## 1. NAME OF THE MEDICINAL PRODUCT

Besremi 250 mcg/0.5 mL
Besremi 500 mcg/0.5 mL

## 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 slightly yellowish liquid.

## 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 x $10^9$/L and leukocytes <10 x $10^9$/L). The maximum recommended single dose is 500 micrograms injected every two weeks.

*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).

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 can be adjusted to administer doses in 50 microgram intervals 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 characterized 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 Product discontinued 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

### 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 $<400 \times 10^9$/L and leukocytes $<10 \times 10^9$/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

## 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 7504.0 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 6021.3 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.

### 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
Benzyl alcohol
Sodium chloride
Sodium acetate, anhydrous
Acetic acid
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
The expiry date of the product is indicated on the packaging materials.

Besremi 500 micrograms/0.5 mL, solution for injection in pre-filled pen
The expiry date of the product is indicated on the packaging materials.

*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 µg, 100 µg, 150 µg, 200 µg and 250 µg.
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 :
- Packs containing 1 pre-filled pen and 2 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. REGISTRATION HOLDER

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## 8. MANUFACTURER

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## 9. REGISTRATION NUMBERS

**Besremi 250 micrograms/0.5 mL**: 166-66-36574

**Besremi 500 micrograms/0.5 mL :** 166-67-36575

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