Summary Report of Benefit-Risk Assessment

BESREMI SOLUTION FOR INJECTION IN PREFILLED SYRINGE 500 MICROGRAMS/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Ropeginterferon alfa-2b
Product Registrant	Pharmaessentia Singapore Pte. Ltd
Product Registration Number	SIN17014P
Application Route	Abridged evaluation
Date of Approval	29 May 2024

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A INTRODUCTION

Besremi is indicated as monotherapy in adults for the treatment of polycythemia vera (PV).

The active substance, ropeginterferon alfa-2b, is a long-acting, mono-pegylated proline-interferon (IFN) alpha-2b. In polycythemia vera, interferon alfa binds to a transmembrane receptor (interferon alfa receptor [IFNAR]), which initiates a downstream signalling cascade through the activation of Janus kinase 1 (JAK1), tyrosine kinase 2 (TYK2), and signal transducer and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls gene-expression and results in various cellular effects.

Besremi is available as solution for injection containing 500 micrograms/mL of ropeginterferon alfa-2b in a prefilled syringe. Other ingredients in the syringe are benzyl alcohol, glacial acetic acid, polysorbate 80, sodium acetate, sodium chloride, and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, ropeginterferon alfa-2b, is manufactured at PharmaEssentia Corporation, Taichung Plant, Taiwan. The drug product, Besremi solution for injection in prefilled syringe 500 micrograms/ mL, is manufactured at the same site.

Drug substance:

Adequate controls have been presented for the cell substrate, intermediates and raw materials. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications are established in accordance with ICH Q6B guidelines, and the impurity limits have been appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 (R2) guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The packaging is type I glass bottle. The stability data presented was adequate to support the storage of the drug substance at 5ºC ± 3ºC for a shelf-life of 12 months.

Drug product:

The manufacturing process involves pooling and dilution of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B guidelines and impurity limits have been adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 (R2) guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The container closure system is type I glass prefilled syringes. The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at 2-8ºC.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of ropeginterferon alfa-2b in the treatment of PV was based primarily on one pivotal Phase I/II study, PEGINVERA. The Phase III study, PROUD-PV, despite being designed as an active comparator study, had significant design deficiencies that rendered its results uninterpretable, thus could not be appropriately accepted as supporting evidence for the requested indication.

PEGINVERA study

The PEGINVERA study was an open-label, multicentre, single-arm, Phase I/II dose escalation study conducted in two stages. Stage 1 aimed to determine the maximum tolerated dose (MTD) of ropeginterferon alfa-2b using a 3+3 design in patients with PV. Stage 2 was designed to determine the long-term efficacy and safety of ropeginterferon alfa-2b at individually adjusted optimum dose levels. The study's planned duration was 3 years, while for patients who responded to and tolerated the treatment well were to continue treatment for up to 7.5 years. Despite the absence of a comparator, the study design was acceptable considering the natural history of PV where spontaneous remission does not occur randomly.

In stage 1, the MTD was determined using the 3+3 design, exploring the following dose levels for ropeginterferon alfa-2b administered via subcutaneous injection: 50 µg, 100 µg, 150 µg, 225 µg, 300 µg, 360 µg, 450 µg and 540 µg. As no dose-limiting toxicity was observed, the MTD was determined to be 540 µg.

In stage 2, doses of ropeginterferon alfa-2b were escalated from 100 to 450 mcg every 2 weeks, provided that treatment remained effective and tolerable. Patients not undergoing any active treatment and patients currently treated with hydroxyurea (HU) could be included in stage 2. For patients concomitantly using HU while being titrated to the next dose of ropeginterferon alfa-2b, the dose of HU was reduced by 20-40% every two weeks, depending on the patients' blood parameters. HU was to be completely discontinued by the end of Week 12. Prior to the first administration of ropeginterferon alfa-2b, all patients were phlebotomised until haematocrit (HCT) levels reached ≤45%. Subsequently, phlebotomies were only allowed as rescue therapy if the HCT level exceeded 45%. Patients who participated in the first 12 months of treatment on the once every 14-day schedule were eligible for administration of ropeginterferon alfa-2b every 4 weeks after 12 months.

The primary efficacy endpoint was haematological response rate, defined as complete haematological response (CHR) or partial haematological response (PHR). CHR was defined as HCT <45% without phlebotomy in the previous two months, platelet (PLT) count ≤400 x 10^9/L, white blood cell (WBC) count ≤10 x 10^9/L, normal spleen size measured by ultrasound

(longitudinal diameter ≤12 cm for females and ≤13 cm for males) and absence of thromboembolic events. PHR was defined as HCT <45% without phlebotomy but with persistent splenomegaly or elevated (>400 x 10^9/L) PLT count or reduction of phlebotomy requirements by at least 50%. Patients on concomitant HU were considered complete responders two weeks after their last HU administration. The key secondary efficacy endpoint was molecular response rate, with complete molecular response defined as the reduction of any molecular abnormality to undetectable levels and partial molecular response defined as reduction of ≥50% in patients with <50% JAK2 mutant allele burden, or reduction of ≥25% in patients with >50% JAK2 mutant allele burden. All study data were analysed using descriptive statistical procedures.

The study enrolled a total of 51 patients (25 in stage 1 and an additional 26 patients in stage 2). Of these, 46 patients who did not have major protocol violations were included in the full analysis set (FAS) for efficacy analysis.

The median age was 56 years (range 35 to 82 years), with 42% of patients aged 65 years and above. There were more males (60.8%), and the majority of patients (98.0%) were Caucasian. At baseline, 84.3% had known disease history with a mean disease duration of 51 months and 15.7% were newly diagnosed. All subjects had the JAK2V617F mutation present at baseline, and 33.3% were on treatment with HU. Enlarged spleens were observed in 51.6% of male patients and 60.0% of female patients. Baseline mean haematological values were: HCT 44.8%, PLT count 457.9 x 10^9/L, and WBC count 11.8 x 10^9/L.

Summary of key efficacy results (PEGINVERA)

	Ropeginterferon alfa-2b
Primary endpoint	
Best observed individual hematological response, n	42*
Complete hematological response, n (%)	27 (64.3%)
Partial hematological response, n (%)	14 (33.3%)
Secondary endpoints	
Best observed individual molecular response, n	42*
Complete molecular response, n (%)	12 (28.6%)
Partial molecular response, n (%)	19 (45.2%)
Changes in individual laboratory parameters from baseline by Week 50	
Absolute WBC count, mean	Decreased from 11.8 x 10^9/L to 5.8 x 10^9/L
HCT, mean	Decreased from 45.1% to 43.05%
PLT, mean	Decreased from 455.9 x 10^9/L to 246.6 x 10^9/L.

* Four patients in the FAS discontinued study drug before first assessment visit at Week 10, therefore only 42 patients were included in the response analysis.

The best observed individual haematological response[1] was a CHR for 27 out of 42 patients (64.3%). The median duration of response was 14.3 months, with a median time to CHR of approximately 34 weeks of treatment with ropeginterferon alfa-2b. In the subgroup of HU-pretreated patients, the best observed individual haematological response was a CHR for 11 out of 13 patients (84.6%), while in HU-naïve patients, the best observed individual response was a CHR for 16 out of 29 (55.2%) patients.

In terms of secondary endpoints, the best observed individual molecular response was a complete molecular response for 12 out of 42 patients (28.6%). By Week 50, a reduction from baseline was demonstrated for the individual laboratory parameters: the mean absolute WBC

[1] Best individual response is defined as the most favourable response achieved by a patient at any time point during the study period, regardless of the duration of that response.

count decreased from 11.8 x 10^9/L to 5.8 x 10^9/L, the mean HCT reduced from 45.1% to 43.05%, and the mean PLT count dropped from 455.9 x 10^9/L to 246.6 x 10^9/L. The reasonably high CHR of 64.3% and the observed reductions in the haematological parameters from baseline were unlikely due to spontaneous remissions given the natural history of PV.

PROUD-PV study

The PROUD-PV study was an open-label, randomised, controlled Phase III study comparing the efficacy and safety of ropeginterferon alfa-2b versus HU in the treatment of PV over 12 months. Patients were randomised to receive either ropeginterferon alfa-2b or HU. Ropeginterferon alfa-2b was administered subcutaneously at a starting dose of 100 µg every 2 weeks and titrated up to a maximum dose of 500 µg every 2 weeks for a treatment duration of up to 12 months. Patients concurrently receiving HU who were randomised into the ropeginterferon alfa-2b arm initiated treatment at a lower starting dose of 50 µg and had their HU dose gradually decreased over a 12-week period until completely discontinued. In the HU arm, the drug was administered orally at a starting dose of 500 mg daily for the first 2 weeks and titrated to a maximum tolerated dose of 3000 mg daily. Concomitant low dose aspirin (100 mg/day) was administered to all patients, unless contraindicated. The use of HU as an active comparator was acceptable as the drug is recommended in established clinical practice guidelines as first-line cytoreductive therapy for the treatment of PV.

Multiple amendments were made to the study design post-hoc, potentially leading to biased results. The primary efficacy endpoint was initially defined as disease response rate at 12 months, comprising CHR and normal spleen size. CHR was defined as HCT <45% for at least 3 months since last phlebotomy, PLTs <400 x 10^9/L and WBC <10 x 10^9/L. Normal spleen size was defined as a longitudinal diameter of <12 cm for females and <13 cm for males. However, the key secondary endpoint, which was the disease response rate at 12 months based solely on CHR without the spleen size criteria, was subsequently converted to the primary endpoint post-hoc. According to the applicant, this change was made for several reasons: nearly half of the patients had normal spleen size at baseline, with the remainder having only marginally increased spleen size; significantly enlarged spleens (>17 cm according to the European LeukemiaNet [ELN] criteria) were evident in only 9.4% and 11.8% of patients in the ropeginterferon alfa-2b and HU arms, respectively; observed changes in spleen size were marginal and not clinically relevant in both treatment arms; less than 5% of patients had symptomatic splenomegaly, with clinical symptoms not correlating with spleen size; and no formal threshold had been established for 'spleen normality'. The initial objective of the study was to demonstrate superiority of ropeginterferon alfa-2b over HU in disease response rate. However, upon study completion, the study objective was revised to demonstrate non-inferiority, initially with a margin of 10.5%, and subsequently widened to 20.0%.

A total of 257 patients were randomised in the study, with 254 patients receiving at least one dose and included in the FAS: 127 in the ropeginterferon alfa-2b arm and 127 in the HU arm. Of these, 229 patients (115 in the ropeginterferon alfa-2b arm and 114 in the HU arm) were eligible for the per-protocol set (PPS). The FAS was the primary analysis set used for efficacy analyses while the PPS was used for sensitivity analyses.

The median age was 60 years (range 21 to 85 years), with approximately 48% of patients over 60 years old. There were 46.9% of male patients and 53.1% of female patients. The median duration of PV was 1.9 months (range 0 to 146 months) in the ropeginterferon alfa-2b arm and 3.6 months (range 0 to 126 months) in the HU arm. In the ropeginterferon alfa-2b arm, 45 patients (35.4%) were pre-treated with HU, with a median duration of previous treatment with HU of 10.2 months (range 1 to 34 months). In the HU arm, 37 patients (29.1%) were pre-

treated with HU, with a median duration of previous treatment with HU of 7.9 months (range 1 to 36 months). Baseline haematological parameters were comparable between the two treatment arms: mean HCT was around 49.5% and 49.8% in the ropeginterferon alfa-2b and HU arms respectively. Mean WBCs (12.19 vs 12.56 x 10^9/L) and PLTs (556.7 vs 528.3 x 10^9/L) at baseline were also similar between the two arms. At baseline, 98.8% of patients were JAK2V617F positive, with a median JAK2 allelic burden of 37.4%.

Summary of key efficacy results (PROUD-PV)

Analysis set	FAS		PPS	
	Ropeginterferon alfa-2b	HU	Ropeginterferon alfa-2b	HU
Initial primary endpoint (Disease response rate comprising CHR and normal spleen size)				
Disease response rate, n*	122	123	115	114
Responder, n (%)	26 (21.3%)	34 (27.6%)	26 (22.6%)	33 (29.0%)
Absolute difference, % (95% CI)	-6.6% (-17.2%, 4.1%)		-6.3% (-17.5%, 4.9%)	
P-value	0.2233		0.2353	
Revised primary endpoint (Disease response rate comprising CHR only)				
Disease response rate, n**	123	125	113	114
Responder, n (%)	53 (43.1%)	57 (45.6%)	50 (44.3%)	53 (46.5%)
Absolute difference, % (95% CI)	-3.0% (-15.6%, 9.5%)		-2.6% (-15.8%, 10.5%)	
P-value	0.0028		0.0036	

* For the initial primary endpoint, 9 patients (5 in the ropeginterferon alfa-2b arm and 4 in the HU arm) in the FAS did not have data for disease response criteria at the end of the 12-month treatment period.
** For the revised primary endpoint, 6 patients in the FAS (4 in the ropeginterferon alfa-2b arm, 2 in the HU arm) and 2 patients in the PPS (both in the ropeginterferon alfa-2b arm) did not have data for disease response criteria at the end of the 12-month treatment period.

For the initial primary endpoint comprising of CHR and normal spleen size, the disease response rate at 12 months in the FAS was 21.3% (26/122 patients) for ropeginterferon alfa-2b and 27.6% (34/123 patients) for HU, with a difference of -6.6% (95% CI: -17.2% to 4.1%; p=0.2233). In the Per-Protocol Set (PPS), response rates were 22.6% (26/115 patients) and 29.0% (33/114 patients) respectively, with a difference of -6.3% (95% CI: -17.5% to 4.9%; p=0.2353). Non-inferiority was not demonstrated as the lower bounds of the 95% CI were below the -10.5% margin.

With the redefined endpoint based solely on CHR without the spleen size criteria and a widened non-inferiority margin of 20.0%, non-inferiority was met. Disease response rates increased to 43.1% (53/123) for ropeginterferon alfa-2b and 45.6% (57/125) for HU in the FAS, with a difference of -3.0% (95% CI: -15.6% to 9.5%; p=0.0028), and to 44.3% (50/113) and 46.5% (53/114) respectively in the PPS, with a difference of -2.6% (95% CI: -15.8% to 10.5%; p=0.0036). Non-inferiority was demonstrated as the lower bounds of the 95% CI were above the new -20.0% margin.

The study's main limitations arose from multiple post-hoc changes. The primary endpoint was modified by removing spleen size criteria, the study objective changed from superiority to non-inferiority testing, and the non-inferiority margin was widened from 10.5% to 20.0%. While the modified analysis showed non-inferiority of ropeginterferon alfa-2b to HU, the original primary endpoint analysis did not meet this threshold, making the results difficult to interpret with confidence.

Overall, the clinical efficacy of ropeginterferon alfa-2b in the treatment of PV was based primarily on the Phase I/II single-arm PEGINVERA study, which demonstrated a clinically

relevant complete haematological response of approximately 64%. The magnitude of response is considered clinically meaningful. Of note, the haematological response observed was unlikely to be attributed to spontaneous remission considering the natural history of PV, which typically follows a progressive course. Considering the rarity of myeloproliferative neoplastic disease and the limited therapeutic options available for this condition, the results of the study was considered reasonably adequate to support the efficacy of the treatment.

While the PROUD-PV study was a Phase III active comparator study, the deficiencies in the study design, particularly the post-hoc changes to the statistical plan and endpoint, resulted in the findings of this study being inadequately interpretable and not contributing to the overall body of evidence supporting the approval of the requested indication.

D ASSESSMENT OF CLINICAL SAFETY

The safety population comprised a total of 178 patients on ropeginterferon alfa-2b from the Phase I/II study PEGINVERA, Phase III study PROUD-PV as well as two supportive studies CONTINUATION-PV and PEN-PV. The CONTINUATION-PV study was an open-label, multicentre, Phase III, extension study of the PROUD-PV study, assessing the long-term efficacy and safety of ropeginterferon alfa-2b. The PEN-PV study was an open-label, single-arm, multicentre, Phase III study to assess the self-administration of ropeginterferon alfa-2b using a pre-filled pen using dedicated questionnaires.

Long term safety data is available from study PEGINVERA (up to 7 years from some patients) and CONTINUATION-PV. Data from PROUD-PV (and the extension trial CONTINUATION-PV) allow a safety comparison with hydroxyurea (or Best Available Therapy [BAT]).

Overall ropeginterferon alfa-2b exposure

	PROUD-PV + PEN-PV + CONTINUATION-PV (N=127)	**PEGINVERA (N=51)**	**All ropeginterferon alfa-2b combined (N=178)**
Mean (months)	53	46	51
Median (months)	74	61	66

Overview of safety profile

AE	**Ropeginterferon alfa-2b (N=178)**	**HU/BAT (N=127)**
Any adverse event (AE)	165 (92.7%)	115 (90.6%)
Treatment-related AE	143 (80.3%)	100 (78.7%)
Serious AE (SAE)	51 (28.7%)	23 (18.1%)
Treatment-related SAE	11 (6.2%)	5 (3.9%)
Discontinuations due to AEs	PEGINVERA: 21/51 (41.2%) PROUD-PV & CONT'-PV: 14/127 (11.0%)	PROUD-PV & CONT'-PV: 3/127 (2.4%)
Deaths due to AEs	6 (3.4%)	5 (3.9%)
Treatment-related deaths due to AEs	0 (0%)	1 (0.78%)

A total of 2,813 AEs were reported in 165/178 (92.7%) patients on ropeginterferon alfa-2b while 1083 AEs were reported in 115/127 (90.6%) patients in the HU/BAT arm. The overall incidence of AEs in the pooled clinical studies was similar in both arms, but the safety profile was different as expected based on the different mechanisms of action.

The most commonly reported AEs (>10%) in the pooled ropeginterferon alfa-2b arm were anaemia (10.1%), nausea (10.1%), alanine aminotransferase increased (10.7%), pain in extremity (10.7%), myalgia (12.4%), influenza-like illness (12.9%), pyrexia (12.9%), back pain (14.0%), dizziness (14.0%), nasopharyngitis (15.7%), diarrhoea (16.3%), gamma-glutamyl transferase increased (16.3%), headache (16.9%), leukopenia (19.1%), thrombocytopenia (19.1%), arthralgia (21.9%), and fatigue (23.0%). Most of the AEs were mild (67.9%) to moderate (27.4%) in severity.

The most commonly reported AEs (>10%) in the HU/BAT arm were nasopharyngitis (10.2%), diarrhoea (11.0%), nausea (11.8%), headache (12.6%), fatigue (14.2%), leukopenia (22.8%), anaemia (25.2%), and thrombocytopenia (29.1%). Most of the AEs were also mild (67.0%) to moderate (26.7%) in severity.

A total of 104 SAEs were reported in 51/178 (28.7%) patients in the pooled ropeginterferon alfa-2b arm. Out of the 104 SAEs, 16 SAEs in 11/178 (6.2%) patients were considered as treatment-related. Treatment-related SAEs in the pooled ropeginterferon alfa-2b arm included depression (1.1%), atrial fibrillation (1.1%), anaemia (0.6%), microcytic anaemia (0.6%), fatigue (0.6%), influenza-like illness (0.6%), pyrexia (0.6%), anti-thyroid antibody positive (0.6%), antinuclear antibody increased (0.6%), transaminases increased (0.6%), arthralgia (0.6%), rheumatoid arthritis (0.6%), and acute stress disorder (0.6%).

In the HU/BAT arm, a total of 35 SAEs were reported in 23/127 (18.1%) patients. Out of the 35 SAEs, 7 SAEs in 5/127 (3.9%) patients were considered as treatment-related. Treatment-related SAEs in the HU/BAT arm included basal cell carcinoma (1.6%), malignant melanoma (0.8%). anaemia (0.8%), granulocytopenia (0.8%), leukopenia (0.8%), and acute leukaemia (0.8%).

There were 6 fatal AEs in the ropeginterferon alfa-2b arm and 5 in the HU arm. One death in the HU arm due to acute leukaemia was considered to be related to HU, consistent with its known risk of carcinogenicity. All other deaths were not assessed to be treatment-related by the investigator.

The AEs of special interest reported with ropeginterferon alfa-2b and were known to be associated with interferons included cardiac disorders, endocrine disorders, eye disorders, gastrointestinal disorders, immune system disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders and vascular disorders. The most frequently occurring AEs of special interest (>2%) were musculoskeletal and connective tissue disorders (2.2%), cardiac disorders (3.9%), endocrine disorders (6.7%), and psychiatric disorders (7.9%). These AEs have been adequately described in the warnings and precautions section in the package insert.

Summary of AEs of special interest

	HU/BAT (N=127)		**Ropeginterferon alfa-2b (N=178)**	
	AE	**N (%)**	**AE**	**N (%)**
Cardiac disorders	***5***	***2 (1.6%)***	***9***	***7 (3.9%)***
Atrial fibrillation	1	1 (0.8%)	7	5 (2.8%)
Cardiac failure	1	1 (0.8%)	1	1 (0.6%)
Cardiac failure acute	2	1 (0.8%)	-	-
Intracardiac thrombus	-	-	1	1 (0.6%)
Pericardial effusion	1	1 (0.8%)	-	-
Endocrine disorders	***1***	***1 (0.8%)***	***12***	***12 (6.7%)***
Autoimmune thyroiditis	1	1 (0.8%)	2	2 (1.1%)

Hyperthyroidism	-	-	5	5 (2.8%)
Hypothyroidism	-	-	5	5 (2.8%)
Musculoskeletal and connective tissue disorders	***-***	***-***	***4***	***4 (2.2%)***
Rheumatoid arthritis	-	-	2	2 (1.1%)
Sjogren's syndrome	-	-	2	2 (1.1%)
Psychiatric disorders	***2***	***2 (1.6%)***	***20***	***14 (7.9%)***
Anxiety	-	-	2	2 (1.1%)
Depression	2	2 (1.6%)	11	10 (5.6%)
Irritability	-	-	2	2 (1.1%)
Mood altered	-	-	2	2 (1.1%)
Nervousness	-	-	3	2 (1.1%)

Overall, no new safety signals were observed for ropeginterferon alfa-2b in the clinical studies. The safety profile of ropeginterferon alfa-2b appeared similar to that of other interferon products as characterised by haematological effects, constitutional symptoms, musculoskeletal complaints, gastrointestinal disturbances, neurological symptoms, and liver enzyme elevations. Overall, the safety profile of ropeginterferon alfa-2b in PV appeared manageable and no major safety concerns were raised.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Current treatment options for PV include phlebotomy, antiplatelet agents and cytoreductive therapy such as HU. Established clinical practice guidelines recommend both HU and interferon alpha as first-line cytoreductive therapies. However, the use of hydroxyurea is often limited by its teratogenicity and cytotoxicity. Therefore, there remains an unmet medical need for interferon alfa for the treatment of PV, especially in young patients requiring long-term treatment. No interferon products are currently approved locally for the treatment of PV.

Complete haematological response, defined as HCT <45% without phlebotomy in the previous two months, platelet count ≤400 x 10^9/L, WBC count ≤10 x 10^9/L, normal spleen size and absence of thromboembolic events, was observed in 64.3% of patients in the Phase I/II single-arm PEGINVERA study. Although the study lacked an active comparator, the observed response rate was unlikely due to spontaneous remissions considering the natural history of PV. The study also demonstrated a reduction from baseline to Week 50 for the individual laboratory parameters: mean absolute WBC count decreased from 11.8 x 10^9/L to 5.8 x 10^9/L, mean HCT reduced from 45.1% to 43.05%, and mean PLT count dropped from 455.9 x 10^9/L to 246.6 x 10^9/L. These objective measures of clinical improvement, reflecting changes towards normal reference ranges, further support the efficacy of ropeginterferon alfa-2b in cytoreduction.

The results from PROUD-PV study were questionable and could not be accepted as supporting evidence. The study was flawed given the post-hoc changes to the primary efficacy endpoint and the statistical plan.

The safety profile of ropeginterferon alfa-2b was similar to that of other interferon products. Ropeginterferon alfa-2b demonstrated AESIs consistent with those known to be associated with interferons. These included disorders affecting the cardiac, endocrine, ocular, gastrointestinal, immune, musculoskeletal and connective tissue, psychiatric, dermatological and vascular systems. The package insert contained adequate descriptions of these AEs as well as the related warnings and precautions.

Overall, the benefit-risk profile of ropeginterferon alfa-2b for the treatment of polycythaemia vera was considered to be favourable since efficacy was demonstrated in terms of a high and clinically meaningful complete haematological response rate and the safety profile was manageable and consistent with what is known for interferon products that have been previously approved.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of ropeginterferon alfa-2b for the treatment of polycythaemia vera was deemed favourable and approval of the product registration was granted on 29 May 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

FULL PRESCRIBING INFORMATION OF BESREMi SOLUTION FOR INJECTION IN PREFILLED SYRINGE 500 MICROGRAMS/mL

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

Besremi is indicated as monotherapy in adults for the treatment of polycythemia vera (see Section 14 Clinical Studies).

2 DOSAGE AND ADMINISTRATION

2.1 Pre-Treatment Testing

Pregnancy testing is recommended prior to BESREMi treatment in females of reproductive potential *[see Use in Specific Populations (8.3)]*.

2.2 Recommended Dosage

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 (hematocrit less than 45%, platelets less than 400 x 10^9/L, and leukocytes less than 10 x 10^9/L).

Patients Transitioning from Hydroxyurea:

- 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 x 10^9/L, and leukocytes less than 10 x 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.

During the titration phase the efficacy to reduce the cardiovascular and thromboembolic risk of the underlying disease may not be fully established. Monitor patients closely especially during the titration phase. Perform complete blood counts (CBC) regularly, every2 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

Monitor CBC every 2 weeks during the titration phase and dose modification phase. Phlebotomy as rescue treatmentto 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 1). 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 1 Dose Modifications for BESREMi Adverse Reactions

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-modifications.
Liver enzyme elevation	>5 x the upper limit of normal (ULN) but ≤20 x ULN	Decrease dose by 50 mcg; if toxicity does not improve, continue decreasing at biweekly intervals until alanine aminotransferase (ALT) and aspartate aminotransferase (AST) recover < 3 x ULN if baseline was normal; 3 x baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to < 2.5 x ULN if baseline was normal; 2.5 x baseline if baseline was abnormal. If the interrupted dose is 50 mcg, refrain from treatment until recovery.
	>20 x ULN	Interrupt treatment until ALT and AST recover to < 3 x ULN if baseline was normal; 1.5 x baseline if baseline was abnormal, and gamma-glutamyltransferase (GGT) recovers to < 2.5 x ULN if baseline was normal; 2 x baseline if baseline was abnormal. Consider permanent discontinuation if toxicity persists after four dose-modifications.
Cytopenia	Anemia: Hemoglobin (Hgb) < 8 g/dL Thrombocytopenia: platelet count < 50,000/mm^3 but ≥25,000/mm^3 Leukopenia: white blood cell count (WBC) <2000/mm^3 but ≥1,000/mm^3	Decrease dose by 50 mcg; if toxicity does not improve, continue decreasing at biweekly intervals until recovery of Hgb >10.0 g/dL, platelets >75,000/mm^3, and WBC >3,000/mm^3 If the interrupted dose is 50 mcg, refrain from treatment until recovery.
	Anemia: Hemoglobin levels are life threatening, or urgent intervention needed	Interrupt treatment until recovery of Hgb >10.0 g/dL, platelets

	Thrombocytopenia: platelet count <25,000/mm^3 Leukopenia: WBC <1000/mm^3	>75,000/mm^3, and WBC >3,000/mm^3. Consider permanent discontinuation if toxicity persists after four dose-modifications.
Depression	Mild, without suicidal ideation	Consider psychiatric consultation if persistent (>8 weeks).
	Moderate, without suicidal ideation	Consider dose reduction and psychiatric consultation.
	Severe, or any severity with suicidal ideation	Discontinue therapy, recommend psychiatric consultation.

[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. 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 from the refrigerator. Keep the prefilled syringe in the carton and lay it flat on a clean work surface for 15-30 minutes to allow the prefilled syringe to reach room temperature 15 ˚C to 25 ˚C.

Before injection, visually inspect BESREMi in the prefilled syringe for particulate matter and discoloration before administration (do not use if the solution in the syringe is cloudy, discolored, contains particulate matter or if the syringe shows any sign of damage).

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

- 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 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 a sharps disposalcontainer.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mcg/mL clear and colorless to slightly yellowish solution in a single-dose prefilled syringe.

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. Serious neuropsychiatric reactions have been observed in 3% of patients treated with BESREMi during the clinical development program. Among the 178 patients in the clinical development program of BESREMi, 17 cases of depression, depressive symptoms, depressed mood, and listlessness occurred. Of these seventeen 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. Eight cases of hyperthyroidism (4.5%), seven cases of hypothyroidism (3.9%) and five cases (2.8%) of autoimmune thyroiditis/thyroiditis occurred in the development program of BESREMi.

Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease *[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 and coronary artery ischemia *[see Adverse Reactions (6.1)]*. Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.

5.4 Decreased Peripheral Blood Counts

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). Thrombocytopenia of grade 3 (platelet counts <50,000 – 25,000/mm^3) or greater occurred in 2% of BESREMi-treated patients. Anemia of grade 3 (Hgb < 8 g/dL) or greater occurred in 1% of BESREMi-treated patients. Leukopenia of grade 3 (WBC counts <2,000 – 1,000/mm^3) or greater occurred in 2% of BESREMi-treated patients. Infection occurred in 48% of BESREMi treated patients, while serious infections occurred in 8% of BESREMi treated 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). 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. 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

Fatal and serious 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, 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, 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. Hyperlipidemia,

hypertriglyceridemia, or dyslipidemia occurred in 3% of patients receiving BESREMi. 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 times the upper limit of normal (ULN), AST ≥3 times the ULN, GGT ≥3 times the ULN, and bilirubin >2 times the ULN have been observed in patients treated with BESREMi.

In the clinical development program of BESREMi, 36 patients (20%) experienced liver enzyme elevations, 33 of whom had elevations of 1.25-5x 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. Reduce BESREMi dosage by 50 mcg for increased AST/ALT/GGT then monitor AST/ALT/GGT weekly until the values return to baseline or grade 1 (ALT and AST < 3 x ULN if baseline was normal; 1.5 - 3 x baseline if baseline was abnormal, and GGT < 2.5 x ULN if baseline was normal; 2 - 2.5 x baseline if baseline was abnormal) *[see Dosage and Administration (2.3)]*. If toxicity does not improve, continue decreasing the BESREMi dose at biweekly intervals until recovery to grade 1. Hold if AST/ALT/GGT > 20 x ULN and consider permanent discontinuation if increased liver enzyme levels persist after four dose-reductions. 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, <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 Clinical Pharmacology (12.1) and Use in Specific Populations (8.1)]*. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an

effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose *[see Dosage and Administration (2.1) and Use in Specific Populations (8.1, 8.3)]*.

5.17 Benzyly alcohol

Benzyl alcohol might cause allergic reactions.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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)]*
- Decreased Peripheral Blood Counts *[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)]*

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.

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/CONTINUATION PV*]. The mean age at baseline was 58.6 years (range 30-85 years), 88 (49.4%) women, 90 (50.6%) 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.

Summary of the safety profile

The most common adverse reactions are leukopenia (19.1%), thrombocytopenia (18.5%), arthralgia(12.9%), fatigue (12.4%), increased gamma-glutamyltransferase (11.2%), influenza-like illness (10.7%), myalgia (10.7%), anaemia (7.9%), increased alanine aminotransferase (8.4%), neutropenia (6.7%), pyrexia (7.9%), increased aspartate aminotransferase (6.2%), pruritus (6.7%), pain in extremity (6.7%), alopecia (6.7%), headache (6.2%), diarrhoea (5.1%), injection site reaction (3.9%), chills (5.1%), and dizziness (5.1%).
Serious adverse reactions are depression (1.1%), atrial fibrillation (1.7%) and acute stress disorder(0.6%).

Tabulated list of adverse reactions

Following treatment-related adverse reactions were reported with ropeginterferon alfa-2b in clinical studies in 178 polycythaemia vera adult patients. Adverse reactions are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated fromavailable data)

System organ class	Frequency	Adverse reaction
Infections and infestations	*common*	respiratory tract infection, influenza, rhinitis, fungal skin infection
	uncommon	oral herpes, herpes zoster, oral candidiasis, sinusitis, oesophageal candidiasis, vulvovaginal mycotic infection, hordeolum, onychomycosis
	very common	leukopenia, thrombocytopenia
Blood and lymphatic system disorders	*common*	pancytopenia, neutropenia, anaemia
Immune system disorders	*uncommon*	sarcoidosis
	very rare	idiopathic or thrombotic thrombocytopenic purpura[#]
	not known	Vogt-Koyanagi-Harada disease[#], acute hypersensitivity reactions[#]**
Endocrine disorders	*common*	hypothyroidism, hyperthyroidism, thyroiditis
	uncommon	Basedow's disease,diabetes mellitus[#]
Metabolism and nutrition disorders	*common*	hypertriglyceridaemia, decreased appetite
Psychiatric disorders	*common*	depression, aggression#, insomnia, anxiety, mood altered, mood swings, mood disorders
	uncommon	suicide attempt[#], suicidal ideation[#], confusional state[#], acute stress disorder, hallucination, emotional distress, nervousness nightmare, irritability
	rare	bipolar disorder[#], mania[#]
Nervous system disorders	*common*	headache, dizziness, hypoesthesia, somnolence, paraesthesia
	uncommon	polyneuropathy, peripheral motor neuropathy, radiculopathy, migraine, mental impairment, tremor, aura
Eye disorders	*common*	dry eye
	uncommon	retinal haemorrhage[#], retinal exudates[#], visual impairment,visual acuity reduced, vision blurred, ocular discomfort, eczema eyelids
	rare	retinopathy[#], optic neuropathy[#], retinal artery occlusion[#], retinal vein occlusion[#],
	very rare	blindness[#]
	not known	retinal detachment[#]
Ear and labyrinth disorders	*uncommon*	deafness, tinnitus, vertigo
Cardiac disorders	*common*	atrial fibrillation
	uncommon	myocardial infarction[#], atrioventricular block, intracardiacthrombus, aortic valve incompetence, cardiovascular disorder
	rare	cardiomyopathy[#], angina pectoris[#]
	very rare	myocardial ischemia[#]
Vascular disorders	*common*	microangiopathy
	uncommon	Raynaud's phenomenon, hypertension, haematoma, flushing
Respiratory, thoracic and mediastinal disorders	*common*	dyspnoea
	uncommon	pneumonitis, cough, epistaxis, throat irritation
	very rare	lung infiltration[#]
	not known	pulmonary fibrosis[#], pneumonia[#], pulmonary arterial hypertension[#]*

Gastrointestinal disorders	*common*	diarrhoea, nausea, abdominal pain, constipation, abdominal distension, dry mouth
	uncommon	gastritis, abdominal wall disorder, flatulence, frequent bowel movements, odynophagia, gingival bleeding
	not known	tooth disorder[#], periodontal disease[#]
	very common	gamma-glutamyltransferase increased
Hepatobiliary disorders	*common*	liver disorder, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
	uncommon	hepatotoxicity, hepatitis toxic, hepatomegaly, porphyria non-acute
	rare	hepatic failure[#]
Skin and subcutaneous tissue disorders	*common*	pruritus, alopecia, rash, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, hyperhidrosis, dry skin
	uncommon	photosensitivity reaction, skin exfoliation, nail dystrophy
	not known	skin depigmentation[#]
Musculoskeletal and connective tissue disorders	*very common*	arthralgia, myalgia
	common	Sjogren's syndrome, arthritis, pain in extremity, musculoskeletal pain, bone pain, muscle spasms
	uncommon	muscular weakness, neck pain, groin pain
Renal and urinary disorders	*uncommon*	cystitis haemorrhagic, dysuria, micturition urgency, urinary retention
Reproductive system and breast disorders	*uncommon*	erectile dysfunction, haematospermia
General disorders and administration site conditions	*very common*	influenza-like illness, fatigue
	common	pyrexia, injection site reaction, asthenia, chills, general physical health deterioration, injection site erythema
	uncommon	injection site pain, injection site pruritus, sensitivity to weather change
	not known:	tongue hyperpigmentation[#]
Investigations	*common*	antithyroid antibody positive, blood thyroid stimulating hormone increased, body temperature increased, antinuclear antibody positive, blood lactate dehydrogenase increased, weight decreased
	uncommon	platelet count increased, blood uric acid increased, Coombs test positive

[#]Reported as adverse reactions during treatment with other interferon alfa medicinal products.
*Class label for interferon medicinal products, see section 5.8 pulmonary toxicity..
**e.g., urticaria, angioedema, bronchoconstriction, or anaphylaxis.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other interferon alfa-2b products may be misleading.

The incidence of binding antibodies to ropeginterferon alfa-2b was 1.4% (2/146) and they were observed as early as 8 weeks post-dosing. Among the patients who tested positive for binding antibodies, none developed neutralizing antibodies.

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)]*.

7.4 Telbivudine

The concomitant use of pegylated interferon alfa-2a with telbivudine was associated with an increased risk of peripheral neuropathy, with the underlying mechanism remaining unknown. As such risk cannot be excluded for other interferons, concomitant use of ropeginterferon alfa-2b with telbivudine should be avoided.

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. Animal studies assessing reproductive toxicity of BESREMi have not been conducted. Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy *(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.

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 may 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

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. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

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.

11 DESCRIPTION

Ropeginterferon alfa-2b, 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 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) injection is a sterile, clear and colorless to slightly yellowish solution for subcutaneous use supplied in a single dose prefilled syringe.

Each prefilled syringe delivers 1 mL of solution containing 500 mcg of ropeginterferon alfa-2b 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.

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 in the bone marrow by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through the activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. The actions involved in the therapeutic effects of interferon alfa in polycythemia vera are not fully elucidated.

12.2 Pharmacodynamics

The efficacy of ropeginterferon alfa-2b is dependent on the stabilization of hematological parameters (hematocrit <45%, platelets <400 × 10^9/L and leukocytes <10 × 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 ≤400 x 10^9/L and leukocytes ≤10 x 10^9/L) increased with increasing ropeginterferon alfa-2b concentration over time. Based on the exposure-response (E-R) analysesusing data from the PEGINVERA study, 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 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 1011 – 7809 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 and clearance of BESREMi is approximately 7 days and 1.7-2.5 L/h in patients with polycythemia vera over a dose range of 100 mcg to 500 mcg, respectively.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

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 x10^9/L ± 187 x10^9/L and 11.8 x 10^9/L ± 5.2 x 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. However, it is noted that enrollment of symptomatic splenomegaly is limited. Eleven patients (22%) had a prior history of a major cardiovascular eventincluding 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 x 10^9/L and leukocytes ≤10 x 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).

An open label, randomised phase III study (PROUD-PV) evaluated the efficacy and safety of ropeginterferon alfa-2b in comparison to hydroxycarbamide in 254 adult polycythaemia vera patients (randomisation 1:1). Patients were stratified by previous exposure to hydroxycarbamide, age at screening (≤60 or >60 years) and presence of thromboembolic events in the past. Characteristics of the study population are presented in Table 2.

Table 2. **Patient characteristics at screening in the PROUD-PV Study**.

	Ropeginterferon alfa-2b treatment arm (n=127)	**Control treatment arm (n=127)**
Age		
Years*	58.5 ±10.81	57.9±13.10
Gender		
Female n (%)	68 (53.5)	67 (52.8)
Male n (%)	59 (46.5)	60 (47.2)
Race		
White n (%)	127 (100.0)	127 (100.0)
Duration of PV (months)*	12.6±24.70	15.7±25.65
***JAK2*V617F allele burden** (%)*	41.9±23.49	42.8±24.14
Haematological parameters		
Haematocrit (%)*	47.8±5.22	48.6±5.39
Platelets (10^9/L)*	537.7±273.08	516.8±254.43
Leukocytes (10^9/L)*	11.5±4.76	11.9±4.88
Presence of splenomegaly		
No n (%)	115 (90.6)	112 (88.2)
Yes n (%)	12 (9.4)	15 (11.8)

*values are mean ±SD.
Enrollment of patients with symptomatic splenomegaly were limited.

Hydroxycarbamide treatment-naïve (n=160) or hydroxycarbamide treated (n=94) patients were randomised to receive ropeginterferon alfa-2b or hydroxycarbamide. The dose was gradually increased depending on disease response and tolerability (for ropeginterferon alfa-2b, from 50 to 500 micrograms administered subcutaneously every two weeks). The mean dose after 12 months of treatment was 382 (±141) micrograms for ropeginterferon alfa-2b. The disease response (defined as haematocrit <45% without phlebotomy [at least 3 months since last phlebotomy], platelets <400 x 10^9/L and leukocytes <10 x 10^9/L after 12 months of treatment) was 43.1% [53/123 of patients] in the ropeginterferon alfa-2b arm after 12 months of treatment.
An open-label, phase IIIb extension study (CONTINUATION-PV) enrolled 169 adult polycythaemia vera patients who previously completed the PROUD-PV Study to evaluate the long-term efficacy and safety of ropeginterferon alfa-2b. Ninety-five patients continued to receive ropeginterferon alfa-2b (from 50 to 500 micrograms administered subcutaneously every two, three or four weeks). The mean doses after 36 and 72 months of treatment (12-month treatment duration in the PROUD-PV study and 24- and 60-month treatment duration in the extension study) was 363 (±149) micrograms and 356 (±144) micrograms for ropeginterferon alfa-2b, respectively.

The response to ropeginterferon alfa-2b treatment is presented in Table 3 and Table 4. After 72 months of treatment, disease response defined as complete haematological response only was 54.5% and 39.8% of patients showed a complete haematological response with an improvement in disease burden. Patients showed a statistically significant difference in the JAK2V617F allele burden (16.6%) and JAK2V617F allele change from baseline (-26.0%).

Table 3. Disease response after 12 to 72 months of ropeginterferon alfa-2b.

Disease response	**Patients with of ropeginterferon alfa-2b treatment Responder N (%)**			
	12 months	**24 months[1]**	**36 months[2]**	**72 months[3]**
Complete haematological response[a]	59 (62.1)	67 (70.5)	67 (70.5)	48 (54.5)
Complete haematological response[a] and improvement in disease burden[b]	44 (46.32)	48 (50.53)	51 (53.68)	35 (39.77)

[a] defined as haematocrit <45% without phlebotomy (at least 3 months since last phlebotomy), platelets <400 x 10^9/L and leukocytes <10 x10^9/L.
[b] defined as the improvement of disease-related signs (clinically significant splenomegaly) and disease-related symptoms

(microvascular disturbances, pruritus, headache).
[1]12-month treatment duration in the PROUD-PV Study and 12-month treatment duration in the extension study
[2]12-month treatment duration in the PROUD-PV Study and 24-month treatment duration in the extension study
[3]12-month treatment duration in the PROUD-PV Study and 60-month treatment duration in the extension study

The mean JAK2V617F allele burden continuously declined throughout the 6-year ropeginterferon alfa-2b treatment, from 42.8% at baseline (before treatment in PROUD-PV) to 15.5% at 72 months.

Table 4. *JAK2*V617F allele burden [%] absolute values and changes from baseline in the CONTINUATION-PV extension study.

Study month	n	Mean (±SD)	Change from baseline
Baseline	94	42.8 (±23.40)	-
M12	92	30.1 (±23.03)	-12.13 (±17.04)
M24[1]	73	18.5 (±17.09)	-24.59 (±22.07)
M36[2]	71	16.6 (±18.22)	-25.43 (±24.39)
M72[3]	51	15.5 (±20.38)	-25.97 (±27.29)

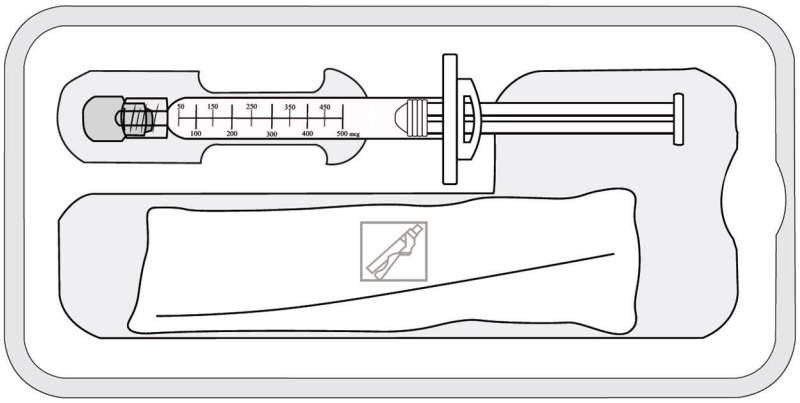
[1]12-month treatment duration in the PROUD-PV Study and 12-month treatment duration in the extension study
[2]12-month treatment duration in the PROUD-PV Study and 24-month treatment duration in the extension study
[3]12-month treatment duration in the PROUD-PV Study and 60-month treatment duration in the extension study

16 NATURE AND CONTENTS OF CONTAINER/STORAGE AND HANDLING

16.1 Nature and contents of container

Type and material of the container in contact with the medicinal product:
Solution for injection is contained in the pre-filled syringe, which is made up of Type I glass syringe barrel closed with a luer tip cap at the front and a rubber plunger stopper at the back end (see Figure A).

How Supplied
BESREMi (ropeginterferon alfa-2b) 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 safety needle as shown on Figure 1.



(Figure 1)

16.2 Storage and Handling

Store in a refrigerator at 2 °C to 8 °C in the original carton to protect from light.Do not freeze.

Manufactured by:
PharaEssentia Corporation, Taichung Plant
3F, No. 28, Keya West Rd., Daya Dist., Taichung, Taiwan

INSTRUCTIONS FOR USE
BESREMi [bez-reh-me]
(ropeginterferon alfa-2b)
injection, for subcutaneous use
Single-dose prefilled syringe

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

Guide to Prefilled syringe and Needle Parts (Figure A)

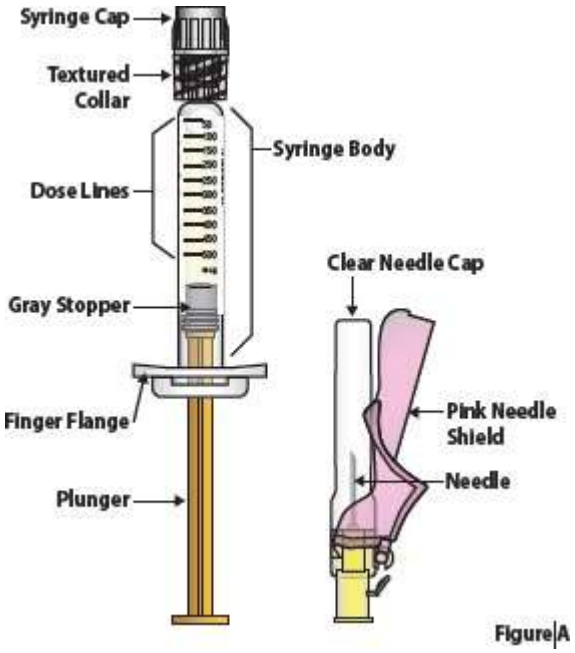


Figure A

Storing BESREMi

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

- Keep your BESREMi prefilled syringes in their original carton (Figure B) while stored.
- **Do not** freeze the prefilled syringes.
- **Do not** use a prefilled syringe that has been frozen or left in direct sunlight.
- Keep BESREMi prefilled syringes, needles, and all medicines out of the reach of children.

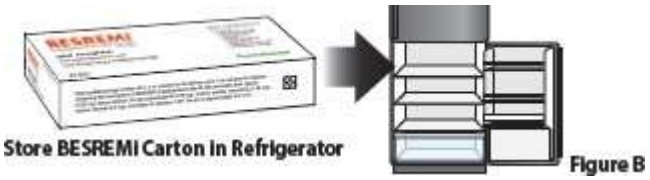


Figure B

Important information you need to know before injecting BESREMi

Read this Instructions for Use before using your single-dose BESREMi prefilled syringe for the first time 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 and the right amount of BESREMi to measure in the prefilled syringe for your dose. Each time you inject, be sure that you know the prescribed dose of BESREMi to inject. Your dose may change over time.
- BESREMi is for subcutaneous (under the skin) injection only.
- BESREMi is for one-time use only. **Do not** reuse your prefilled syringe or needle.
- **Do not** use a prefilled syringe or needle that is damaged or broken. Contact your healthcare provider for a replacement prefilled syringe or additional needles.
- Inject BESREMi into the top of the thighs or lower stomach-area just under the skin. **Do not** inject BESREMi into any other area of the body.
- Throw away (dispose of) the BESREMi prefilled syringe with needle attached right away after use, even if there is medicine left in the prefilled syringe. See Step 10 in the section "**Dispose of used prefilled syringes and needles."**

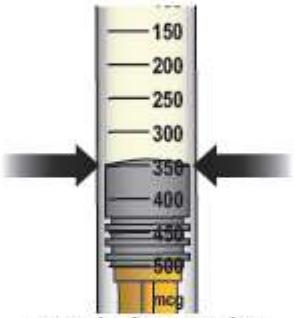
Read Me

How to Adjust the Medicine Level for Your Prescribed Dose

When setting your dose in Step 8, you will need to line up the top outer edge of the gray stopper with the specific dose line and number on the syringe that matches your prescribed dose (Figure C).

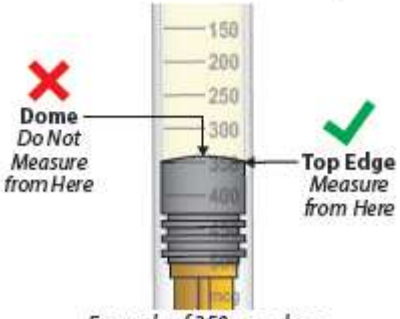
Do not line up the dome (at the top of the stopper) with the dose line (Figure D).

Align Top Outer Edge of Stopper to Dose Line



Example of 350 mcg dose

Figure C



Example of 350 mcg dose

Figure D

Gather and check supplies

1. Prepare BESREMi Prefilled Syringe

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

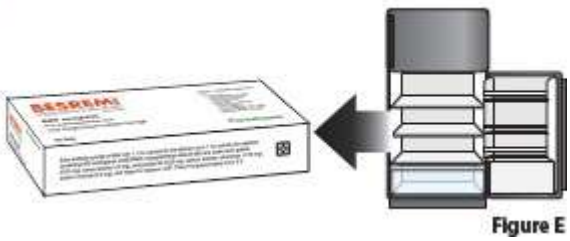


Figure E

1.2. Check the expiration date (“EXP”) on the top panel of the carton to make sure it has not passed (Figure F).

Do not use the prefilled syringe if the expiration date has passed.

Figure F

1.3. Let carton containing the BESREMi prefilled syringe sit on a clean work surface for **15 to 30 minutes** to allow it to come to room temperature (Figure G).
Do not warm the prefilled syringe any other way.

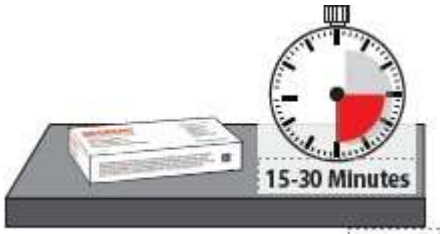


Figure G

2. Gather supplies for injection

2.1. After allowing the prefilled syringe to come to room temperature for 15 to 30 minutes inside the carton, gather the following additional supplies.

Alcohol Swab (Figure H).

Figure H

Sharps Disposal Container (Figure I)

Figure I

A paper towel, sink, or trash can to minimize mess during dose adjustment (Figure J).

Figure J

Optional Items: Gauze or Cotton Ball and a Small Adhesive Bandage (Figure K).

Figure K

3. Wash hands and remove syringe from tray

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

Figure L

3.2. Open the carton and remove the clear plastic tray that holds the BESREMi prefilled syringe and needle package (Figure M).

Figure M

3.3. Remove the needle package and BESREMi Prefilled syringe from the plastic tray. Hold the prefilled syringe by the middle of the syringe body during removal (Figure N).

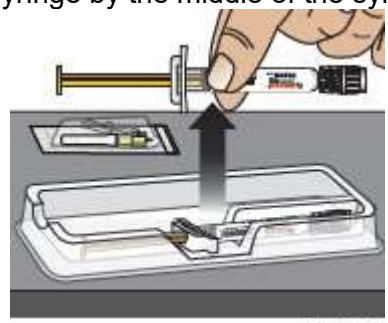


Figure N

4. Check the liquid medicine in the BESREMi prefilled syringe

4.1. Check the liquid medicine in the prefilled syringe (Figure O). The liquid should be clear and colorless to slightly yellow, and should not have particles.
Do not use the prefilled syringe if the liquid is cloudy, discolored, or contains particles. Contact your healthcare provider or pharmacist.

4.2. Check the syringe to see if it is damaged or broken (Figure O).
Do not use if it shows any signs of damage or breakage. Contact your healthcare provider or pharmacist.

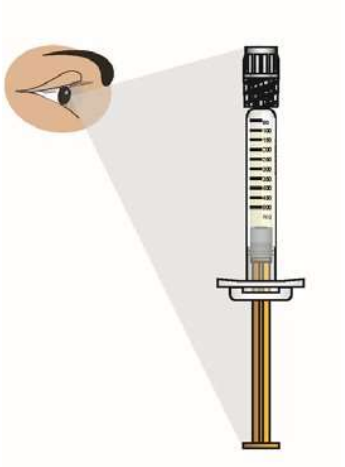


Figure O

Prepare syringe for injection

5. Attach the needle to the BESREMi prefilled syringe

5.1. Carefully open the needle package, remove the needle, and set it aside (Figure P).
Throw away the packaging into household trash.

Figure P

5.2. Hold the prefilled syringe as shown. Remove the prefilled syringe cap by unscrewing it counter• clockwise (Figure Q).
Throw away the syringe cap into household trash.
Do not allow the tip of the prefilled syringe to touch anything.

Figure Q

5.3. Attach the needle to the prefilled syringe by firmly pushing it into the collar of the syringe and then screwing (turn clock-wise) it on until it feels securely attached (Figure R).

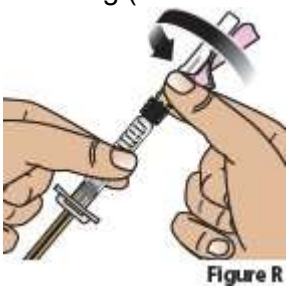


Figure R

The needle should now be assembled to the prefilled syringe (Figure S).

Figure S

6. Choose and clean injection site

6.1. Choose one of the following injection sites (Figure T):

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

Do not inject into skin that is irritated, red, bruised, infected, or scarred.
BESREMi is for subcutaneous (under the skin) injection only.
Rotate (change) the injection site for each injection.

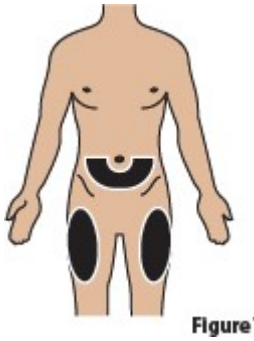


Figure T

6.2. Clean the chosen injection site with an alcohol swab and let it air dry (Figure U).
Do not blow on or touch the injection site after it has been cleaned.

Figure U

7. Uncap needle and move air bubbles to top

7.1. Pull the pink needle shield back (Figure V).
Note: The pink needle shield will be used after the injection to cover the needle and protect you from needle-stick injuries.

Figure V

7.2. Hold the syringe from the syringe body.
Remove the clear needle cap by pulling it straight off (Figure W). Throw away the needle cap into household trash.
Do not recap needle.

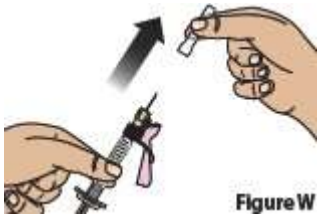


Figure W

7.3. 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 (Figure X).

Figure X

8. Set your dose

8.1. Check your prescription to identify your prescribed dose. (Figure Y). Depending on your prescribed dose, you may have to adjust the dose in the syringe by getting rid of (discarding) some medicine from the prefilled syringe before you inject the medicine.

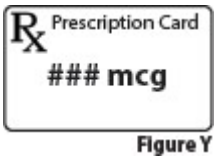


Figure Y

8.2. To set your dose follow the 4 steps below:

1. Hold the prefilled syringe at eye level with the needle **pointing straight up** over a paper towel, sink, or trash can.

2. Check that you can see the dose lines and number markings on the prefilled syringe.

3. Pinch the end of the plunger as shown (Figure Z).

4. Slowly push up on the plunger to remove liquid medicine until the top edge of the gray stopper lines up with the marking for **your prescribed dose** (Figure Z). **Keep holding straight up as you set the dose.**

Important: If you accidentally remove too much liquid medicine, **do not** inject. Contact your healthcare provider or pharmacist.

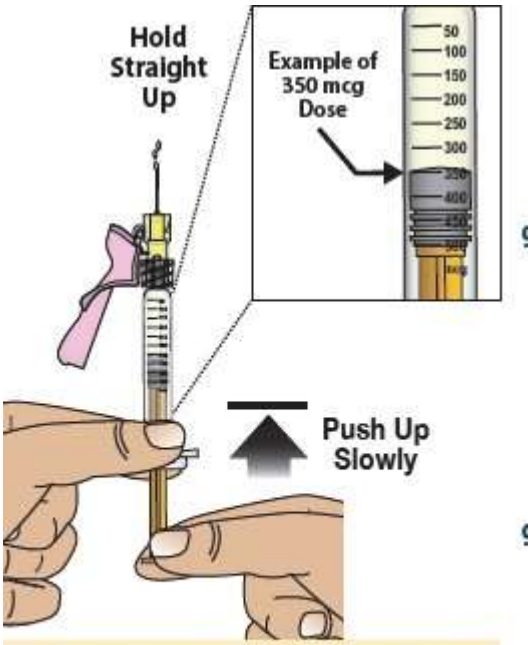


Figure Z

Inject BESREMi

9. Give Injection

9.1. Pinch the chosen injection site (Figure AA).

Figure AA

9.2. While pinching the skin, insert the needle at a 45 to 90 degree angle into the pinched skin (Figure AB).
Then release the pinched skin.

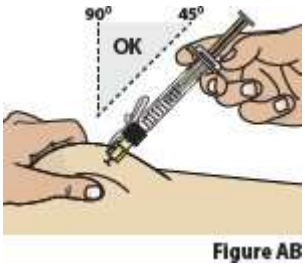


Figure AB

9.3. Inject the medicine by slowly pressing down on the plunger all the way until it stops (Figure AC).

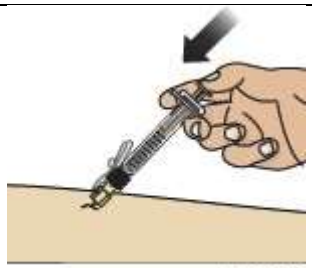


Figure AC

9.4. After all the liquid medicine is injected, remove the needle from the skin (Figure AD).

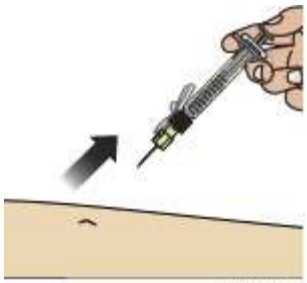


Figure AD

9.5 Cover needle

Carefully push the pink needle shield over the needle until it snaps into place and covers the needle (Figure AE). This helps prevent needle-stick injuries.

Do not recap the needle using the needle cap. Only use the pink needle shield to cover the needle.

Figure AE

Do not reuse the prefilled syringe and needle.

Disposing of used prefilled syringes and needles

10. Dispose of used prefilled syringes and needles.

- Put your used prefilled syringes and needles in a sharps disposal container right awayafter use (Figure AF). **Do not throw away (dispose of) loose prefilled syringes and needles in the household trash.**

Figure AF

- If you do not have a sharps disposal container, you may use a household container thatis:
  - 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.
- Do not dispose of your 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.

11 Check injection site.

11.1 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).

11.2 **Do not** rub the injection site. If needed, you may apply a small adhesive bandage.

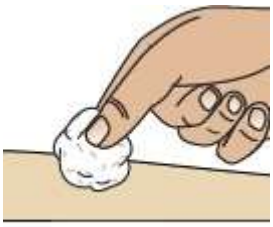


Figure AG

Revised on 26/4/2024