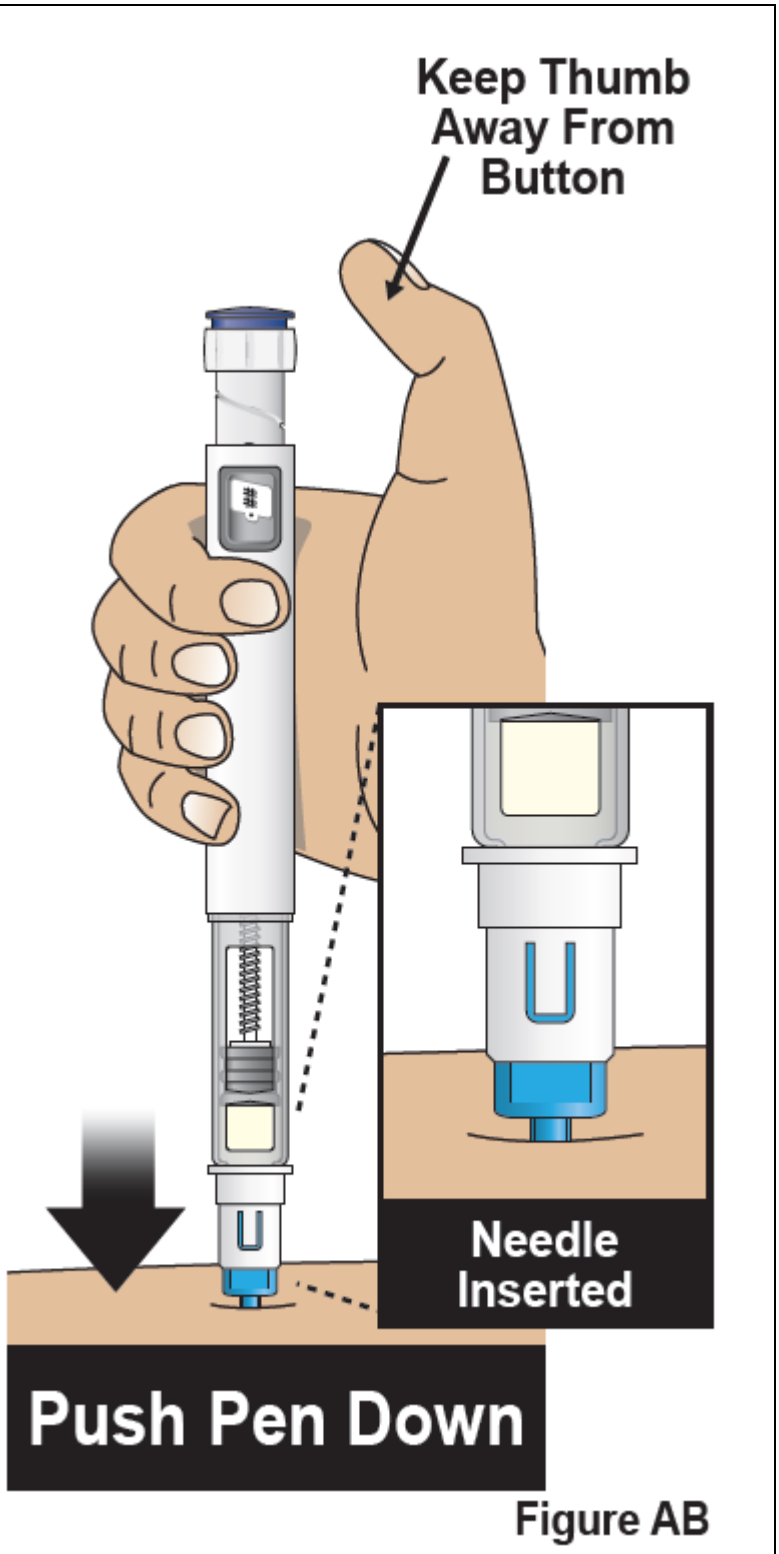
7.2 Remove the needle cover by **pulling it off** (Figure T) and throw it away. **Do not** recap the needle.	 Figure T
Remove Air	
8 Remove air from the drug Cartridge	
8.1 Turn the dose selector until the flow check **drop symbol** "💧" **is centered** in the dose window (Figure U). **Do not** dial your prescribed dose when doing the flow check. You will be instructed to do so in Step 10.1.	 Figure U

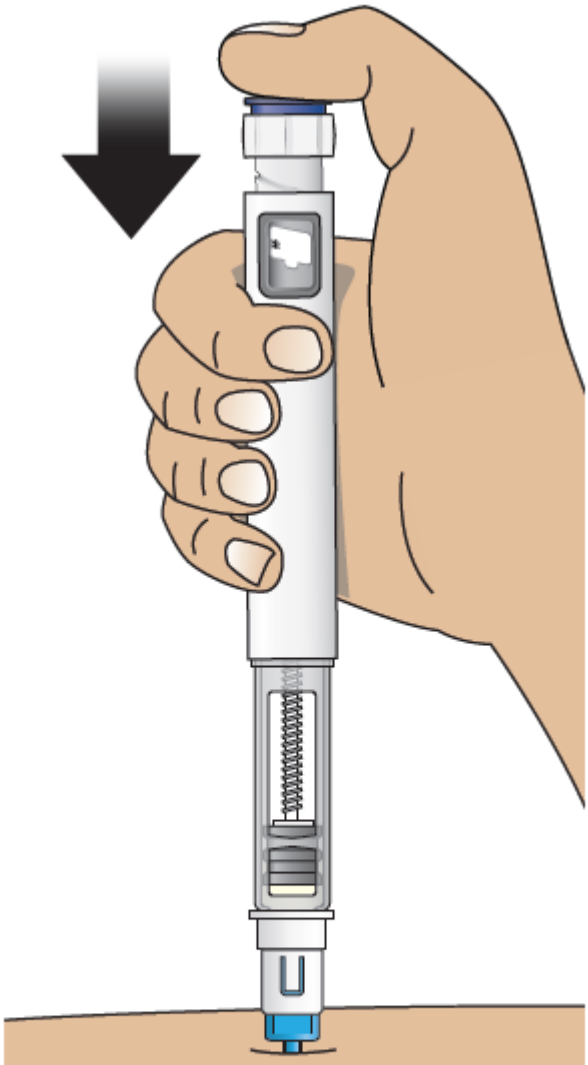
8.2 Hold the BESREMi Pen with the needle pointing up (Figure V). **8.3 Press and hold the injection button** all the way in until the dose window returns to “0” (Figure V).	 Figure V
8.4 Repeat Steps 8.1 to 8.3 (dial to drop symbol and press injection button) **3 more times for a total of 4 cycles** (Figure W)**.**	 Figure W
9 Check needle for liquid medicine	

9.1 After 4 cycles (see step 8.4), **check the tip of the needle** to make sure there is liquid medicine (Figure X).	 Figure X
9.2 If you do not see liquid at the tip of the needle, repeat Steps 8.1 to 8.3 again (dial to drop symbol and press injection button) **up to 3 more times for a total of 7 cycles.** **Important: If you still do not see liquid at the tip of the needle after 7 cycles,** get a new BESREMi Pen carton and start over from Step 1.	
Inject BESREMi Pen	
10 Set your dose	
10.1 Check your prescription to make sure you know your prescribed dose (Figure Y). You will need to set your prescribed dose before giving the injection.	 Figure Y

10.2 Set your dose by turning the dose selector clockwise until the prescribed dose is centered in the dose window (Figure Z). It is normal to hear a clicking sound as you dial. **Check to make sure the number in the dose window is the correct prescribed dose before giving the injection.** If you accidentally turn the dose selector past the prescribed dose, turn the dose selector back to the correct dose.	 Figure Z

11 Insert the needle	
11.1 Hold the BESREMi Pen over the cleaned injection site at a 90-degree angle (Figure AA).	 Figure AA

11.2 Without touching the injection button, **push the BESREMi Pen down to fully insert the needle into the skin** (Figure AB).	 Figure AB

12 Give injection	
12.1 Press and hold the injection button all the way down until it stops. The number in the dose window will go back to “0” (Figure AC).	 Figure AC

12.2 Keep holding the injection button down after the dose window returns to "0" and count to 5 to make sure the full dose is delivered (Figure AD).

Note: There may still be liquid remaining in the pen cartridge after the injection. This is normal.

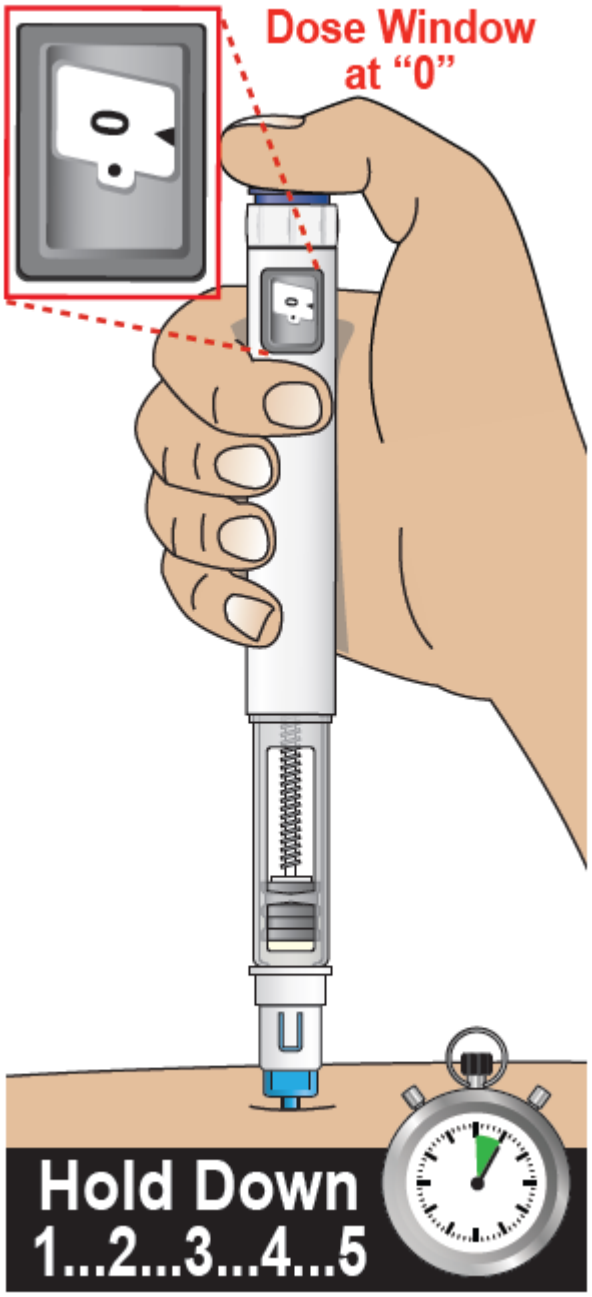
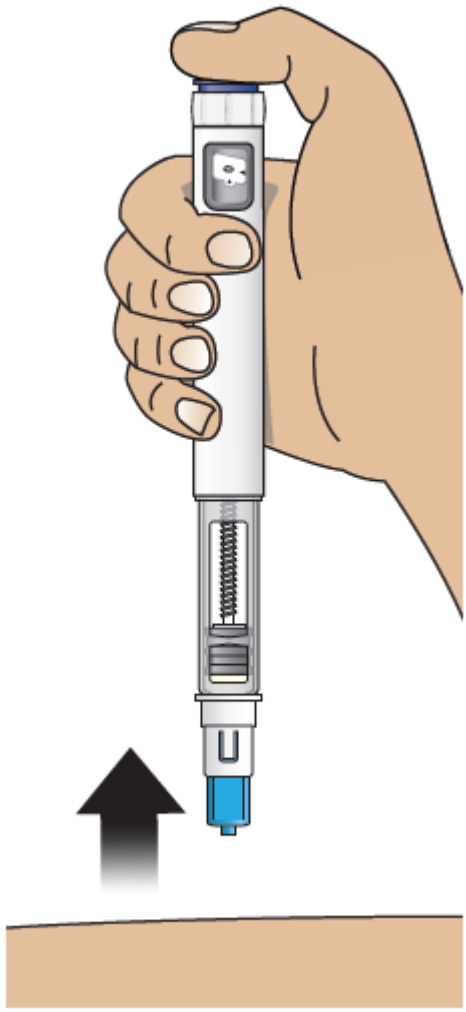
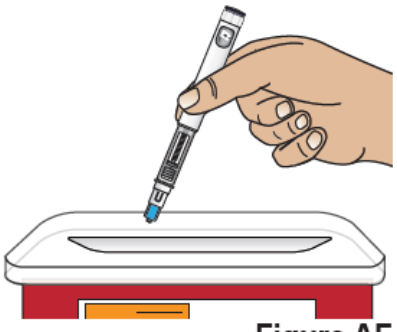


Figure AD

Dispose of Used BESREMi Pen

13 Remove needle from skin

13.1 Remove the needle from the skin by lifting the pen straight up (Figure AE). The blue needle shield will cover the needle.	 Figure AE
14 Throw away (dispose of) pen and treat injection site	
14.1 Put the used BESREMi Pen, **with the needle still attached,** into a sharps disposal container right away after use (Figure AF). **Important: Do not** recap the needle or attempt to remove it.	 Figure AF

Do not reuse the BESREMi Pen. **Throw it away in a sharps disposal container after use,** even if there is still medicine left in the BESREMi Pen.	

- If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- **Always keep the sharps disposal container out of the reach of children.**

14.2 If there is a small amount of blood or liquid at the injection site, press a gauze or cotton ball over the injection site until the bleeding stops (Figure AG). If needed, you may apply a small adhesive bandage. **Do not** rub the injection site.	 Figure AG

Additional Information

For additional information about BESREMi Pen and a video demonstration on how to use BESREMi Pen, go to:
www.BESREMi.com

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INSTRUCTIONS FOR USE

BESREMi Pen [bez-reh-me p-eh-n]
(ropeginterferon alfa-2b-njft)
injection, for subcutaneous use

Single-dose prefilled pen injector

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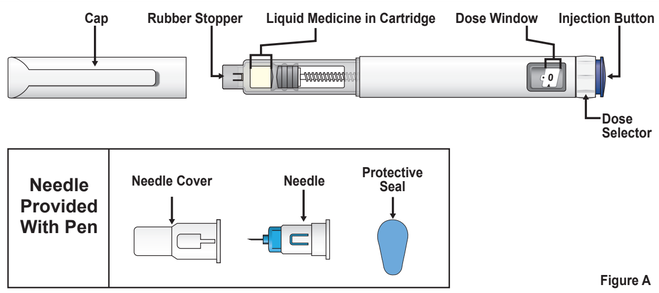

Figure A

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- Inject BESREMi into the lower stomach (abdomen) area or top of the thighs. **Do not** inject BESREMi into any other area of the body. See Step 5 for injection site information.
- Throw away (dispose of) the BESREMi Pen with the needle attached into a sharps disposal container right away after use, even if there is still medicine in the pen. See Step 14 for disposal instructions.

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Keep the BESREMi Pen, needles, and all medicines out of the reach of children.

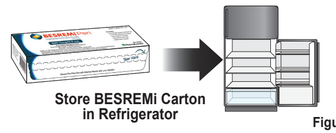

Figure B

Prepare to Inject BESREMi Pen

1 Prepare BESREMi Pen

1.1 Take the BESREMi Pen carton out of the refrigerator (Figure C).

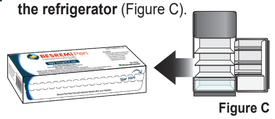

Figure C

1.2 Let the carton containing the BESREMi Pen sit on a flat, clean work surface for **15 to 30 minutes to allow it to come to room temperature between 59°F to 77°F (15°C to 25°C).** (Figure D).

Do not warm the BESREMi Pen any other way.

Figure D

2 Gather supplies for injection

2.1 After allowing the BESREMi Pen to come to room temperature, **gather the following additional supplies** not provided in the BESREMi Pen carton (Figure E, Figure F, and Figure G).

- **Alcohol**

Figure E

- **Sharps Disposal Container**

Figure F

- **Optional Items:** Gauze or Cotton Ball and a Small Adhesive

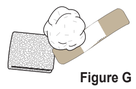

Figure G

3 Wash hands, check expiration date, and remove BESREMi Pen from carton

3.1 Wash your hands with soap and water, then dry your hands (Figure H).

Figure H

3.2 Check the expiration date (EXP) on the carton to make sure it has not passed

Do not use the BESREMi Pen if the expiration date has passed.

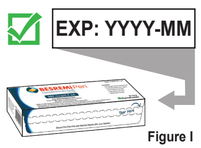

Figure I

3.3 Open the carton and **remove the BESREMi Pen and needle** (Figure J).

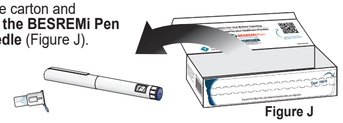

Figure J

4 Remove the pen cap, check BESREMi Pen, and check liquid medicine

4.1 Remove the pen cap by pulling it straight off the BESREMi Pen (Figure K) and throw away.

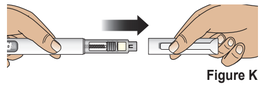

Figure K

4.2 Check the BESREMi Pen to see if it is damaged or broken (Figure L).

Do not use the BESREMi Pen if it shows any signs of damage or breakage.

Figure L

4.3 Check the liquid medicine in the BESREMi Pen (Figure M). The liquid should appear clear and colorless to slightly yellow in color.

Do not use the BESREMi Pen if the liquid is cloudy, discolored, or contains particles.

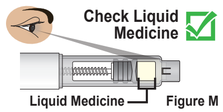

Figure M

5 Choose and clean injection site

5.1 Choose one of the following injection sites (Figure N):

- **Lower stomach (abdomen)** area, at least 2 inches away from the belly button, or
- **Top of thighs.**

Rotate (change) the injection site for each injection.

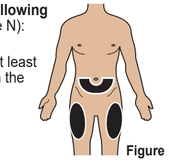

Figure N

Do not inject into skin that is irritated, red, bruised, infected, or scarred.

Do not inject into a vein. BESREMi Pen is for subcutaneous (under the skin) injection only.

5.2 Clean the chosen injection site with an alcohol swab and let it air dry (Figure O). Throw away the alcohol swab after use.

Do not blow on or touch the cleaned injection site.

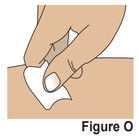

Figure O

6 Clean the rubber stopper and peel off needle seal

6.1 Clean the rubber stopper on the tip of the pen with a new alcohol swab (Figure P).

Throw away the alcohol swab after use.

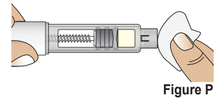

Figure P

6.2 Peel off the protective seal from the needle and throw it away (Figure Q).

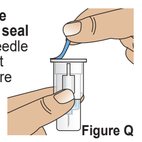

Figure Q

7 Attach the needle to the BESREMi Pen and remove the needle cover

7.1 Attach the capped needle straight onto the BESREMi Pen **until you feel or hear it "snap"** into place (Figure R).

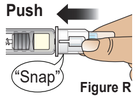

Figure R

Turn or rotate the needle in either direction **until it "clicks"** into place (Figure S).

The needle is attached when it no longer turns or rotates freely.

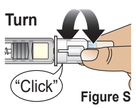

Figure S

7.2 Remove the needle cover by **pulling it off** (Figure T) and throw it away.

Do not recap the needle.

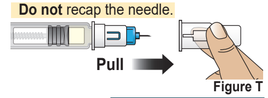

Figure T

Remove Air

8 Remove air from the drug Cartridge

8.1 Turn the dose selector until the flow check **drop symbol "💧" is centered** in the dose window (Figure U).

Do not dial your prescribed dose when doing the flow check. You will be instructed to do so in Step 10.1

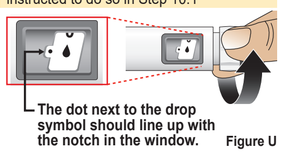

Figure U

8.2 Hold the BESREMi Pen with the needle pointing up (Figure V).

8.3 Press and hold the injection button all the way in until the dose window returns to "0" (Figure V).

8.4 Repeat Steps 8.1 to 8.3 (dial to drop symbol and then press injection button) **3 more times for a total of 4 cycles** (Figure W).

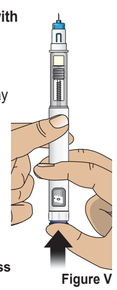

Figure V

Figure W

9 Check needle for liquid medicine

9.1 After 4 cycles (see step 8.4), **check the tip of the needle** to make sure there is liquid medicine (Figure X).

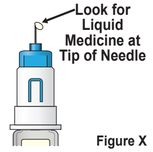

Figure X

9.2 If you do not see liquid at the tip of the needle, repeat Steps 8.1 to 8.3 again (dial to drop symbol and press injection button) **up to 3 more times for a total of 7 cycles.**

Important: If you still do not see liquid at the tip of the needle after 7 cycles, get a new BESREMi Pen carton and start over from Step 1.

Inject BESREMi Pen

10 Set your dose

10.1 Check your prescription to make sure you know your prescribed dose (Figure Y). You will need to set your prescribed dose before giving the injection.

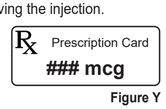

Figure Y

10.2 Set your dose by turning the dose selector clockwise until the prescribed dose is centered in the dose window (Figure Z).

It is normal to hear a clocking sound as you dial.

Check to make sure the number in the dose window is the correct prescribed dose before giving the injection.

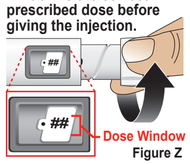

Figure Z

If you accidentally turn the dose selector past the prescribed dose, turn the dose selector back to the correct dose.

11 Insert the needle

11.1 Hold the BESREMi Pen over the cleaned injection site at a 90-degree angle (Figure AA).

11.2 Without touching the injection button, **push the BESREMi Pen down to fully insert the needle into the skin** (Figure AB).

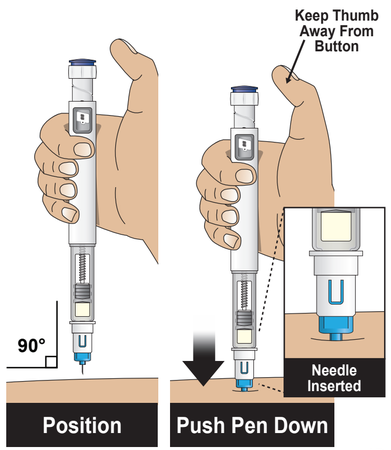

Figure AA

Figure AB

12 Give injection

12.1 Press and hold the injection button all the way down until it stops. The number in the dose window will go back to "0" (Figure AC).

12.2 Keep holding the injection button down after the dose window returns to "0" and count to 5 to make sure the full dose is delivered (Figure AD).

Note: There may still be liquid remaining in the pen cartridge after the injection. This is normal.

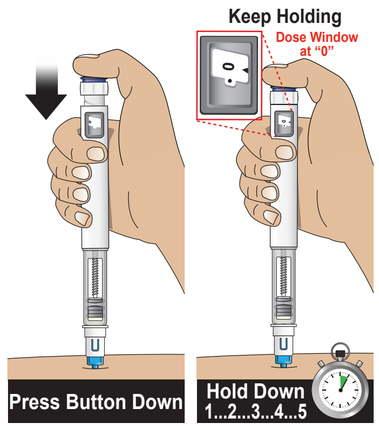

Figure AC

Figure AD

Dispose of Used BESREMi Pen

13 Remove needle from skin

13.1 Remove the needle from the skin by lifting the pen straight up (Figure AE).

The blue needle shield will cover the needle.

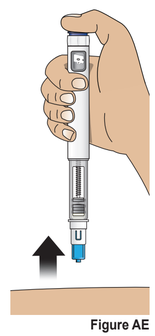

Figure AE

14 Throw away (dispose of) pen and treat injection site

14.1 Put the used BESREMi Pen, **with the needle still attached**, into a sharps disposal container right away after use (Figure AF).

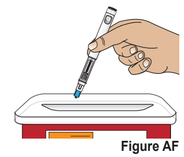

Figure AF

Important: Do not recap the needle or attempt to remove it.

Do not reuse the BESREMi Pen. **Throw it away in a sharps disposal container after use**, even if there is still medicine left in the BESREMi Pen.

If you do not have a sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container.

There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

14.2 If there is a small amount of blood or liquid at the injection site, press a gauze or cotton ball over the injection site until the bleeding stops (Figure AG).

If needed, you may apply a small adhesive

Do not rub the injection site.

Figure AG

Additional Information

For additional information about BESREMi Pen and a video demonstration on how to use BESREMi Pen, go to: www.BESREMi.com

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