ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen
Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen

Each pre-filled pen of 0.5 mL solution contains 250 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 500 micrograms/mL.

Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen

Each pre-filled pen of 0.5 mL solution contains 500 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 1 000 micrograms/mL.

The strength indicates the quantity of the interferon alpha-2b moiety of ropeginterferon alfa-2b without consideration of the pegylation.

Ropeginterferon alfa-2b is a covalent conjugate of the protein interferon alpha-2b, produced in *Escherichia coli* cells by recombinant DNA technology, with a methoxypolyethylene glycol (mPEG) moiety.

The potency of this medicinal product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class (see section 5.1).

Excipient with known effect

Each pre-filled pen contains 10 mg benzyl alcohol and 0.05 mg polysorbate 80 per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection).

Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the management of the disease.

Posology

Titration phase
The dose is titrated individually with a recommended starting dose of 100 micrograms (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 micrograms every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the haematological parameters is achieved (haematocrit < 45%, platelets < 400 × 10^9/L and leukocytes < 10 × 10^9/L). The maximum recommended single dose is 500 micrograms injected every two weeks. Phlebotomy as rescue treatment to normalise blood hyperviscosity may be necessary.

Maintenance phase
The dose at which stabilisation of the haematological parameters is achieved should be maintained in a two-week administration interval for at least 1.5 years. After that, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient.

If adverse events develop during therapy, the administered dose should be reduced or treatment discontinued temporarily until adverse events abate; further, treatment should be re-initiated with a lower dose than the dose that caused adverse events.

If an increase of haematological parameters (haematocrit, platelets, leukocytes) is observed, the dose and/or dosing interval needs to be adapted individually.

Special populations

Hepatic impairment
In patients with compensated cirrhosis (i.e., Child-Pugh A), another pegylated interferon alfa medicinal product (pegylated interferon alfa-2a) has been shown to be safe. No ropeginterferon alfa-2b dose adjustment is required for adult patients with mild liver impairment.

The use of interferon alfa has not been evaluated in patients with decompensated cirrhosis (i.e., Child-Pugh B or C) and is contraindicated in these patients (see section 4.3).

Increased liver enzyme levels have been observed in patients treated with ropeginterferon alfa-2b. When the increase in liver enzyme levels is progressive and persistent, the dose should be reduced. If the increase in liver enzymes is progressive and clinically significant despite dose reduction, or if there is evidence of hepatic decompensation, therapy should be discontinued (see section 4.4).

Renal impairment
The pharmacokinetic profile of other interferon alfa medicinal products (pegylated interferon alfa-2a and pegylated interferon alfa-2b) was evaluated in renal impaired patients (see section 5.2).

No dose adjustment for ropeginterferon alfa-2b is required for adult patients with mild (GFR 60-89 mL/min) or moderate (GFR 30-59 mL/min) renal impairment. A reduced starting dose for ropeginterferon alfa-2b of 50 micrograms is recommended for patients with severe (GFR 15-29 mL/min) renal impairment. Ropeginterferon alfa-2b is contraindicated in patients with end stage renal disease (GFR < 15 mL/min) (see section 4.3).

Elderly
Adjustments in the recommended dose for ropeginterferon alfa-2b are not necessary when starting therapy in elderly patients (see section 5.2).

Obese or underweighted patients
The pharmacokinetic profile of ropeginterferon alfa-2b has not been determined in obese and underweighted patients. No recommendation on dose adjustment for ropeginterferon alfa-2b can be given for these patients.

Paediatric population
The safety and efficacy of Besremi in children and adolescents has not been established. No data are available (see section 4.4).

Race
No dose adjustment is necessary based on race (see section 5.2).

Method of administration

For subcutaneous use. The medicinal product is intended for long-term treatment and can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections with the pre-filled pen. The instructions for use in the package leaflet should be followed.

The recommended injection site is the abdominal skin around but not within 5 cm of the navel or the thigh. Do not inject into an area where the skin is irritated, reddened, bruised, infected, or scarred. The pen allows for adjustable dosing increments in the range of 50 to 250 micrograms or 50 to 500 micrograms.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Pre-existing thyroid disease unless it can be controlled with conventional treatment
- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt
- Severe pre-existing cardiovascular disease, (i.e., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction
- History or presence of autoimmune disease
- Immunosuppressed transplant recipients
- Combination with telbivudine (see section 4.5)
- Decompensated cirrhosis of the liver (Child-Pugh B or C)
- End stage renal disease (GFR < 15 mL/min)

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Dose titration phase

The recommended posology for the titration phase of ropeginterferon alfa-2b (see section 4.2) results in a prolonged time to reach the individual optimal dose compared to hydroxycarbamide. In a clinical study in polycythaemia vera, the end of the mean individual titration phase for ropeginterferon alfa-2b was reached after approximately 3.7 months, for hydroxycarbamide after approximately 2.6 months of treatment. Thus, other products (e.g., hydroxycarbamide) may be preferred in patients for whom an early reduction in elevated blood counts is necessary to prevent thrombosis and bleeding.

During the titration phase the efficacy to reduce the cardiovascular and thromboembolic risk of the underlying disease may not be fully established. Patients should be closely monitored, particularly during the titration phase; complete blood counts including determination of haematocrit level, leukocyte and platelet counts should be performed regularly also after the individual optimal dose has been established. Phlebotomy as rescue treatment to normalise blood hyperviscosity may be necessary.

Endocrine system

Before ropeginterferon alfa-2b therapy, any pre-existing thyroid disease needs to be treated and controlled with conventional therapy (see section 4.3). Patients who develop symptoms indicative of a thyroid dysfunction during ropeginterferon alfa-2b therapy, should evaluate their thyroid stimulating hormone (TSH) levels. If TSH levels can be controlled within the normal range, the therapy can be continued.

Diabetes mellitus have been observed with other interferon alfa medicinal products (see section 4.8). Patients with this condition who cannot be effectively controlled by medicinal products should not begin ropeginterferon alfa-2b therapy. Patients who develop this condition during treatment and cannot be controlled by medicinal products should discontinue ropeginterferon alfa-2b therapy.

Central nervous system (CNS)

CNS effects, particularly depression, have been observed in some patients treated with ropeginterferon alfa-2b during the clinical development program (see section 4.8). Other CNS effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa medicinal products. Patients should be closely monitored for any symptoms of psychiatric disorders and therapeutic management should be considered by the treating physician if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue ropeginterferon alfa-2b therapy. Ropeginterferon alfa-2b must not be administered in patients with existence of or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt (see section 4.3).

Cardiovascular system

Cardiac events including cardiomyopathy, myocardial infarction, atrial fibrillation and ischaemic coronary artery disorders have been associated with interferon alfa treatment (see section 4.8). Patients with pre-existing or a history of cardiovascular disorders should be closely monitored during ropeginterferon alfa-2b therapy. This medicinal product is contraindicated in patients with severe pre-existing cardiovascular disease or patients who had recently suffered from a stroke or myocardial infarction (see section 4.3).

Respiratory system

Respiratory disorders such as lung infiltration, pneumonitis, pneumonia, or pulmonary arterial hypertension have been observed rarely in patients treated with interferon alfa (see section 4.8). Patients who develop respiratory symptoms should be monitored closely and if necessary, ropeginterferon alfa-2b therapy should be discontinued.

Visual system

Severe eye disorders such as retinopathy, retinal haemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness have been observed rarely in patients treated with interferon alfa (see section 4.8). Patients should have eye examinations before and during ropeginterferon alfa-2b therapy, specifically in those patients with retinopathy associated disease such as diabetes mellitus or hypertension. Any patient reporting a decrease or loss of vision or reporting other eye symptoms should have an immediate eye examination. Discontinuation of ropeginterferon alfa-2b should be considered in patients who develop new or worsening eye disorders.

Acute hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed with other interferon alfa medicinal products. If this occurs, ropeginterferon alfa-2b therapy must be discontinued and appropriate medical therapy instituted immediately. Transient rashes do not necessitate interruption of treatment.

Liver function

Interferon alfa therapy has been associated with hepatotoxicity characteried by potentially significant increases in liver enzymes. Hepatic failure in hepatitis C virus infected patients was reported with other interferon alfa medicinal products (see section 4.8).

Increases in ALT (≥ 3 times the upper limit of normal), AST (≥ 3 times the upper limit of normal), GGT (≥ 3 times the upper limit of normal) and bilirubin (> 2 times the upper limit of normal) levels have been observed in patients treated with ropeginterferon alfa-2b. These elevations were mostly transient and occurred during the first treatment year.

Liver disorders have been reported in patients after long-term ropeginterferon alfa-2b therapy (see section 4.8). Liver enzymes and hepatic function should be regularly controlled in patients with long-term ropeginterferon alfa-2b therapy. Treatment with ropeginterferon alfa-2b should be discontinued when, despite dose reduction, the increase in liver enzyme levels is progressive and clinically significant. In patients who develop evidence of hepatic decompensation during treatment, ropeginterferon alfa-2b should be discontinued. Ropeginterferon alfa-2b is contraindicated in patients with decompensated cirrhosis of the liver (see section 4.3).

Renal function

Regardless of the starting dose or degree of renal impairment, patients should be monitored. If renal function decreases during treatment, ropeginterferon alfa-2b therapy should be discontinued. Ropeginterferon alfa-2b is contraindicated in patients with end stage renal disease (see section 4.3).

Dental and periodontal disorders

Dental and periodontal disorders, which may lead to loss of teeth, have been reported with other interferon alfa medicinal products (see section 4.8). In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with ropeginterferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations.

Skin disorders

The use of ropeginterferon alfa-2b is associated with skin disorders (pruritus, alopecia, rash, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, hyperhydrosis). In case of appearance or worsening of this skin disorders, the stop of the treatment must be envisaged.

Excipients

Besremi contains benzyl alcohol.
High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Besremi contains polysorbate 80.
This medicinal product contains 0.025 mg of polysorbate 80 in each 0.5 mL. Polysorbates may cause allergic reactions.

Besremi contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Enzymes of the protein catabolism are considered to be involved in the metabolism of ropeginterferon alfa-2b. The involvement of transport proteins in absorption, distribution and elimination of ropeginterferon alfa-2b is not known. Interferon alfa has shown to influence the activity of cytochrome P450 (CYP) isozymes CYP1A2 and CYP2D6.

No interaction studies have been performed with ropeginterferon alfa-2b.

Interaction studies of other pegylated interferon alfa medicinal products
Co-administration of pegylated interferon alfa-2a with telbivudine in patients with hepatitis B increased the risk of developing peripheral neuropathy. A combination therapy with telbivudine and ropeginterferon alfa-2b is contraindicated (see section 4.3).

Administration of 180 micrograms of pegylated interferon alfa-2a once weekly for 4 weeks in healthy male subjects did not show any effect on mephenytoin, dapsone, debrisoquine and tolbutamide pharmacokinetics profiles, suggesting that pegylated interferon alfa-2a has no effect on *in vivo* metabolic activity of cytochrome P450 (CYP) 3A4, 2C9, 2C19 and 2D6 isozymes. In the same study, a 25% increase in the AUC of theophylline (CYP1A2 substrate) was observed, demonstrating that pegylated interferon alfa-2a is an inhibitor of CYP1A2 activity.

Co-administration of pegylated interferon alfa-2b showed no significant interaction with tolbutamide (CYP2C9 substrate), midazolam (CYP3A4 substrate), dapsone (N-acetyltransferase substrate) and modestly increased the exposure of caffeine (CYP1A2 substrate) and desipramine (CYP2D6 substrate).

Therefore, care should be taken when ropeginterferon alfa-2b is co-administered with CYP1A2 substrates notably those having a narrow therapeutic margin such as theophylline or methadone. Likewise, caution is recommended with CYP2D6 substrates (e.g., vortioxetine, risperidone) combined with ropeginterferon alfa-2b. Ropeginterferon alfa-2b may inhibit the activity of CYP1A2 and CYP2D6 and thus may increase the blood concentrations of these medicinal products.

No dose adaptions for ropeginterferon alfa-2b should be necessary when concomitantly administered with medicinal products metabolised via CYP2C9/19, CYP3A4 or by N-acetyltransferase.

Caution must be exercised when administering ropeginterferon alfa-2b in combination with other potentially myelosuppressive/chemotherapeutic agents.
Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with ropeginterferon alfa-2b.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective contraception during the treatment with ropeginterferon alfa-2b, unless otherwise discussed with the physician.

Pregnancy

There are no or limited amount of data from the use of interferon alfa in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3).
As ropeginterferon alfa-2b may have the same effect, Besremi is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether ropeginterferon alfa-2b is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Besremi therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of ropeginterferon alfa-2b therapy on the fertility of females or males.

4.7 Effects on ability to drive and use machines

Besremi has minor influence on the ability to drive and use machines. Patients who experience dizziness, somnolence or hallucination (see section 4.8) during Besremi therapy should avoid driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are leukopenia (20.2%), thrombocytopenia (18.5%), arthralgia (13.5%), fatigue (12.4%), increased gamma-glutamyltransferase (11.2%), influenza-like illness (11.2%), myalgia (10.7%), anaemia (9.6%), increased alanine aminotransferase (8.4%), neutropenia (7.9%), pyrexia (7.9%), increased aspartate aminotransferase (7.3%), pruritus (6.8%), pain in extremity (6.7%), alopecia (6.7%), headache (6.2%), diarrhoea (5.7%), injection site reaction (5.6%), chills (5.1%), and dizziness (5.1%).

Serious adverse reactions are depression (1.1%), atrial fibrillation (1.1%) 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 from available 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
Blood and lymphatic system disorders	*very common*	leukopenia, thrombocytopenia
	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, intracardiac thrombus, 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[#]
Hepatobiliary disorders	*very common*	gamma-glutamyltransferase increased
	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 below pulmonary arterial hypertension.
**e.g., urticaria, angioedema, bronchoconstriction, or anaphylaxis.

Description of selected adverse reactions

Most common adverse reactions
The most common adverse reactions (including number of patients, incidence rate, severity grade, necessity for dose adaptation and outcome) reported during the ropeginterferon alfa-2b clinical development program are summarised in Table 1.

Table 1. Most common adverse reactions during ropeginterferon alfa-2b treatment.

ADR >10% PT	N (%) N = 178	IR	CTCAE intensity grade ≥3 N (%)	Dose reduced N (%)	Medicinal Product interrupted N (%)	Medicinal Productdiscontinued N (%)	Recovered N (%)
Leukopenia	36 (20.2)	21.2	3 (8.3)	24 (66.7)	7 (19.4)	n.r.	35 (97.2)
Thrombo-cytopenia	33 (18.5)	11.2	4 (12.1)	13 (39.4)	3 (9.1)	1 (3.0)	30 (90.9)
Arthralgia	24 (13.5)	5.2	1 (4.2)	5 (20.8)	5 (20.8)	1 (4.2)	22 (91.7)
Fatigue	22 (12.4)	6.6	n.r.	4 (18.2)	1 (4.5)	1 (4.5)	21 (95.5)
Gamma-glutamyl-transferase increased	20 (11.2)	7.9	7 (35.0)	9 (45.0)	5 (25.0)	n.r.	17 (85.0)
Influenza like illness	20 (11.2)	4.9	n.r.	4 (20.0)	3 (15.0)	n.r.	19 (95.0)
Myalgia	19 (10.7)	3.5	n.r.	6 (31.6)	1 (5.3)	n.r.	17 (89.5)

No CTCAE grade 5 (death) adverse reactions reported for these preferred terms; 1 AE grade 4 (life-threating or disabling) reported for Gamma-glutamyltransferase increased.
Abbreviations: CTCAE, common terminology criteria for adverse events; n.r., not reported; ADR, adverse drug reaction; PT, preferred term; IR, incidence rate of mean adverse events per 100 patients per year; n, number of patients.
N (%) number and percentage of patients with given AE

Gastrointestinal disorders
Gastrointestinal disorders have been reported with other interferon alfa medicinal products and have been reported in 15.7% of patients with ropeginterferon alfa-2b treatment. The most common

gastrointestinal disorders reported in these studies were diarrhoea (5.1%; incidence rate: 2.8 [events/100 patients per year]) and nausea (4.5%; incidence rate: 1.2 events/100 patients per year]).

CNS
In the clinical development program of ropeginterferon alfa-2b, two cases of serious depression (1.1%; incidence rate: 0.4 events/100 patients per year) occurred. The patients recovered completely after permanent medicinal product discontinuation. One patient who experienced serious acute stress disorder (0.6%; incidence rate: 0.2 events/100 patients per year) with moderate intensity recovered completely after the dose of ropeginterferon alfa-2b was reduced. CNS effects including suicide attempt, suicidal ideation, aggression, bipolar disorder, mania and confusion have been reported with interferon alfa (see section 4.4).

Cardiovascular system
During ropeginterferon alfa-2b therapy, three cases of atrial fibrillation (1.1%; incidence rate: 0.3 events/100 patients per year) with intensity grade 1 to 3 occurred in two patients. Ropeginterferon alfa-2b treatment was continued, and the patients received appropriate medicinal products to treat these events. Patients recovered from the two events; one event was ongoing at the time of assessment.

Respiratory system
Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa.

Visual system
Serious eye disorders have been reported with interferon alfa such as retinopathy, retinal haemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During the clinical study program, one accidental case of overdose has been reported with ropeginterferon alfa-2b. The patient received a 10-time higher starting dose as recommended and developed flu-like symptoms for three days which were rated as non-serious. The patient recovered completely after paracetamol administration and temporary discontinuation of ropeginterferon alfa-2b therapy.

There is no antidote for the medicinal product available. In case of an overdose, close monitoring of the patient and symptomatic treatment, if necessary, are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB15

Ropeginterferon alfa-2b is a recombinant interferon alfa-2b conjugated with a two-arm mPEG at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 60 kDa, of which the PEG moiety constitutes approximately 40 kDa .

Mechanism of action

Interferon alfa belongs to the class of type I interferons which exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signalling cascade through the activation of kinases, particularly Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and signal transducer and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. Interferon alfa was shown to have an inhibitory effect on the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonised the action of growth factors and other cytokines that have a role in the development of myelofibrosis. These actions may be involved in the therapeutic effects of interferon alfa in polycythaemia vera.

Further, it was demonstrated that interferon alfa is able to decrease the mutated *JAK2*V617F allele burden in patients with polycythaemia vera (a V617F point mutation in the JAK2 kinase is a hallmark of polycythaemia vera and is present in approximately 95% of patients).

Clinical efficacy and safety

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.

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 × 10^9/L and leukocytes < 10 × 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 *JAK2*V617F allele burden (16.6%) and *JAK2*V617F allele change from baseline (-25.4%).

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

Disease response	Patients treated with ropeginterferon alfa-2b 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)

* At 12, 24, 36 and 72 months respectively, 0, 7, 12, and 25 patients were considered non-responders due to study discontinuation for any reason
[a] 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; discontinued patients were considered non-responders
[b] defined as the improvement of disease-related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache); discontinued patients were considered non-responders
[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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Besremi in all subsets of the paediatric population in the treatment of polycythaemia vera (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absorption of ropeginterferon alfa-2b is sustained in patients with peak serum concentrations reached after 3 to 6 days.

The absolute bioavailability of subcutaneous administered ropeginterferon alfa-2b was not investigated in humans. Thus, no valid estimation of the absolute bioavailability could be done. Based on data in monkeys, it is approx. 80%, similar to that seen for pegylated interferon alfa-2a.

Distribution

Ropeginterferon alfa-2b is found mainly in the bloodstream and extracellular fluid as seen by the volume of distribution at steady-state (V_d) of 6.6 to 17 litres in patients after subcutaneous administration (dose range 50 – 450 micrograms). Mean C_{max} was 2.4 ng/mL (with a dose of 50 – 80 micrograms) to 49 ng/mL (with a dose of 450 micrograms) and AUC_{0-t} ranged from 28.5 ng*h/mL (with a dose of 50 – 80 micrograms) to 552.6 ng*h/mL (with a dose of 450 micrograms) in patients after subcutaneous multiple dose administration. Inter-subject variability was observed with 25% and 35% for AUC and C_{max}, respectively, in healthy volunteers.

In patients who received ropeginterferon alfa-2b at 2-weeks interval (400 – 500 micrograms, PK Group 1) or at 4-weeks interval (100 - 500 [mean 350] micrograms, PK Group 2) at steady-state, mean Vd_{ss} was 10.7 L in PK Group 1 and 18.3 L in PK Group 2. In PK Group 1 mean $C_{max,ss}$ was 28.26 ng/mL, $AUC_{tau,ss}$ was 7 504.0 ng*h/mL and C_{min} was 14.52 ng/mL. In PK Group 2 mean $C_{max,ss}$ was 18.82 ng/mL, $AUC_{tau,ss}$ was 6 021.3 ng*h/mL and C_{min} was 2.10 ng/mL.

From mass balance, tissue distribution and whole body autoradioluminography studies performed in rats, it was shown that a similar interferon alfa medicinal product (pegylated interferon alfa-2a) was distributed to the liver, kidney and bone marrow in addition to being highly concentrated in the blood.

Biotransformation

The metabolism of ropeginterferon alfa-2b is not fully characterised. The attachment of interferon alfa-2b to a high molecular weight (40 kDa) branched polyethylene glycol moiety is considered as the main reason for the differences in the elimination compared to unpegylated interferons. Studies in rats with a similar interferon alfa medicinal product (pegylated interferon alfa-2a) showed a primarily elimination via hepatic metabolism. The same elimination route is considered for ropeginterferon alfa-2b.

Pharmacokinetic interaction studies in humans with pegylated interferon alfa-2a indicated a moderate inhibitory effect on substrates metabolised by CYP1A2 and CYP2D6 (see section 4.5).

Elimination

The elimination of ropeginterferon alfa-2b is not fully characterised. Studies with a similar interferon alfa medicinal product (pegylated interferon alfa-2a) indicated that the kidney is a major organ for excretion of radiolabelled metabolic products (study in rats) and that the systemic clearance of pegylated interferon alfa-2a in humans is about 100-fold lower compared to the native, unpegylated interferon alfa-2a.

After subcutaneous multiple dose administration (dose range 50 – 500 micrograms), the terminal half-life of ropeginterferon alfa-2b in patients is approximately 6 to 10 days and the clearance of ropeginterferon alfa-2b is 0.023 to 0.066 L/h.
The involvement of transport proteins in absorption, distribution, and elimination of ropeginterferon alfa-2b is not known.

Linearity/non-linearity

Over a dose range of 24 to 270 micrograms, ropeginterferon alfa-2b C_{max} increased proportionally with dose in a pharmacokinetic study with healthy subjects. A higher than proportional increase in exposure was observed. Inter-subject variability for ropeginterferon alfa-2b was 35% (C_{max}) and 25% (AUC).

Hepatic impairment

Comparable exposure and pharmacokinetic profile were reported for another interferon alfa medicinal product (pegylated interferon alfa-2a) in cirrhotic (Child-Pugh A) and non-cirrhotic patients. Pharmacokinetics were not evaluated in patients with increased severity of hepatic impairment.

Renal impairment

The pharmacokinetic profile in patients with moderate or severe renal impairment and in patients with end stage renal disease (ESRD) has been evaluated only for other pegylated interferon alfa medicinal products.

Patients with moderate or severe renal impairment receiving 180 micrograms of pegylated interferon alfa-2a once weekly showed a comparable or 60% higher drug plasma exposure, respectively, compared to subjects with normal renal function.

In 13 patients with ESRD requiring chronic haemodialysis, administration of 135 micrograms pegylated interferon alfa-2a once weekly resulted in a 34% lower drug exposure than in patients with normal renal function.

Patients with renal impairment receiving a single dose of 1.0 micrograms/kg pegylated interferon alfa-2b showed an increased relation of C_{max}, AUC, and half-life to the degree of renal impairment. Following multiple dosing of pegylated interferon alfa-2b (1.0 micrograms/kg subcutaneously administered every week for four weeks), the clearance of pegylated interferon alfa-2b was reduced by a mean of 17% and 44% in patients with moderate or severe renal impairment, respectively, compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on haemodialysis and in patients who received haemodialysis.

Elderly

Only limited pharmacokinetic data are available from the use of ropeginterferon alfa-2b in the elderly. Based on the results from the PROUD-PV and CONTINUATION-PV Study on drug exposure, pharmacodynamic response and tolerability, a dose adjustment for ropeginterferon alfa-2b is not considered necessary in the elderly population.

Obese or underweight patients

The pharmacokinetic profile of ropeginterferon alfa-2b has not been determined in obese and underweight patients.

Race

Race had no clinically meaningful effect on the pharmacokinetics of ropeginterferon alfa-2b based on an analysis of available pharmacokinetic data, including Caucasian, Japanese and Chinese subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Reproductive and developmental studies were not performed with ropeginterferon alfa-2b. Interferon alfa was shown to be abortifacient in primates and ropeginterferon alfa-2b is expected to have a similar effect. Effects on fertility was not assessed.

It is unknown if the active substance of the medicinal product is excreted into experimental animal or human milk (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate, anhydrous
Acetic acid, glacial
Benzyl alcohol
Polysorbate 80
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen

3 years.

Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen

3 years.

After first use

The pre-filled pen may be stored for a maximum of 30 days in the refrigerator (2 °C - 8 °C) when stored with the pen cap on and kept in the outer carton in order to protect from light. The pre-filled pen may be used up to two times within these 30 days. Any medicinal product remaining in the pre-filled pen after the second use and/or after 30 days must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen

The pre-filled pen is made of white polypropylene, with a grey push button and the strength "250 mcg/0.5 mL" highlighted in grey on the label. It delivers doses of 50 micrograms to 250 micrograms. Each click and each dot in the dosing window represents 5 micrograms. Every other click and dot is additionally labelled with the number of micrograms (i.e. in 10 micrograms steps).

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen is available in 2 pack-sizes:
- Packs containing 1 pre-filled pen and 2 injection needles
- Packs containing 3 pre-filled pens and 6 injection needles

Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen

The pre-filled pen is made of white polypropylene, with a blue push button and the strength "500 mcg/0.5 mL" highlighted in blue on the label. It delivers doses of 50 micrograms, 100 micrograms, 150 micrograms, 200 micrograms, 250 micrograms, 300 micrograms, 350 micrograms, 400 micrograms, 450 micrograms and 500 micrograms.

Each pack of Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen contains:
- 1 pre-filled pen and 2 injection needles.

Each pre-filled pen contains a cartridge (type 1 colourless glass) with a grey plunger (bromobutyl rubber) and a flanged cap (aluminium) with a stopper (bromobutyl rubber). The cartridge is sealed in a pen injector. Each cartridge contains 0.5 mL of solution.

6.6 Special precautions for disposal and other handling

Before use, the pre-filled pen should be brought to room temperature (15 °C - 25 °C) for up to 15 minutes.

Since Besremi is a solution, it does not require resuspension before use. Inspect the solution before use. It may only be used if the solution is clear, colourless to pale yellow, with no particles visible.

The pre-filled pen label must always be checked before each injection to avoid medication errors between Besremi 250 micrograms/0.5 mL solution for injection and Besremi 500 micrograms/0.5 mL solution for injection. The 250 micrograms/0.5 mL pre-filled pen has a grey push button. The 500 micrograms/0.5 mL pre-filled pen has a blue push button.

A new, sterile needle as provided with the pre-filled pen must be carefully attached onto the pre-filled pen before each injection. Needles must be discarded immediately after use.

If the pre-filled pen is used for the first time, the pen is prepared for injection by turning the dose knob until the icon of a "drop" in the dosing window is seen. While holding the pre-filled pen with the needle pointing upwards, tap the pre-filled pen gently with the fingers so that any air bubbles rise towards the needle. Then press the push button until the dosing window shows "0". This may be repeated up to six times. Once a droplet of liquid appears at the needle tip, the pre-filled pen and the needle are working properly.

The dose can be selected by rotating the dose knob. If a certain dose cannot be set, an insufficient quantity of medicinal product may be left in the pen and a new pen must be used.

The needle should be inserted into the skin. The push button should be pressed in completely and held down for at least 10 seconds before removing the needle.

To prevent possible transmission of disease or any kind of contamination, the use of Besremi pre-filled pen should remain strictly for a single patient, even when the needle is changed. The pre-filled pen may not be used more than twice and must be discarded 30 days after the first use, regardless of any medicinal product remaining in the pre-filled pen.

Empty pens must never be reused and must be properly discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1352/001
EU/1/18/1352/002
EU/1/18/1352/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2019
Date of latest renewal: 7 December 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
PharmaEssentia Corp.
3F, No. 28, Keya West Road
Daya District
428 Taichung
TAIWAN

Name and address of the manufacturer(s) responsible for batch release
AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen
ropeginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 mL solution contains 250 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 500 micrograms/mL.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, anhydrous sodium acetate, glacial acetic acid, water for injections, and benzyl alcohol.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen

1 pre-filled pen + 2 injection needles
3 pre-filled pens + 6 injection needles
0.5 mL solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after first use: may be stored for a maximum of 30 days in the refrigerator (2 °C - 8 °C) when stored with the pen cap on and kept in the outer carton in order to protect from light.
Opened date:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1352/001
EU/1/18/1352/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Besremi 250 micrograms/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Besremi 250 mcg/0.5 mL injection
ropeginterferon alfa-2b
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen
ropeginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of 0.5 mL solution contains 500 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 1,000 micrograms/mL.

3. LIST OF EXCIPIENTS

Also contains sodium chloride, polysorbate 80, anhydrous sodium acetate, glacial acetic acid, water for injections, and benzyl alcohol.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen
1 pre-filled pen + 2 injection needles
0.5 mL solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after first use: may be stored for a maximum of 30 days in the refrigerator (2 °C - 8 °C) when stored with the pen cap on and kept in the outer carton in order to protect from light.
Opened date:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1352/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Besremi 500 micrograms/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Besremi 500 mcg/0.5 mL injection
ropeginterferon alfa-2b
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen
ropeginterferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Besremi is and what it is used for
2. What you need to know before you use Besremi
3. How to use Besremi
4. Possible side effects
5. How to store Besremi
6. Contents of the pack and other information

1. What Besremi is and what it is used for

Besremi contains the active substance ropeginterferon alfa-2b, which belongs to the class of medicines called interferons. Interferons are produced by your immune system to block the growth of cancer cells.

Besremi is used as monotherapy for the treatment of polycythaemia vera in adults. Polycythaemia vera is a type of cancer in which the bone marrow produces too many red blood cells, white blood cells and platelets (cells that help the blood to clot).

2. What you need to know before you use Besremi

Do not use Besremi
- if you are allergic to ropeginterferon alfa-2b or any of the other ingredients of this medicine (listed in section 6).
- if you have thyroid disease that is not controlled with medicines.
- if you have or had severe mental disorders (such as depression or suicidal thoughts or if you tried to kill yourself).
- if you have recently had severe heart problems (such as heart attack or stroke)
- if you have or had an autoimmune disease (such as rheumatoid arthritis, psoriasis or inflammatory bowel disease).
- if you had an organ transplantation and you take medicines which suppress your immune system.
- if you take telbivudine (a medicine used to treat hepatitis B infection).
- if you have advanced, uncontrolled liver disease.
- if you have severe kidney disease (with your kidneys working at less than 15% of their normal ability).

Warnings and precautions
Talk to your doctor before using Besremi:

- if you have thyroid disease.
- if you have diabetes or high blood pressure – your doctor may ask you to have an eye examination.
- if you have liver problems – you will have blood tests regularly to check how your liver is working if you are on a long-term Besremi therapy.
- if you have kidney problems.
- if you have psoriasis or other skin problems because they may get worse during treatment with Besremi.

Once you have started Besremi treatment, talk to your doctor:
- if you develop symptoms of depression (such as feelings of sadness, dejection, and suicidal thoughts).
- if you develop signs of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while using Besremi – if this is the case you will need to seek medical help immediately.
- if you develop symptoms of a cold or other respiratory infection (such as difficulty in breathing, cough, fever and chest pain).
- if you have changes in your vision – you must tell your doctor and have an immediate eye examination. Severe eye problems may occur during Besremi therapy. Your doctor will usually check your vision before starting your treatment. If you have health problems which may lead to eye problems such as diabetes or high blood pressure, you doctor should check your vision also during treatment. If your vision worsens, your doctor may decide to discontinue your treatment.

Dental and gum disorders, which may lead to loss of teeth, can occur with interferon medicines. In addition, dry mouth could damage teeth and the lining of the mouth during long-term treatment with Besremi. You should brush your teeth thoroughly twice daily and have regular dental checks.

It will need a certain time to reach your individual optimal dose of Besremi. Your doctor will decide if it is necessary to treat you with another medicine for an early reduction of your blood cell number to prevent blood clots and bleeding.

Children and adolescents
Do not give this medicine to children and adolescents because no information is available on the use of Besremi in this age group.

Other medicines and Besremi
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Do not use Besremi if you are taking telbivudine (for treating hepatitis B) since the combination of these medicines increases the risk of peripheral neuropathy (numbness, tingling, or burning sensations in the arms and legs). Tell your doctor if you are being treated with telbivudine.

Tell your doctor especially if you are taking any of the following medicines:
- theophylline (a medicine used to treat respiratory diseases such as asthma)
- methadone (a medicine used to treat pain or opioid dependence)
- vortioxetine or risperidone (medicines used to treat mental disorders)
- anti-cancer medicines such as those stopping or slowing the growth of blood-forming cells in the bone marrow (e.g. hydroxycarbamide)
- medicines that work on the central nervous system to relieve pain, help you sleep, or have a calming effect (e.g. morphine, midazolam)

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

<u>Pregnancy</u>

The effect of Besremi during pregnancy is not known. The use of Besremi is not recommended during pregnancy. If you are a woman of childbearing potential, your doctor will discuss with you if effective birth control should be used during your treatment with Besremi.

Breast-feeding
It is not known if Besremi is present in breast milk. Your doctor will help you decide if you have to stop breast-feeding when you are using this medicine.

Driving and using machines
Do not drive or use machines if you feel dizzy, sleepy or confused while using Besremi.

Besremi contains benzyl alcohol
This medicine contains 5 mg benzyl alcohol in each 0.5 mL. Benzyl alcohol may cause allergic reactions.
Ask your doctor or pharmacist for advice:
- if you are pregnant or breast-feeding.
- if you have a liver or kidney disease.

This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

Besremi contains polysorbate 80
This medicine contains 0.025 mg of polysorbate 80 in each 0.5 mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Besremi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

3. How to use Besremi

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The dose will be set individually for you by your doctor for your condition. The usual starting dose of Besremi is 100 microgram every 2 weeks. Your doctor will then increase your dose stepwise and may adjust your dose during treatment.
Your doctor will reduce your starting dose to 50 micrograms if you have severe kidney problems.

This medicine is for subcutaneous use which means that it is injected in the tissue under your skin. It should not be injected into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred.
If you are injecting this medicine yourself, you will get clear instructions on how to prepare and inject it.
To prevent passing on infectious diseases, you should never share Besremi pre-filled pen with anyone else, even when the needle is changed.

Details on how to prepare and inject Besremi are given in the Instructions for Use. Read them before you start using Besremi.

If you use more Besremi than you should
Tell your doctor as soon as possible.

If you forget to use Besremi
You should inject the dose as soon as you remember. However, if more than 2 days have passed since you missed the dose, leave out the dose and inject the next dose when it is due. Do not inject a double dose to make up for a forgotten dose. Check with your doctor or pharmacist if you are not sure.

If you stop using Besremi
Do not stop using Besremi before you have talked to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you notice any of the following serious side effects during your treatment with Besremi:

Common side effects (may affect up to 1 in 10 people):
- changes in your heartbeat (when the heart beats very fast and uneven)

Uncommon side effects (may affect up to 1 in 100 people):
- attempted suicide, thoughts about killing yourself
- loss of vision which may be caused by bleeding in the retina (the retina is the light-sensitive layer in the eye), or by build-up of fat in or under the retina

Rare side effects (may affect up to 1 in 1,000 people):
- loss of vision which may be caused by damage to the retina (such as obstruction of the blood vessels in the eye) or the optic nerve

Very rare side effects (may affect up to 1 in 10,000 people):
- blindness
- breathing problems including shortness of breath, cough and chest pain which may be caused by lung infiltration, pneumonia (lung infection), pulmonary arterial hypertension (high blood pressure in the blood vessels bringing blood from the heart to the lungs) and pulmonary fibrosis (a lung disease where scars are formed in the lung tissue)

Side effects with frequency not known (cannot be estimated from the available data):
- detachment of the retina (you may experience eye problems including changes in vision)

Other side effects

Very common side effects (may affect more than 1 in 10 people):
- decrease in the number of a type of white blood cells (called leucocytes) and in blood clotting cells (called platelets)
- joint or muscle pain
- flu-like symptoms, feeling tired
- in blood tests: increase of an enzyme called gamma-glutamyltransferase

Common side effects (may affect up to 1 in 10 people):
- infection of the respiratory tract, runny or stuffy nose, fungal infections, flu
- decrease in the number or size of red blood cells
- increase or decrease in the thyroid gland activity, increase of thyroid stimulating hormone, inflammation of the thyroid gland
- increase of triglycerides (a type of lipid) in the blood, decreased appetite
- aggressive behaviour, feeling depressed, feeling anxious, problems with falling asleep or staying asleep, mood changes, lacking bodily energy or motivation
- headache, feeling dizzy, reduced sense of touch or sensation, feeling sleepy, sensation of tingling and ‘pins and needles’
- dry eyes

- damage of the capillaries (very small blood vessels) in the body
- breathing problems
- diarrhoea, nausea, abdominal pain or stomach discomfort, constipation, dry mouth
- liver disorder, increase in certain liver enzymes (shown in blood tests)
- itching, hair loss, rash, redness of skin, psoriasis, dry and scaly skin, acne, thickening of the outer layer of the skin, increased sweating
- a disorder called Sjogren's syndrome where the body's immune system attacks glands that produce fluid (such as the tear and saliva glands), arthritis, pain in arms and legs, bone pain, painful sudden tightening of a muscle
- fever, weakness, chills, general health problems, irritation or redness at the site of injection, decreasing body weight
- in blood tests: antibodies which are produced by the body´s immune system, increase of an enzyme called lactate dehydrogenase

Uncommon side effects (may affect up to 1 in 100 people):
- infection and re-infection with herpes, bacterial infections
- increase in the number of platelets
- autoimmune disorder of the thyroid gland, sarcoidosis (areas of inflamed tissue in different parts of the body)
- diabetes
- panic attack, hallucination (seeing, hearing or feeling things that are not there), feeling stressed, feeling nervous, lack of interest in activities, nightmare, irritability, confusion
- damage to the nervous system, migraine, mental disorder (health condition involving changes in thinking, emotion or behaviour), visual or sensory disturbances, shaky hands
- eye discomfort, eyelid eczema
- hearing loss, ringing in ears (tinnitus), spinning feeling (vertigo)
- heart disorders such as heart block (a disorder in the heart´s electrical activity), blood clots in the blood vessels of the heart, leakage of the aortic valve
- high blood pressure, reduced blood supply to certain parts of the body, haematoma (collection of blood under the skin), flushing
- inflammation of lung tissue, coughing, nosebleed, sore throat
- inflammation of the stomach, abdominal wall disorder, intestinal gas, indigestion, painful swallowing, bleeding gums
- inflammation of the liver, damage to the liver, enlarged liver
- sensitivity to sunlight, peeling of the skin, nail disorder
- muscle weakness, neck pain, groin pain
- inflammation of the bladder, painful urination, increased need to urinate, inability to urinate
- sexual problems
- pain or itching at the site of injection, sensitivity to weather change
- non-acute porphyria (a liver disorder in which substances called porphyrins build up in the skin causing local skin damage, such as rashes, blisters, sores or discomfort, upon sun exposure)
- in blood tests: increase of uric acid, antibodies produced by the body´s immune system against red blood cells

Rare side effects (may affect up to 1 in 1,000 people):
- bipolar disorders (mood disorders with episodes of sadness and excitement), mania (extreme excitement or unreasonable enthusiasm)
- cardiomyopathy (diseases that affect the heart muscle), angina pectoris (a severe chest pain as a result of blockage of the heart vessels)
- liver failure

Very rare side effects (may affect up to 1 in 10,000 people):
- idiopathic or thrombotic thrombocytopenic purpura (increased bruising, bleeding, decreased platelets, anaemia and extreme weakness)
- myocardial ischemia (reduced blood flow to your heart muscle)

Side effects with frequency not known (cannot be estimated from the available data):
- Vogt-Koyanagi-Harada disease (a rare disease that can lead to loss of vision, hearing and skin pigmentation), severe allergic reaction
- discolouration of the skin
- periodontal (affecting gums) and dental disorders, change in colour of the tongue

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Besremi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the outer carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

Once opened, the pre-filled pen may be stored for a maximum of 30 days in the refrigerator (2 °C - 8 °C) when stored with the pen cap on and kept in the outer carton in order to protect from light.

Do not use this medicine if you notice that the pre-filled pen appears damaged, the solution is cloudy, has particles or flakes, or has any colour other than colourless to slightly yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Besremi contains
- The active substance is ropeginterferon alfa-2b.
  Each pre-filled pen of 0.5 mL solution contains 250 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 500 micrograms/mL.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, anhydrous sodium acetate, glacial acetic acid, and water for injections. For benzyl alcohol, polysorbate 80 and sodium, see section 2 "Besremi contains benzyl alcohol", "Besremi contains polysorbate 80" and "Besremi contains sodium".

What Besremi looks like and contents of the pack
Besremi is presented as a solution for injection (injection) in a pre-filled pen. Each pre-filled pen contains 0.5 mL of solution. It is available in packs containing:
1 pre-filled pen and 2 injection needles (Type: mylife AutoProtect PRO 29G × 8 mm)
- 3 pre-filled pens and 6 injection needles (Type: mylife AutoProtect PRO 29G × 8 mm).

Marketing Authorisation Holder and Manufacturer
AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for Use

Please read this leaflet carefully before using the Besremi 250 micrograms pre-filled pen. If you have any further questions, ask your doctor or pharmacist.

Your doctor or pharmacist will show you how to use the pen.
The Besremi 250 micrograms pre-filled pen can be used to inject doses within the range of 50 to 250 micrograms in 5 microgram increments. The same pen can be used twice, as long as the sum of the two doses does not exceed 250 micrograms. Your doctor will tell you the dose you need. Please note down your injection dates and dose as instructed by your doctor.
If you need a dose of more than 250 micrograms, you require two Besremi 250 microgram pre-filled pens. You must use a different injection site for each of the two pens. Your doctor or pharmacist will explain to you how to use the two pens.

Store the pen in the outer carton in the refrigerator.
Remove the pen from the refrigerator 15 minutes before the injection to let it reach room temperature.
Find a quiet and well-lit area for the injection.

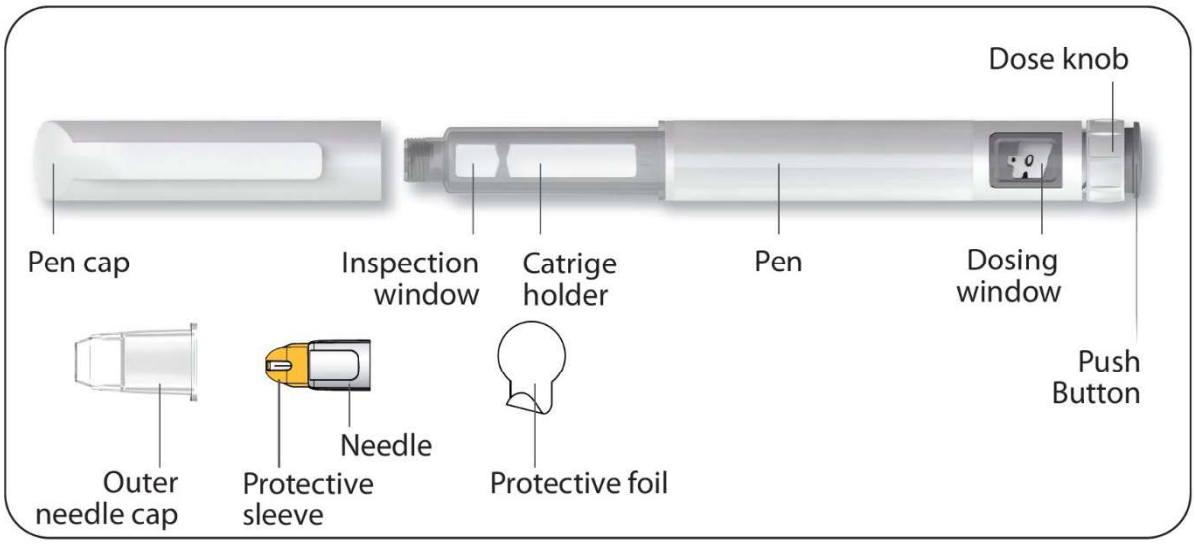
You will need the following supplies for your injection:
• Besremi pre-filled pen
• Needle (Type: mylife AutoProtect PRO 29G × 8 mm)
• Alcohol wipe (not supplied)
• Optional: adhesive plaster (not supplied)

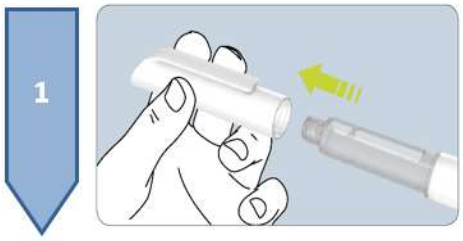
The Besremi pre-filled pen comes with two or six needles (depending on the pack-size). Always use a new needle for each injection.

Note: The pen is also compatible with the following needles:
• AutoShield Duo, 30G × 8 mm safety pen needle
• Ultra-Fine or Micro-Fine or embecta, 31G × 8 mm pen needle
Both needle types can be purchased separately. Please ask your doctor or pharmacist if you wish to use any of these needles instead of the co-packaged needles.

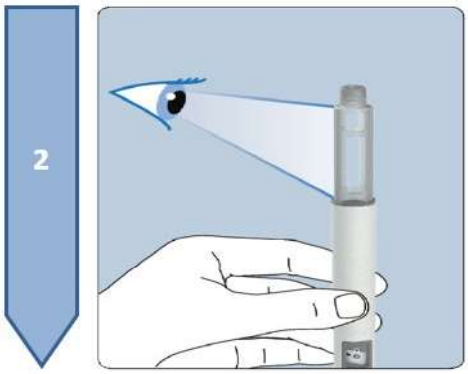
Do not use the pen if it appears damaged. If at any time during the use of the pen, you feel you may have damaged it (e. g. by dropping it or using excessive force), do not continue to use the pen. Get a new pen and start over.

Description Besremi 250 micrograms pre-filled pen

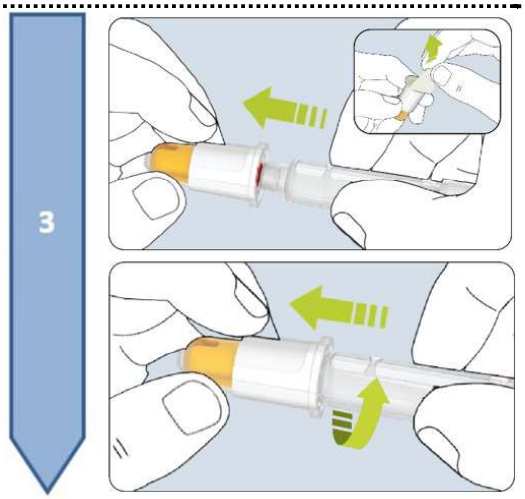




- Wash your hands before using Besremi.
- Check that the product has not expired.
- Remove the cap from the pen.

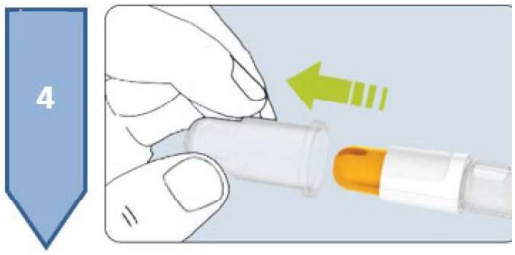


- Check the solution through the inspection windows along the sides of the cartridge holder.
- Do not use the pen if the solution is cloudy, has particles or flakes, or is any colour other than colourless to slightly yellow.

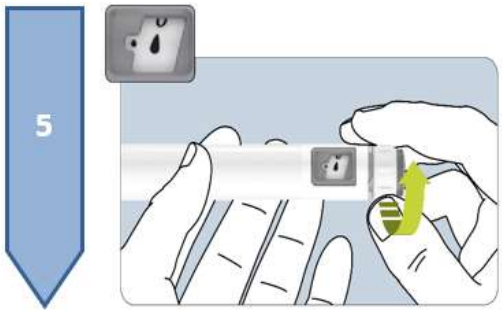


- Take a new needle and remove the protective foil.
- Place the pen straight and centrally arranged onto the needle to prevent it from buckling or bending.
- Make sure that it is firmly attached.

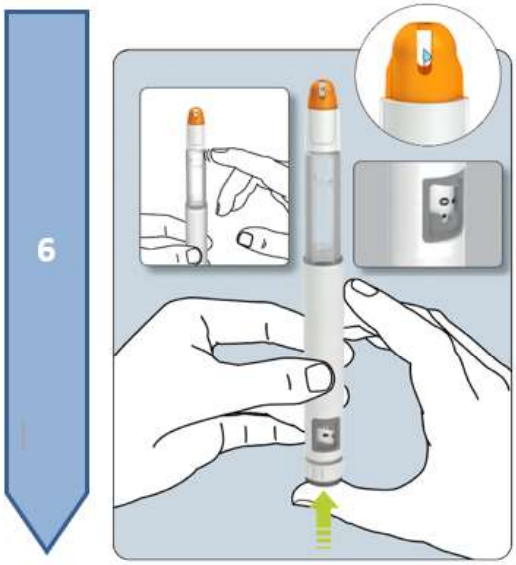
- Screw the needle onto the pen by turning the pen clockwise with gentle pressure until it stops.



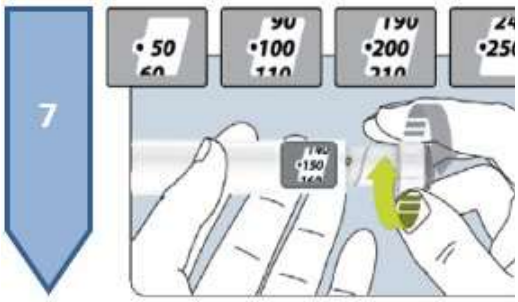
- Remove the outer needle cap from the needle.
- Do not put the outer needle cap back on the needle until you have injected the medicine. Do not touch the needle tip at any time.
- If you have used your Besremi 250 microgram pre-filled pen once before and are using it a second time, continue directly with step 7.
- If you are using this pen for the first time, continue with preparation of the pen in step 5.



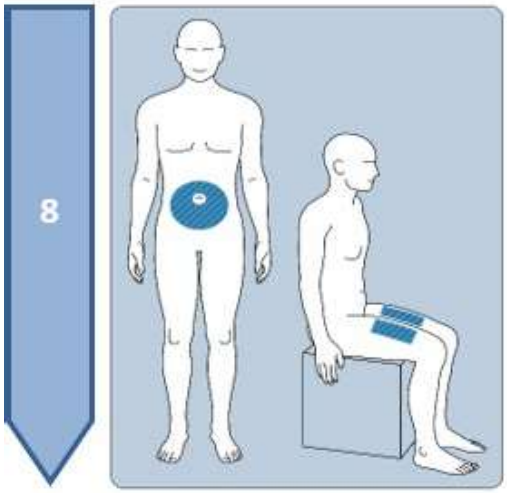
- If you are using this pen for the first time, prepare the pen for injection by turning the dose knob until you see the icon of a “drop” and the dot in the dosing window. The icon of a “drop” must be aligned with the dot in the dosing window.



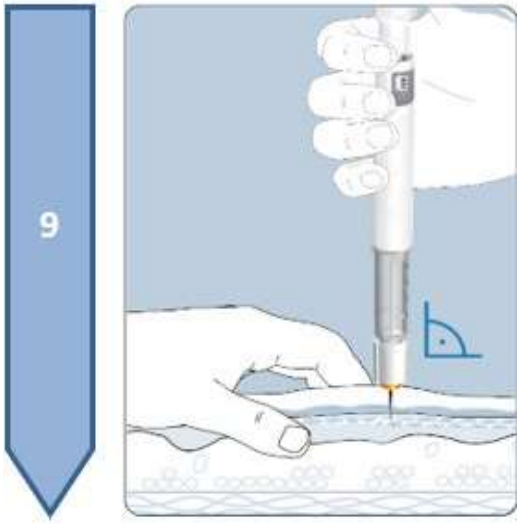
- Hold the pen with the needle pointing upwards and make sure the dosing window is facing you.
- Do not point towards your face or anyone else’s face.
- Tap the pen (cartridge holder) gently with your fingers to allow any air bubbles to rise to the top of the cartridge holder.
- Press the push button with your thumb until the “0” mark is aligned with the dot in the dosing window.
- You will see the window changes between the “drop” icon and the “0” mark, and you will hear gentle clicks when the button moves.
- If you look through the small gap at the top of the orange needle protective sleeve, you should see a droplet of liquid appearing at the needle tip.
- If you do not see a droplet at the needle tip, repeat steps 5 and 6 up to six times until a droplet appears.
- If you do not see the droplet after the seventh time, ask your doctor or pharmacist for advice.



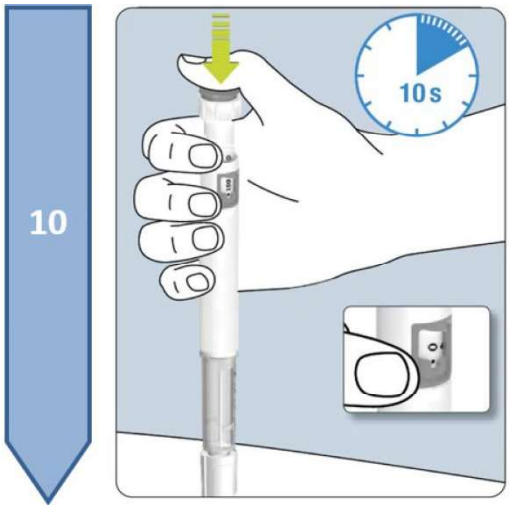
- Between each 10-microgram mark, a dot without a number represents the intermediate 5-microgram dose.
- Set the dose your doctor advised by turning the dose knob until the prescribed dose is visible. The selected dose must align with the dot in the dosing window. If necessary, correct the dose by turning the dose knob up and down.
- If you are unable to reach the required dose setting by turning the dose knob, your pen may be out of sufficient medicine. Do not use any further force. Instead, get a new pen.



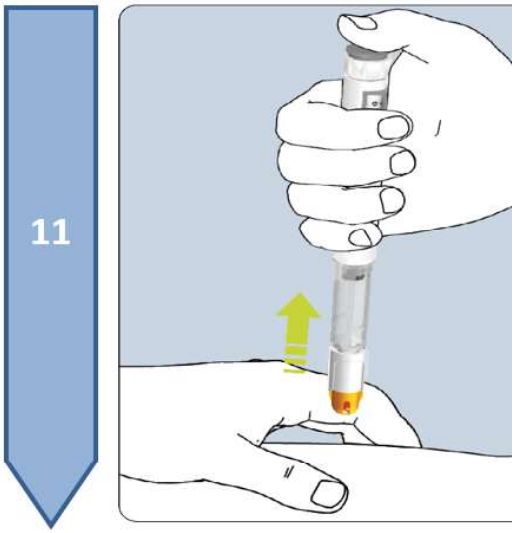
- Disinfect your skin in the injection area using an alcohol swab before the injection.
- Let the area dry before you inject the medicine.
- You must inject the medicine subcutaneously (under the skin). Your doctor will tell you where you must inject it.
- Possible injection sites are the belly (more than five centimetres away from the belly button) or the thigh.
- If you need two pens, use a different injection site for each pen (e. g. right and left side of belly or right and left thigh).
- Do not inject into irritated, reddened, bruised, infected or scarred skin in any way.



- Hold the pen so that the dosing window and the label are visible during the injection.
- Raise a fold of skin between the thumb and forefinger.
- Insert the needle at a 90 degrees angle until the orange protective sleeve on the needle is no longer visible.

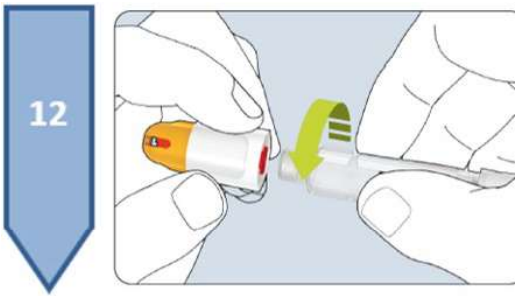


- Press the push button all the way down until the “0” mark is aligned with the dot in the dosing window.
- The soft clicking sounds will stop when the injection is complete.
- Continue pressing the push button while keeping the needle in your skin.
- Count slowly to 10. Do not lift or move the pen during injection.
- If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered.



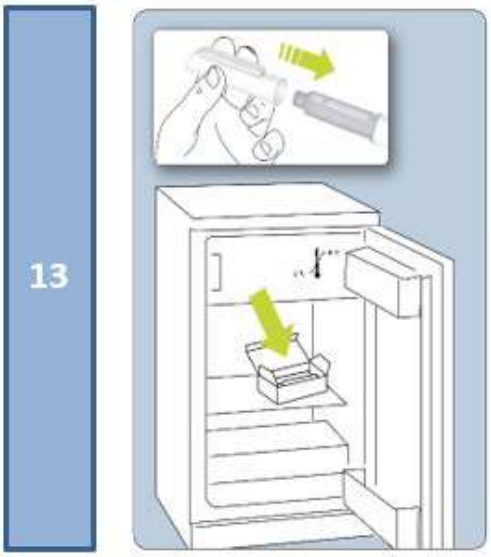
- Carefully remove the needle from the skin by pulling straight upwards.
- Keep the injection site clean until the small injection wound has closed. Apply an adhesive plaster if needed.

Note:
- The orange protective sleeve locks automatically and the now visible red locking indicator covers the needle for your protection. If this is not the case, please ask your doctor or pharmacist.
- After removing the needle, a small droplet of liquid may remain on your skin. This droplet is normal and does not mean that you underdosed.



- Rotate the pen counterclockwise and dispose of the needle properly.

Note:
- Once the needle has been unscrewed, another red locking indicator covers the bottom of the needle for additional safety.



Note: Put the cap back on the pen securely.

Reuse of the pen:
- Your doctor will tell you if you may use the pen for a second injection. In this case, put the pen back into the outer carton and store it in the refrigerator for the next use. Do not use the pen after 30 days.

Disposal of the pen and needle:
- Discard the pen and needle after use according to local regulations or as instructed by your doctor or pharmacist.

Package leaflet: Information for the user

Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen
ropeginterferon alfa-2b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Besremi is and what it is used for
2. What you need to know before you use Besremi
3. How to use Besremi
4. Possible side effects
5. How to store Besremi
6. Contents of the pack and other information

1. What Besremi is and what it is used for

Besremi contains the active substance ropeginterferon alfa-2b, which belongs to the class of medicine called interferons. Interferons are produced by your immune system to block the growth of cancer cells.

Besremi is used as monotherapy for the treatment of polycythaemia vera in adults. Polycythaemia vera is a type of cancer in which the bone marrow produces too many red blood cells, white blood cells and platelets (cells that help the blood to clot).

2. What you need to know before you use Besremi

Do not use Besremi
- if you are allergic to ropeginterferon alfa-2b or any of the other ingredients of this medicine (listed in section 6).
- if you have thyroid disease that is not controlled with medicines.
- if you have or had severe mental disorders (such as depression or suicidal thoughts or if you tried to kill yourself).
- if you have recently had severe heart problems (such as heart attack or stroke)
- if you have or had an autoimmune disease (such as rheumatoid arthritis, psoriasis or inflammatory bowel disease).
- if you had an organ transplantation and you take medicines which suppress your immune system.
- if you take telbivudine (a medicine used to treat hepatitis B infection).
- if you have advanced, uncontrolled liver disease.
- if you have severe kidney disease (with your kidneys working at less than 15% of their normal ability).

Warnings and precautions
Talk to your doctor before using Besremi:
- if you have thyroid disease.

- if you have diabetes or high blood pressure – your doctor may ask you to have an eye examination.
- if you have liver problems – you will have blood tests regularly to check how your liver is working if you are on a long-term Besremi therapy.
- if you have kidney problems.
- if you have psoriasis or other skin problems because they may get worse during treatment with Besremi.

Once you have started Besremi treatment, talk to your doctor:
- if you develop symptoms of depression (such as feelings of sadness, dejection, and suicidal thoughts).
- if you develop signs of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while using Besremi – if this is the case you will need to seek medical help immediately.
- if you develop symptoms of a cold or other respiratory infection (such as difficulty in breathing, cough, fever and chest pain).
- if you have changes in your vision – you must tell your doctor and have an immediate eye examination. Severe eye problems may occur during Besremi therapy. Your doctor will usually check your vision before starting your treatment. If you have health problems which may lead to eye problems such as diabetes or high blood pressure, you doctor should check your vision also during treatment. If your vision worsens, your doctor may decide to discontinue your treatment.

Dental and gum disorders, which may lead to loss of teeth, can occur with interferon medicines. In addition, dry mouth could damage teeth and the lining of the mouth during long-term treatment with Besremi. You should brush your teeth thoroughly twice daily and have regular dental checks.

It will need a certain time to reach your individual optimal dose of Besremi. Your doctor will decide if it is necessary to treat you with another medicine for an early reduction of your blood cell number to prevent blood clots and bleeding.

Children and adolescents
Do not give this medicine to children and adolescents because no information is available on the use of Besremi in this age group.

Other medicines and Besremi
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Do not use Besremi if you are taking telbivudine (for treating hepatitis B) since the combination of these medicines increases the risk of peripheral neuropathy (numbness, tingling, or burning sensations in the arms and legs). Tell your doctor if you are being treated with telbivudine.

Tell your doctor especially if you are taking any of the following medicines:
- theophylline (a medicine used to treat respiratory diseases such as asthma)
- methadone (a medicine used to treat pain or opioid dependence)
- vortioxetine or risperidone (medicines used to treat mental disorders)
- anti-cancer medicines such as those stopping or slowing the growth of blood-forming cells in the bone marrow (e.g. hydroxycarbamide)
- medicines that work on the central nervous system to relieve pain, help you sleep, or have a calming effect (e.g. morphine, midazolam)

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy
The effect of Besremi during pregnancy is not known. The use of Besremi is not recommended during pregnancy. If you are a woman of childbearing potential, your doctor will discuss with you if effective birth control should be used during your treatment with Besremi.

Breast-feeding
It is not known if Besremi is present in breast milk. Your doctor will help you decide if you have to stop breast-feeding when you are using this medicine.

Driving and using machines
Do not drive or use machines if you feel dizzy, sleepy or confused while using Besremi.

Besremi contains benzyl alcohol
This medicine contains 5 mg benzyl alcohol in each 0.5 mL. Benzyl alcohol may cause allergic reactions.
Ask your doctor or pharmacist for advice:
- if you are pregnant or breast-feeding.
- if you have a liver or kidney disease.

This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

Besremi contains polysorbate 80
This medicine contains 0.025 mg of polysorbate 80 in each 0.5 mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Besremi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

3. How to use Besremi

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The dose will be set individually for you by your doctor for your condition. The usual starting dose of Besremi is 100 microgram every 2 weeks. Your doctor will then increase your dose stepwise and may adjust your dose during treatment.
Your doctor will reduce your starting dose to 50 micrograms if you have severe kidney problems.

This medicine is for subcutaneous use which means that it is injected in the tissue under your skin. It should not be injected into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred.
If you are injecting this medicine yourself, you will get clear instructions on how to prepare and inject it.
To prevent passing on infectious diseases, you should never share Besremi pre-filled pen with anyone else, even when the needle is changed.

Details on how to prepare and inject Besremi are given in the Instructions for Use. Read them before you start using Besremi.

If you use more Besremi than you should
Tell your doctor as soon as possible.

If you forget to use Besremi

You should inject the dose as soon as you remember. However, if more than 2 days have passed since you missed the dose, leave out the dose and inject the next dose when it is due. Do not inject a double dose to make up for a forgotten dose. Check with your doctor or pharmacist if you are not sure.

If you stop using Besremi
Do not stop using Besremi before you have talked to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you notice any of the following serious side effects during your treatment with Besremi:

Common side effects (may affect up to 1 in 10 people):
- changes in your heartbeat (when the heart beats very fast and uneven)

Uncommon side effects (may affect up to 1 in 100 people):
- attempted suicide, thoughts about killing yourself
- loss of vision which may be caused by bleeding in the retina (the retina is the light-sensitive layer in the eye), or by build-up of fat in or under the retina

Rare side effects (may affect up to 1 in 1,000 people):
- loss of vision which may be caused by damage to the retina (such as obstruction of the blood vessels in the eye) or the optic nerve

Very rare side effects (may affect up to 1 in 10,000 people):
- blindness
- breathing problems including shortness of breath, cough and chest pain which may be caused by lung infiltration, pneumonia (lung infection), pulmonary arterial hypertension (high blood pressure in the blood vessels bringing blood from the heart to the lungs) and pulmonary fibrosis (a lung disease where scars are formed in the lung tissue)

Side effects with frequency not known (cannot be estimated from the available data):
- detachment of the retina (you may experience eye problems including changes in vision)

Other side effects

Very common side effects (may affect more than 1 in 10 people):
- decrease in the number of a type of white blood cells (called leucocytes) and in blood clotting cells (called platelets)
- joint or muscle pain
- flu-like symptoms, feeling tired
- in blood tests: increase of an enzyme called gamma-glutamyltransferase

Common side effects (may affect up to 1 in 10 people):
- infection of the respiratory tract, runny or stuffy nose, fungal infections, flu
- decrease in the number or size of red blood cells
- increase or decrease in the thyroid gland activity, increase of thyroid stimulating hormone, inflammation of the thyroid gland
- increase of triglycerides (a type of lipid) in the blood, decreased appetite
- aggressive behaviour, feeling depressed, feeling anxious, problems with falling asleep or staying asleep, mood changes, lacking bodily energy or motivation

- headache, feeling dizzy, reduced sense of touch or sensation, feeling sleepy, sensation of tingling and 'pins and needles'
- dry eyes
- damage of the capillaries (very small blood vessels) in the body
- breathing problems
- diarrhoea, nausea, abdominal pain or stomach discomfort, constipation, dry mouth
- liver disorder, increase in certain liver enzymes (shown in blood tests)
- itching, hair loss, rash, redness of skin, psoriasis, dry and scaly skin, acne, thickening of the outer layer of the skin, increased sweating
- a disorder called Sjogren's syndrome where the body's immune system attacks glands that produce fluid (such as the tear and saliva glands), arthritis, pain in arms and legs, bone pain, painful sudden tightening of a muscle
- fever, weakness, chills, general health problems, irritation or redness at the site of injection, decreasing body weight
- in blood tests: antibodies which are produced by the body´s immune system, increase of an enzyme called lactate dehydrogenase

Uncommon side effects (may affect up to 1 in 100 people):
- infection and re-infection with herpes, bacterial infections
- increase in the number of platelets
- autoimmune disorder of the thyroid gland, sarcoidosis (areas of inflamed tissue in different parts of the body)
- diabetes
- panic attack, hallucination (seeing, hearing or feeling things that are not there), feeling stressed, feeling nervous, lack of interest in activities, nightmare, irritability, confusion
- damage to the nervous system, migraine, mental disorder (health condition involving changes in thinking, emotion or behaviour), visual or sensory disturbances, shaky hands
- eye discomfort, eyelid eczema
- hearing loss, ringing in ears (tinnitus), spinning feeling (vertigo)
- heart disorders such as heart block (a disorder in the heart´s electrical activity), blood clots in the blood vessels of the heart, leakage of the aortic valve
- high blood pressure, reduced blood supply to certain parts of the body, haematoma (collection of blood under the skin), flushing
- inflammation of lung tissue, coughing, nosebleed, sore throat
- inflammation of the stomach, abdominal wall disorder, intestinal gas, indigestion, painful swallowing, bleeding gums
- inflammation of the liver, damage to the liver, enlarged liver
- sensitivity to sunlight, peeling of the skin, nail disorder
- muscle weakness, neck pain, groin pain
- inflammation of the bladder, painful urination, increased need to urinate, inability to urinate
- sexual problems
- pain or itching at the site of injection, sensitivity to weather change
- non-acute porphyria (a liver disorder in which substances called porphyrins build up in the skin causing local skin damage, such as rashes, blisters, sores or discomfort, upon sun exposure)
- in blood tests: increase of uric acid, antibodies produced by the body´s immune system against red blood cells

Rare side effects (may affect up to 1 in 1,000 people):
- bipolar disorders (mood disorders with episodes of sadness and excitement), mania (extreme excitement or unreasonable enthusiasm)
- cardiomyopathy (diseases that affect the heart muscle), angina pectoris (a severe chest pain as a result of blockage of the heart vessels)
- liver failure

Very rare side effects (may affect up to 1 in 10,000 people):
- idiopathic or thrombotic thrombocytopenic purpura (increased bruising, bleeding, decreased platelets, anaemia and extreme weakness)
- myocardial ischemia (reduced blood flow to your heart muscle)

Side effects with frequency not known (cannot be estimated from the available data):
- Vogt-Koyanagi-Harada disease (a rare disease that can lead to loss of vision, hearing and skin pigmentation), severe allergic reaction
- discolouration of the skin
- periodontal (affecting gums) and dental disorders, change in colour of the tongue

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Besremi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the outer carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

Once opened, the pre-filled pen may be stored for a maximum of 30 days in the refrigerator (2 °C - 8 °C) when stored with the pen cap on and kept in the outer carton in order to protect from light.

Do not use this medicine if you notice that the pre-filled pen appears damaged, the solution is cloudy, has particles or flakes, or has any colour other than colourless to slightly yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Besremi contains
- The active substance is ropeginterferon alfa-2b.
  Each pre-filled pen of 0.5 mL solution contains 500 micrograms of ropeginterferon alfa-2b as measured on a protein basis, corresponding to 1000 micrograms/mL.
- The other ingredients are sodium chloride, polysorbate 80, benzyl alcohol, anhydrous sodium acetate, glacial acetic acid, and water for injections. For benzyl alcohol, polysorbate 80 and sodium, see section 2 "Besremi contains benzyl alcohol", "Besremi contains polysorbate 80" and "Besremi contains sodium".

What Besremi looks like and contents of the pack
Besremi is presented as a solution for injection (injection) in a pre-filled pen. Each pre-filled pen contains 0.5 mL of solution. It is available in packs containing:
- 1 pre-filled pen and 2 injection needles (Type: mylife AutoProtect PRO 29G × 8 mm)

Marketing Authorisation Holder and Manufacturer
AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for Use

Please read this leaflet carefully before using the Besremi 500 micrograms pre-filled pen. If you have any further questions, ask your doctor or pharmacist.

Your doctor or pharmacist will show you how to use the pen.
The Besremi 500 micrograms pre-filled pen can be used to inject doses of 50, 100, 150, 200, 250, 300, 350, 400, 450 and 500 micrograms. The same pen can be used twice, as long as the sum of the two doses does not exceed 500 micrograms. Your doctor will tell you the dose you need. Please note down your injection dates and dose as instructed by your doctor.

Store the pen in the outer carton in the refrigerator.
Remove the pen from the refrigerator 15 minutes before the injection to let it reach room temperature.
Find a quiet and well-lit area for the injection.

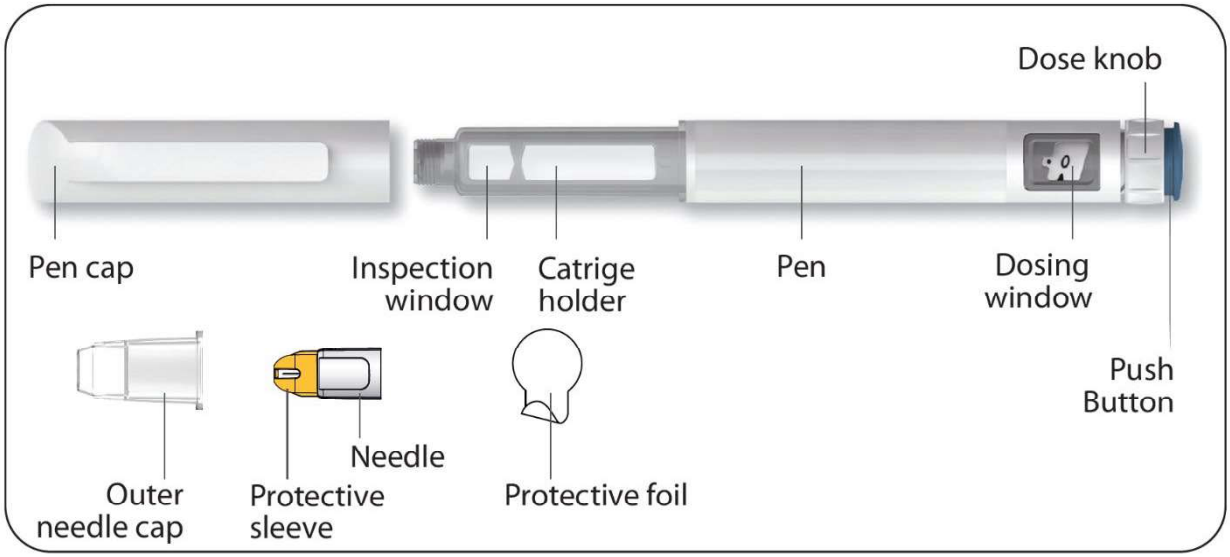
You will need the following supplies for your injection:
• Besremi pre-filled pen
• Needle (Type: mylife AutoProtect PRO 29G × 8 mm)
• Alcohol wipe (not supplied)
• Optional: adhesive plaster (not supplied)

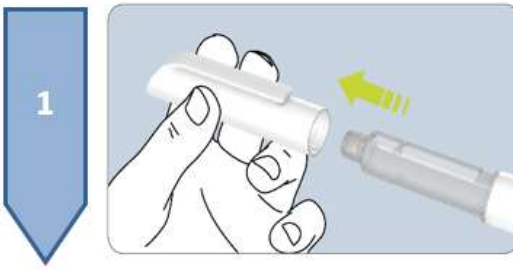
The Besremi pre-filled pen comes with two needles. Always use a new needle for each injection.

Note: The pen is also compatible with the following needle:
• Ultra-Fine or Micro-Fine or embecta, 31G × 8 mm pen needle
This needle can be purchased separately. Please ask your doctor or pharmacist if you wish to use any of these needles instead of the co-packaged needles.

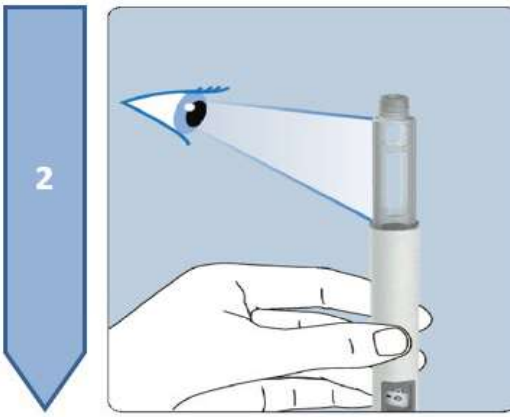
Do not use the pen if it appears damaged. If at any time during the use of the pen, you feel you may have damaged it (e. g. by dropping it or using excessive force), do not continue to use the pen. Get a new pen and start over.

Description Besremi 500 micrograms pre-filled pen

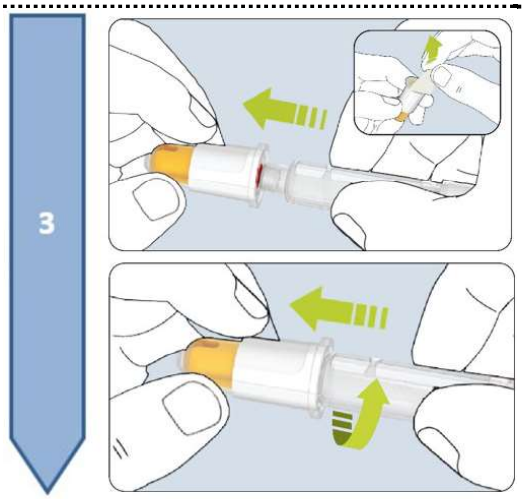




- Wash your hands before using Besremi.
- Check that the product has not expired.
- Remove the cap from the pen.

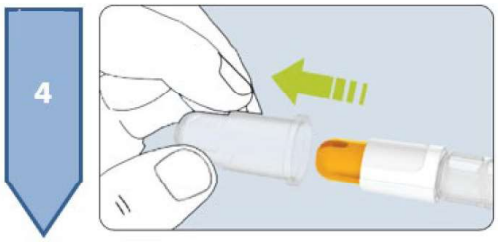


- Check the solution through the inspection windows along the sides of the cartridge holder.
- Do not use the pen if the solution is cloudy, has particles or flakes, or is any colour other than colourless to slightly yellow.

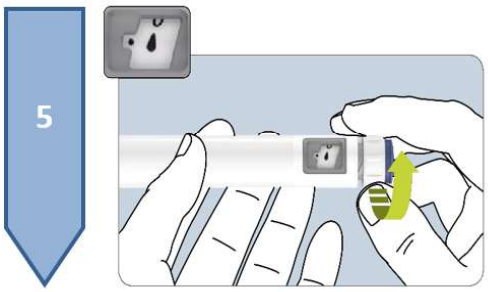


- Take a new needle and remove the protective foil.
- Place the pen straight and centrally arranged onto the needle to prevent it from buckling or bending.
- Make sure that it is firmly attached.

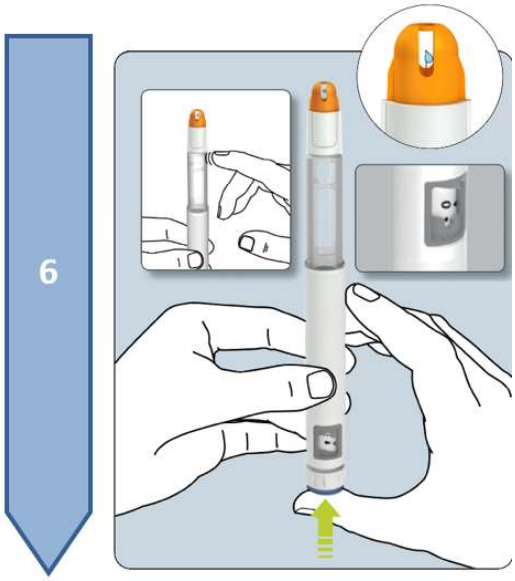
- Screw the needle onto the pen by turning the pen clockwise with gentle pressure until it stops.



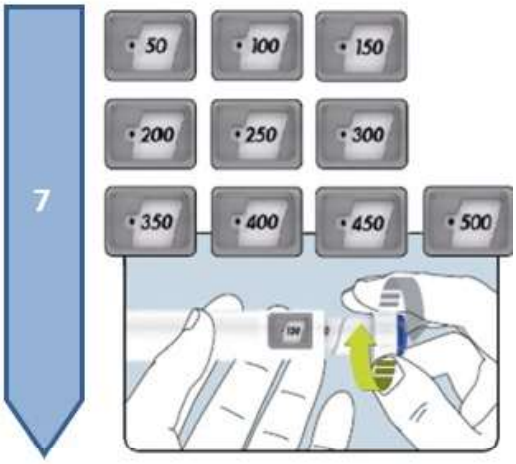
- Remove the outer needle cap from the needle.
- Do not put the outer needle cap back on the needle until you have injected the medicine. Do not touch the needle tip at any time.
- If you have used your Besremi 500 microgram pre-filled pen once before and are using it a second time, continue directly with step 7.
- If you are using this pen for the first time, continue with preparation of the pen in step 5.



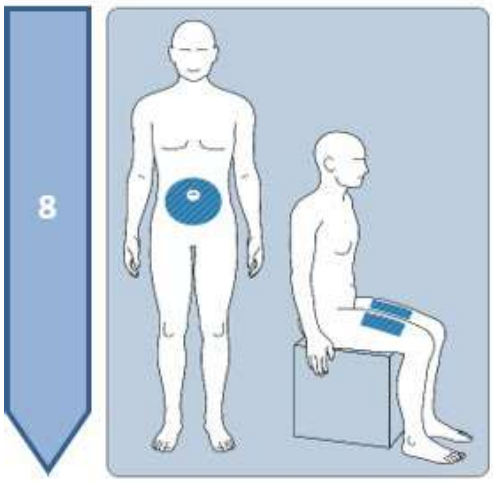
- If you are using this pen for the first time, prepare the pen for injection by turning the dose knob until you see the icon of a “drop” and the dot in the dosing window. The icon of a “drop” must be aligned with the dot in the dosing window.



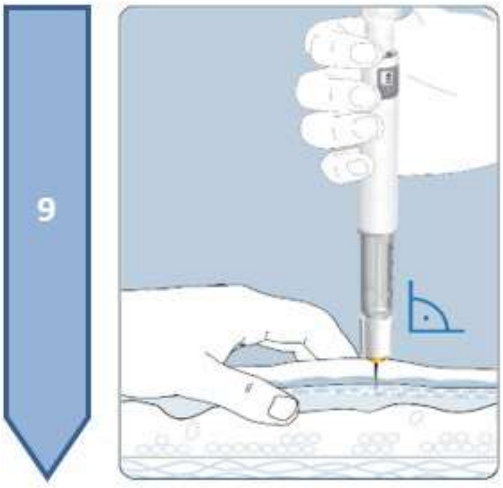
- Hold the pen with the needle pointing upwards and make sure the dosing window is facing you.
- Do not point towards your face or anyone else’s face.
- Tap the pen (cartridge holder) gently with your fingers to allow any air bubbles to rise to the top of the cartridge holder.
- Press the push button with your thumb until the “0” mark is aligned with the dot in the dosing window.
- You will see the window changes between the “drop” icon and the “0” mark, and you will hear gentle clicks when the button moves.
- If you look through the small gap at the top of the orange needle protective sleeve, you should see a droplet of liquid appearing at the needle tip.
- If you do not see a droplet at the needle tip, repeat steps 5 and 6 up to six times until a droplet appears.
- If you do not see the droplet after the seventh time, ask your doctor or pharmacist for advice.



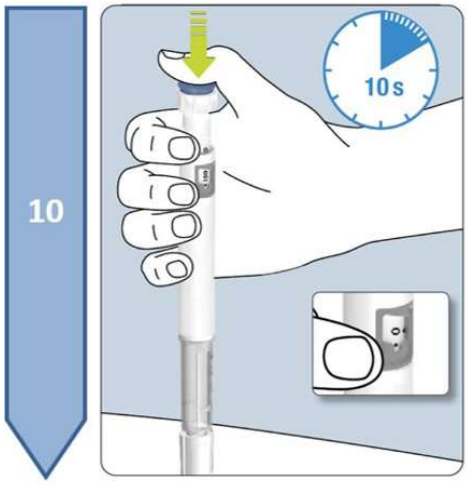
- Set the dose your doctor advised by turning the dose knob until the prescribed dose is visible. The selected dose must align with the dot in the dosing window. If necessary, correct the dose by turning the dose knob up and down.
- If you are unable to reach the required dose setting by turning the dose knob, your pen may be out of sufficient medicine. Do not use any further force. Instead, get a new pen.



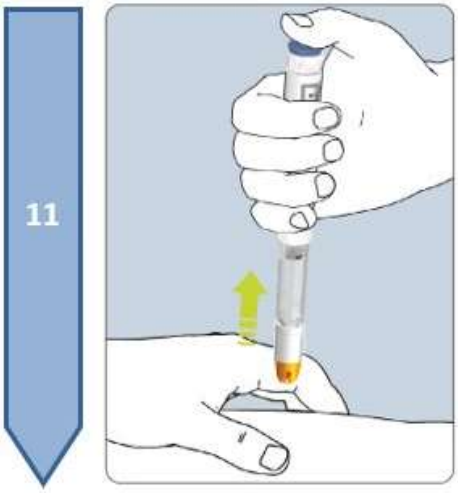
- Disinfect your skin in the injection area using an alcohol swab before the injection.
- Let the area dry before you inject the medicine.
- You must inject the medicine subcutaneously (under the skin). Your doctor will tell you where you must inject it.
- Possible injection sites are the belly (more than five centimetres away from the belly button) or the thigh.
- If you need two pens, use a different injection site for each pen (e. g. right and left side of belly or right and left thigh).
- Do not inject into irritated, reddened, bruised, infected or scarred skin in any way.



- Hold the pen so that the dosing window and the label are visible during the injection.
- Raise a fold of skin between the thumb and forefinger.
- Insert the needle at a 90 degrees angle until the orange protective sleeve on the needle is no longer visible.

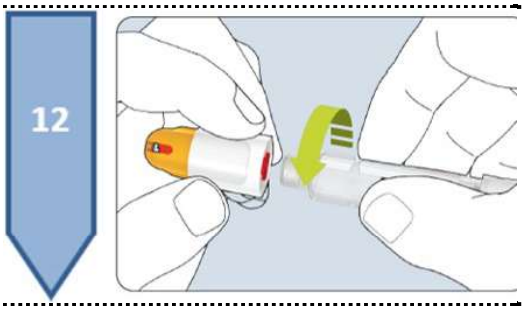


- Press the push button all the way down until the “0” mark is aligned with the dot in the dosing window.
- The soft clicking sounds will stop when the injection is complete.
- Continue pressing the pushd button while keeping the needle in your skin.
- Count slowly to 10. Do not lift or move the pen during injection.
- If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered.



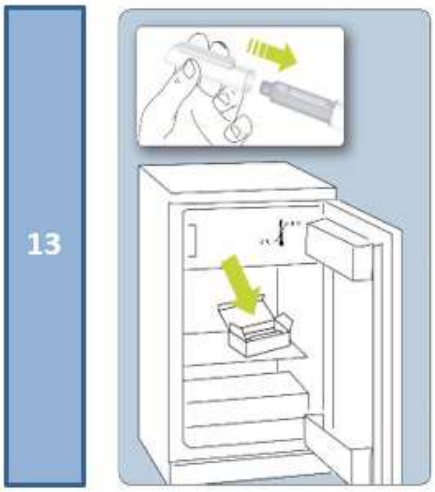
- Carefully remove the needle from the skin by pulling straight upwards.
- Keep the injection site clean until the small injection wound has closed. Apply an adhesive plaster if needed.

Note:
- The orange protective sleeve locks automatically and the now visible red locking indicator covers the needle for your protection. If this is not the case, please ask your doctor or pharmacist.
- After removing the needle, a small droplet of liquid may remain on your skin. This droplet is normal and does not mean that you underdosed.



- Rotate the pen counterclockwise and dispose of the needle properly.

Note:
- Once the needle has been unscrewed, another red locking indicator covers the bottom of the needle for additional safety.



Note: Put the cap back on the pen securely.

Reuse of the pen:
- Your doctor will tell you if you may use the pen for a second injection. In this case, put the pen back into the outer carton and store it in the refrigerator for the next use. Do not use the pen after 30 days.

Disposal of the pen and needle:
- Discard the pen and needle after use according to local regulations or as instructed by your doctor or pharmacist.