Date: 27 August 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Besremi

International non-proprietary name: ropeginterferon alfa-2b
Pharmaceutical form: solution for injection in pre-filled pen
Dosage strength: 500 µg/0.5 mL and 250 µg/0.5 mL
Route(s) of administration: subcutaneous use
Marketing Authorisation Holder: OrPha Swiss GmbH
Marketing Authorisation No.: 67488
Decision and Decision date: approved on 1 July 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AOP2014	Ropeginterferon alfa 2b
API	Active pharmaceutical ingredient
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CPE	Cytopathic effect
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
ERA	Environmental Risk Assessment
ET	Essential thrombocythaemia
FAS	Full analysis set
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
HU	Hydroxyurea
ICH	International Council for Harmonisation
IFN-α	Interferon-alpha
Ig	Immunoglobulin
INN	International Nonproprietary Name
JAK2	Janus-kinase 2
kDa	Kilodaltons
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MF	Myelofibrosis
Min	Minimum
MTD	Maximum tolerated dose
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
peg-IFN-α-2b	Ropeginterferon α 2b
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PPS	Per protocol set
PSP	Pediatric Study Plan (US-FDA)
PV	Polycythaemia vera
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment emergent adverse event
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance ropeginterferon alfa-2b of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 of the TPA.
The Orphan Status was granted on 29 August 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Besremi is indicated as monotherapy for the treatment of adult patients with polycythaemia vera without symptomatic splenomegaly and with an indication for cytoreductive therapy (see "Clinical efficacy").

2.2.3 Requested Dosage

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

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 the adverse events abate; further treatment should be re-initiated with a lower dose than the dose that caused the adverse events.
If an increase of haematological parameters (haematocrit, platelets, leukocytes) is observed, the dose and/or dosing interval will need to be adapted individually.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	22 March 2019
Formal control completed	15 April 2019
List of Questions (LoQ)	31 July 2019
Answers to LoQ	29 October 2019
Predecision	22 January 2020
Answers to Predecision	20 February 2020
Second Predecision	2 April 2020
Answers to Second Predecision:	29 April 2020
Final Decision	01 July 2020
Decision	approval

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3 Medical Context

Polycythaemia vera (PV) is a chronic myeloproliferative neoplasia. The disease is characterised by an increased production of erythrocytes. This increased production is independent of normal regulatory mechanisms of erythropoiesis, particularly of the erythrocyte growth factor erythropoietin. However, the stem cells remain sensitive to this growth factor even though they will also proliferate in its absence. It has been shown in recent years that almost all patients (>95%) present a mutation in the JAK2 tyrosine kinase gene. This mutation seems to be responsible for an increased proliferation not only of the erythrocytic lineage precursors, but also granulocyte and megakaryocyte precursors. The disease progresses in two phases, with an initial polycythaemic phase with increased erythrocyte mass, followed by a spent phase where myelofibrosis with reduced haematopoiesis is observed. The natural evolution can also lead to a myelodysplastic phase and/or leukaemic transformation. Generally, treatment of PV is palliative. The main goals of treatment are to reduce the risk of thromboembolic events, control symptoms and delay possible complications of the late phase of the disease, such as myelofibrosis (MF) and acute myeloid leukaemia (AML).

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4 Quality Aspects

4.1 Drug Substance

Ropeginterferon alfa-2b, the active substance of Besremi, is a covalent conjugate of a recombinant proline-interferon alfa-2b and a two-arm methoxypolyethylene glycol (mPEG) moiety. The molecular mass of ropeginterferon alfa-2b is approximately 60 kilodaltons (kDa).

The manufacturing process for proline-interferon alfa-2b consists of fermentation in *Escherichia coli*, followed by harvesting, centrifugation, as well as purification by several chromatographic and filtration steps. 40kDa-mPEG-aldehyde is synthesised separately and used for the pegylation process step of proline-interferon alfa-2b. Finally, ropeginterferon alfa-2b is obtained by two filtration steps and a chromatography step. The manufacturing process has been validated with four full-scale drug substance batches.

The drug substance and its impurities were characterised using state of the art methods. Biological characterisation of proline-interferon alfa-2b includes a cytopathic effect (CPE)-based potency assay calibrated against an international standard and ligand/receptor binding assay by surface plasmon resonance (SPR) analysis.

The specifications include e.g. identity tests, purity and impurity tests and a CPE-based potency assay. All analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis data for non-clinical batches, clinical batches, and process validation batches were provided. Comparability between batches produced with the phase 1/2 process and batches produced with the commercial manufacturing process was demonstrated.

The drug substance is stored at 2-8°C. No significant changes were observed under the proposed storage conditions. A shelf life of 12 months has been accepted.

4.2 Drug Product

Besremi is supplied as a colourless to slightly yellowish sterile solution, is intended for subcutaneous administration and is available in two presentations (250 µg and 500 µg) with an extractable volume of 0.5 mL. The formulation of ropeginterferon alfa-2b is an aqueous buffered solution at pH 6.0 containing sodium chloride, sodium acetate, acetic acid, polysorbate 80 and benzyl alcohol (for microbial preservation). All excipients comply with the European Pharmacopoeia or United States Pharmacopeia requirements. One package of ropeginterferon alfa-2b contains one multi-dose disposable pen injector (containing one rubber capped glass cartridge with the ropeginterferon alfa-2b solution) and two safety needles for injection.

The manufacturing process for the finished drug product consists of compounding, sterile filtration, filling/stoppering, labelling and inspection steps and further assembling of the pen injector. Process validation studies were executed at commercial scale using four validation batches.

The specifications for the drug product were set based on compendial requirements, experience from clinical trials, and commercial process capability. They include relevant tests and limits, e.g. for appearance of primary container, colour of solution, pH, osmolality, purity and impurity tests, identity, CPE-based potency assay, protein content, extractable volume, sterility and bacterial endotoxins. All non-compendial methods are validated in accordance with ICH guidelines.

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Batch analysis data for four injection pen batches have been provided. All batch release data comply with the commercial drug product specifications.

The primary container closure system for the ropeginterferon alfa-2b medicinal product consists of a clear 3.0 mL borosilicate type I glass cartridge that is closed with a siliconised bromobutyl rubber stopper. The components coming into contact with the finished product comply with European Pharmacopoeia requirements. The prefilled glass cartridge is permanently incorporated into the pen injector to form the final product ropeginterferon alfa-2b prefilled pen. The device has been proven to meet the relevant requirements of ISO 11608-1.

The drug product is stored at 2 to 8°C protected from light. No significant changes were observed under the proposed storage conditions. Shelf lives of 36 months for the 0.5 mg/mL strength and 18 months for the 1.0 mg/mL strength have been accepted.
The manufacturing process for the drug substance and drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Besremi, Swissmedic has conducted an abridged evaluation, which was based on the European Medicines Agency EMA assessment report EMA/CHMP/725151/2018, dated 13 December 2018 and provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Besremi in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no particular safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered sufficient. The nonclinical data relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The available assessment reports and respective product information from the EMA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see Chapter 8.1 of this report.

6.2 Dose Finding and Dose Recommendation

The applicant presents one dose-finding study, PEGINVERA, consisting of a dose-escalation part (stage 1) and a dose-extension part (stage 2). The study enrolled 25 patients in stage 1. Patients were exposed to increasing doses of AOP2014 administered subcutaneously in a 3+3 study design. The dose-limiting toxicity (DLT) period was only 14 days (=1 injection). The maximum dose planned was 540 µg and was reached without reaching the maximum tolerated dose (MTD) (defined as no more than 1 patient out of 6 presenting with a DLT). The MTD was therefore determined as 540 µg. Stage 2 of the study enrolled the patients who had participated in stage 1, as well as 26 additional patients, resulting in 51 patients in total. Patients were individually dose-escalated to their personal MTD, but the maximal dose level was 450 µg. The definition of MTD was slightly different for stage 2 and also included long-lasting grade 2 toxicities if they impacted on the patient's wellbeing.

Stage 2 of the study was planned to continue for as long as patients had benefit. Six years after study initiation, 29/51 patients were still on treatment, and all 29 patients had completed at least two years of study treatment.

No MTD was reached in this dose-finding study, and the highest dose tested, 540 µg every two weeks as subcutaneous injection, was considered the MTD. However, in stage 2 of the study the dose escalation only went up to 450 µg every 2 weeks, and in the PROUD-PV and CONTINUATION-PV efficacy studies, the maximum individual dose was 500 µg every two weeks.

6.3 Efficacy

The PROUD-PV study was a phase 3 multinational, multicentre, randomised 1:1, open-label, parallel 2-arm, non-inferiority study comparing AOP2014 (ropeginterferon alfa-2b) with the standard of care, hydroxyurea (HU). The study ran from September 2013 through April 2016. PROUD-PV enrolled 257 patients, 127 in the AOP2014 arm and 130 in the HU arm. The study was initially designed as a superiority study, and only after the study was concluded was the primary endpoint changed to non-inferiority.

Patients were eligible if they were ≥18 years of age, had signed an informed consent form and had been diagnosed with PV with a JAK2 mutation in need of cytoreductive treatment. Previous treatment with HU for up to 3 years was allowed, as long as patients did not show any intolerance or resistance to that treatment. Patients were stratified according to age (≥60 versus <60 years), prior thromboembolic event (yes or no) and prior HU treatment (yes or no). Several exclusion criteria concerned safety issues, such as prior psychiatric illness, autoimmune diseases, active infections (hepatitis, HIV), pre-existing pulmonary abnormalities or prior organ transplant.

The study was an open-label design, given the comparison of subcutaneous and oral administration of the two drugs and the long-term treatment. In order to control for bias, assessment of response was appropriately performed centrally in a blinded manner. The treatment dosage in both arms was titrated progressively to obtain the best response and tolerability on an individual patient basis.

The primary objective of the study was to demonstrate non-inferiority in terms of disease response rate in both HU pre-treated and HU naïve patients diagnosed with polycythaemia vera, and the

primary endpoint measured to that effect was the disease response rate, defined as normalisation of haematological values and spleen size.

Secondary objectives of the study were safety, quality of life and change in JAK2 allelic burden. The major secondary endpoint was durable disease response rate.

A majority of patients completed the study (12 months of treatment in both arms), with 83.5% in the AOP2014 arm and 87.4% in the HU arm. The most frequent reasons for study discontinuation in the AOP2014 arm were adverse events (AEs) with 11 patients, followed by withdrawal of consent (without indication of reason) by 6 patients and administrative reasons for 4 patients. In the HU arm, the most frequent reasons for withdrawal were “other” and withdrawal of consent. It is not specified what “other” might be. There were 3 patients in the HU arm who discontinued due to AEs and 2 for lack of efficacy (versus 0 in the AOP2014 arm).

Baseline characteristics were well balanced between the two arms. There was a slight difference in the median duration of PV at study entry, with 1.9 months in the AOP2014 arm versus 3.6 months in the HU arm. There was also a slightly longer median duration of HU treatment for patients in the AOP2014 arm versus HU, with 10.2 months versus 7.9 months, respectively. Mean age at inclusion was 58.2 years, with a median of 60 years (range 21 to 85). All patients were white, and 46.9% were male and 53.1% female. Spleen size was comparable between the two treatment arms, with 46.5% of patients presenting with spleen size within the normal range.

The disease response rate at 12 months of treatment was 21.3% for AOP2014 and 27.6% for HU in the full analysis set (FAS) (which did not include 3 patients who never received HU after randomisation), with a difference in responder rates of -6.6 (95% CI: -17.2 to -4.1). Therefore, the PROUD-PV study did not meet its primary endpoint of non-inferiority in response rate of AOP2014 versus HU, neither in the FAS nor in the per protocol set (PPS) population. The study was initially designed as a superiority study and, despite the change in the design of the study to a non-inferiority endpoint after the last patient had completed the study, this endpoint was not reached and the study is formally negative.

When the haematological parameters are considered on their own, not taking into account spleen size normalisation, AOP2014 showed non-inferiority at 12 months. The haematological complete response rate was 43.1% for AOP2014 and 45.6% for HU after 12 months of treatment in this study (p=0.0028; full analysis set). However, this analysis was not planned in the secondary efficacy endpoints. The protocol does state that secondary analysis of the primary efficacy endpoint includes an individual analysis of all components of the primary endpoint using the same methods as for the primary endpoint. Although this may justify the analysis as non-inferiority after completion of study, it does not explain the chosen non-inferiority margin of 20%.

An analysis of the haematological response over time reveals that the haematological parameters are similarly controlled by the two treatments, albeit with a slight delay in the AOP2014 arm due to the longer titration phase to reach the optimal dose (28 weeks versus 8 weeks in the HU arm).

Observation over time of the molecular response shows a continuous deepening of the response in the AOP2014 treated patients that was still ongoing at the end of the study. On the contrary, in the HU treated patients, the maximum molecular response seems to be reached at 6 months, with no further decrease in the JAK2 allele frequency.

Efficacy conclusion: The pivotal study that was originally designed as a superiority study was not able to show non-inferiority for the predefined endpoint of complete response (haematological and spleen size) after 12 months of treatment compared to standard of care hydroxyurea. When considering the haematological parameters on their own without spleen size, non-inferiority, with a non-inferiority

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margin of 20%, was shown. There was an imbalance in treatment exposure due to the longer individual titration times per patient in the AOP2014 arm compared to the HU control arm.

6.4 Safety

The percentage of patients reporting at least one serious treatment-emergent adverse event (TEAE) was comparable between ropeginterferon alfa-2b (PROUD-PV, CONTINUATION-PV and PENPV Study) and the HU/control (PROUD-PV and CONTINUATION-PV Study), i.e. 18.1% in both study arms.

Comparing the incidence of the most frequent TEAEs (>10%) in both treatment arms, similar patterns were found in the CONTINUATION-PV and PROUD-PV studies. HU treatment seemed to cause more haematological adverse events, while AOP2014 caused more investigation events (mostly due to increases in GGT [17.9% vs 3.9%] AST [11.6% vs 2.6%] and ALT [13.7% vs 2.6%]) and, more general disorders and injection site reactions (mostly due to pyrexia and fatigue). However, after longer treatment duration, there were nearly twice as many vascular AEs in the HU treatment arm compared to the AOP2014 arm (mostly driven by hypertension 11.8% vs 5.3%). Finally, ear and labyrinth disorders occurred at an incidence of >10% in the HU arm, but not in the AOP2014 arm, while 10.5% of neoplasms benign, malignant and unspecified (incl. cysts and polyps) occurred in the HU arm versus 5.3% in the AOP2014 arm.
More nausea (7.9% vs 3.2) was observed in the HU arm, as was more diarrhoea (11.8% vs 8.4%).

Two cases of AML and one case of MF were observed in patients treated with HU/control in all studies combined, while none occurred in the AOP2014 arm.

Two patients treated with AOP2014 developed glioblastoma during study treatment, one patient developed spermatocytic seminoma and one patient developed bile duct cancer.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Polycythaemia Vera (PV) is a myeloproliferative disease primarily of the erythroid lineage. Left untreated, it has a short survival time of approximately 18 months, in 60% of cases due to thromboembolic complications. Primary treatment is phlebotomy and anti-aggregation with acetylsalicylic acid (ASA). When this is not possible because of tolerance, or is not sufficient, the standard current treatment is hydroxyurea (HU). However, in spite of treatment, many patients will develop myelofibrosis (MF) (up to 50% after 20 years), and up to 20% will develop secondary acute myeloid leukaemia (AML). It is unclear whether HU is implicated in the development of AML or whether AML is part of the natural course of the disease. However, there is clearly an unmet medical need for better treatment options in this disease, in particular in younger patients who can live several decades after diagnosis.

Clinically, the benefit shown by the AOP2014 long-term data in PV with an acceptable safety profile seems to outweigh the risks. In particular, AOP2014 could be an alternative treatment in young patients for whom long-term exposure to the potential risk of carcinogenicity of hydroxyurea is of concern. However, physicians and patients need to be aware that other agents, in particular hydroxyurea, have a potentially higher activity. This statement is based on the fact that the PROUD-PV study did not show non-inferiority for the initial primary endpoint (complete haematological response and normalisation of spleen size) with a non-inferiority margin of 10.5%, and only showed non-inferiority of an ad-hoc primary endpoint of complete haematological response without spleen size normalisation with a non-inferiority margin of 20%.

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6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Besremi, solution for injection in pre-filled pen, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Besremi

Composition

Active substances

Ropeginterferon alfa-2b (produced from genetically modified *E. coli* bacteria)

Excipients

Sodium chloride, sodium acetate (total sodium content: 1.8 mg per 0.5 mL pen), acetic acid 99%, benzyl alcohol (5 mg per 0.5 mL pen), polysorbate 80, water for injections.

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

Besremi is indicated as monotherapy for the treatment of adult patients with polycythaemia vera without symptomatic splenomegaly and with an indication for cytoreductive therapy (see “Clinical efficacy”).

Dosage/Administration

Treatment should be initiated under supervision of a physician experienced in the management of polycythaemia vera.
In order to ensure the traceability of biotechnologically manufactured medicinal products, it is recommended that the trade name and batch number be documented for each treatment.

Dose adjustment/titration

The dose is titrated individually with a recommended starting dose of 100 micrograms (or 50 micrograms in patients on another cytoreductive therapy). The dose should be gradually increased every two weeks by 50 micrograms (in parallel, other cytoreductive therapy should be decreased gradually, if possible) 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 every two weeks.

Maintenance therapy

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

Dose adjustment following undesirable effects/interactions

If adverse events should occur during therapy, the dose should be reduced or treatment discontinued temporarily until the adverse events abate. Treatment should then be continued with a lower dose than the dose that led to the adverse events.
If an increase in haematological parameters (haematocrit, platelets, leukocytes) is observed, the dose and/or interval needs to be adjusted individually. However, the interval should never be fewer than two weeks.

Special dosage instructions

Patients with impaired hepatic function

In patients with compensated cirrhosis (i.e. Child-Pugh A), another medicinal product with pegylated interferon alfa (pegylated interferon alfa-2a) has been shown to be safe. No dose adjustment for ropeginterferon alfa-2b is required in 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 “Contraindications”).
Increased liver enzyme levels have been observed in patients treated with ropeginterferon alfa-2b. If the increase in liver enzyme levels is progressive and persistent, the dose must 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 must be discontinued (see “Warnings and precautions”).

Patients with impaired renal function

The pharmacokinetic profile of other medicinal products with interferon alfa (pegylated interferon alfa-2a and pegylated interferon alfa-2b) has been evaluated in patients with renal impairment (see “Pharmacokinetics”).

No dose adjustment for ropeginterferon alfa-2b is required in adult patients with mild (GFR 60-89 mL/min) to moderate (GFR 30-59 mL/min) renal impairment.
Post-hoc analyses of the studies performed as part of the clinical development programme for ropeginterferon alfa-2b (N=178) showed no significant differences in the dose administered, duration of treatment, haematological response or in the side effect profile of ropeginterferon alfa-2b between patients with impaired (GFR <60 mL/min; 20/178 patients), mildly impaired (GFR 60-89 mL/min; 74/178) and normal renal function (GFR ≥90 mL/ min; 84/178).
No data are available in 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 "Contraindications").

Elderly patients

Adjustments in the recommended ropeginterferon alfa-2b dose are not necessary when starting therapy in elderly patients (see "Pharmacokinetics").

Children and adolescents

The safety and efficacy of Besremi in children and adolescents has not been established. No data are available (see "Warnings and precautions").

Obese or underweight patients

The pharmacokinetic profile of ropeginterferon alfa-2b has not been determined in obese and underweight patients. Thus, no recommendation on dose adjustment for ropeginterferon alfa-2b can be given for these patients.

Mode of administration

Subcutaneous use. The medicinal product is intended for long-term treatment and can be administered by a physician, nurse, family member or the patients themselves when trained in the administration of subcutaneous injections with the pre-filled pen. The instructions for use in the package leaflet must be followed.
As an injection site, the abdominal skin around the navel (but at a distance of at least 5 cm from the navel) or the thigh is recommended. Injections should not be given into any area where the skin is irritated, reddened, bruised, infected or scarred. The pen can be adjusted so that doses can be administered in 50 microgram intervals in the range of 50 to 250 micrograms or 50 to 500 micrograms.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed under Composition
- Pre-existing thyroid disease, unless it can be controlled with conventional treatment

- Existing 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 pectoris) or stroke or myocardial infarction in the last six months
- History or presence of autoimmune disease
- Immunosuppressed transplant recipients
- Combination with telbivudine (see “Interactions”)
- Decompensated cirrhosis of the liver (Child-Pugh B or C)
- End-stage renal disease (GFR < 15 mL/min)
- Pregnancy

Warnings and precautions

Dose titration phase

When the recommended dosage of ropeginterferon alfa-2b is maintained in the titration phase (see “Dosage/Administration”), the time to reach the individual optimal dose is longer than with hydroxycarbamide. In a clinical study on polycythaemia vera, the end of the individual titration phase for ropeginterferon alfa-2b was reached after approximately 3.7 months of treatment, compared with just approximately 2.6 months of treatment for hydroxycarbamide. Thus, in patients with elevated blood cell counts that need to be rapidly reduced to prevent thrombosis or bleeding, preference may have to be given to other medicinal products (e.g. hydroxycarbamide).
During the titration phase, the efficacy with regard to the cardiovascular and thromboembolic risks of the underlying disease may not yet be fully established. Patients must be closely monitored, especially in the titration phase. Even after the individual optimal dose has been reached, regular monitoring of the blood count, including determination of haematocrit, leukocyte and platelet counts, should be performed. Phlebotomy as an emergency procedure to normalise blood hyperviscosity may be necessary.

Endocrine system

Before the start of therapy with ropeginterferon alfa-2b, any form of pre-existing thyroid disease needs to be treated and controlled with conventional therapy (see “Contraindications”). Patients who develop symptoms indicative of thyroid dysfunction during therapy with ropeginterferon alfa-2b should have their level of TSH (thyroid-stimulating hormone) determined. If TSH concentrations can be brought to levels within the normal range, the therapy can be continued.
In association with other medicinal products containing interferon alfa, development of diabetes mellitus has been observed (see “Undesirable effects”). Patients with existing diabetes mellitus who cannot be optimally managed on medicinal products should not begin therapy with ropeginterferon

alfa-2b. Patients who develop this condition during therapy and cannot be managed on medicinal products should discontinue therapy with ropeginterferon alfa-2b.

Central nervous system (CNS)

Effects on the CNS, especially depression, have been established in some patients treated with ropeginterferon alfa-2b during the clinical development programme (see “Undesirable effects”). CNS effects, e.g. suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion, have also been observed with other medicinal products containing interferon alfa. Patients should be closely monitored for any symptoms of psychiatric disorders. If such symptoms emerge, appropriate treatment should be considered by the treating physician. If psychiatric symptoms worsen, it is recommended to discontinue therapy with ropeginterferon alfa-2b. Ropeginterferon alfa-2b must not be administered in patients with existing or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt (see “Contraindications”).

Cardiovascular system

Cardiac events, including cardiomyopathy, myocardial infarction, atrial fibrillation and ischaemic heart disease, have been associated with interferon alfa treatment (see “Undesirable effects”). Patients with existing or history of cardiovascular disorders should be closely monitored during treatment with ropeginterferon alfa-2b. This medicinal product is contraindicated in patients with severe pre-existing cardiovascular disease and in patients who have recently suffered a stroke or myocardial infarction (see “Contraindications”).

Respiratory system

Airway disorders such as lung infiltration, pneumonitis, pneumonia or pulmonary arterial hypertension have been observed in rare cases among patients on therapy with interferon alfa (see “Undesirable effects”). Patients who develop respiratory symptoms should be monitored closely and, if necessary, therapy with ropeginterferon alfa-2b must 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 in rare cases among patients on therapy with interferon alfa (see “Undesirable effects”). Eye examinations should be performed in patients before and during therapy with ropeginterferon alfa-2b, especially in patients with retinopathy-associated disease such as diabetes mellitus or hypertension. In all patients reporting a worsening or loss of vision or other eye symptoms, an eye examination should be performed without delay. Discontinuation of therapy with ropeginterferon alfa-2b should be considered in patients who experience new or a worsening of pre-existing eye disorders.

Acute hypersensitivity

Serious, acute hypersensitivity reactions (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed in rare cases with other medicinal products containing interferon alfa. In this case, therapy with ropeginterferon alfa-2b must be discontinued and appropriate medical therapy instituted without delay. Transient rashes do not necessitate interruption of treatment.

Liver function

During interferon alfa therapy, hepatotoxic effects with potentially significant increases in liver enzyme levels have been described. Hepatic failure in patients with hepatitis C infection has been reported with other medicinal products containing interferon alfa (see “Undesirable effects”).
Increased levels of 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) have been observed in patients treated with ropeginterferon alfa-2b. These elevations were mostly transient and occurred during the first treatment year.
Liver dysfunction has been reported in patients after long-term therapy with ropeginterferon alfa-2b (see “Undesirable effects”). Liver enzymes and hepatic function should therefore be regularly monitored in patients on long-term therapy with ropeginterferon alfa-2b. Treatment with ropeginterferon alfa-2b must be discontinued if, despite dose reduction, a progressive and clinically significant increase in liver enzyme levels occurs. In patients who develop signs of hepatic decompensation during treatment, ropeginterferon alfa-2b must be discontinued. Ropeginterferon alfa-2b is contraindicated in patients with decompensated cirrhosis of the liver (see “Contraindications”).

Renal function

Regardless of the starting dose or degree of existing renal impairment, the patient’s renal function should be medically monitored. If renal function decreases during treatment, ropeginterferon alfa-2b should be discontinued. Ropeginterferon alfa-2b is contraindicated in patients with end-stage renal disease (see “Contraindications”).

Dental and periodontal disorders

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

Skin disorders

The use of ropeginterferon alfa-2b is associated with the onset of skin disorders (pruritus, alopecia, rash, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, hyperhidrosis). If skin disorders emerge or worsen, discontinuation of treatment must be considered.

Excipients

Besremi contains 5 mg benzyl alcohol per 0.5 mL pen, corresponding to 10 mg/mL.
Benzyl alcohol can cause allergic reactions.
Large volumes should be used with caution and only if absolutely necessary due to the risk of accumulation and toxicity (“metabolic acidosis”), especially in subjects with impaired hepatic or renal function.
The intravenous use of benzyl alcohol has been associated with serious adverse reactions and deaths in newborns (“gasping syndrome”).
The minimum amount of benzyl alcohol at which toxicity occurs is not known.
Young children are at increased risk due to accumulation.
Besremi contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

Interactions

Enzymes of protein catabolism are considered to be involved in the metabolism of ropeginterferon alfa-2b. It is not known to what extent transport proteins are involved in the absorption, distribution and elimination of ropeginterferon alfa-2b. Interferon alfa has been shown to influence the activity of cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2D6.
No interaction studies have been performed with ropeginterferon alfa-2b.

Studies to determine interactions with other medicinal products containing interferon alfa

Co-administration of pegylated interferon alfa-2a with telbivudine in patients with hepatitis B increased the risk of developing peripheral neuropathy. Combination therapy with telbivudine and ropeginterferon alfa-2b is contraindicated (see “Contraindications”).
Administration of 180 micrograms of pegylated interferon alfa-2a once weekly for 4 weeks in healthy male subjects showed no effect on the pharmacokinetic profiles of mephenytoin, dapsone, debrisoquine and tolbutamide. These results suggest that pegylated interferon alfa-2a has no effect on the *in vivo* metabolic activity of cytochrome P450 (CYP) 3A4, 2C9, 2C19 and 2D6 isoenzymes. In the same study, a 25% increase in the AUC of theophylline (CYP1A2 substrate) was observed. This shows that pegylated interferon alfa-2a is an inhibitor of CYP1A2 activity.
Co-administration of pegylated interferon alfa-2b led to no significant interaction with tolbutamide (a CYP2C9 substrate), midazolam (a CYP3A4 substrate) or dapsone (an N-acetyltransferase substrate)

and modestly increased exposure to caffeine (a CYP1A2 substrate) and desipramine (a CYP2D6 substrate).
Therefore, caution should be exercised when ropeginterferon alfa-2b is co-administered with CYP1A2 substrates, especially those having a narrow therapeutic margin, such as theophylline or methadone. Likewise, caution should be exercised when combining CYP2D6 substrates (e.g. vortioxetine, risperidone) with ropeginterferon alfa-2b. Ropeginterferon alfa-2b may inhibit the activity of CYP1A2 and CYP2D6 and thus may increase the blood concentration of these medicinal products.
No dose adjustments for ropeginterferon alfa-2b should be necessary when concomitantly administered with medicinal products metabolised via CYP2C9/19, CYP3A4 or by N-acetyltransferase.
Caution should 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.

Pregnancy, lactation

Pregnancy

Ropeginterferon alfa-2b may be used in women of childbearing potential only if they use a reliable method of contraception during the treatment period. The initiation of treatment during pregnancy is contraindicated (see “Contraindications”). There are no or limited amount of data from the use of interferon alfa in pregnant women.
Animal studies have shown reproductive toxicity (see “Preclinical data”). In primates receiving other medicinal products containing interferon alfa, an abortive effect was observed.

Lactation

It is unknown whether the active substance of the medicinal product is excreted in human milk. A risk to the newborn/infant cannot be excluded. Due to the emergence of possible adverse drug reactions in the breastfed infant, weaning is required before the start of treatment.

Fertility

There are no data on the effect of ropeginterferon alfa-2b on the fertility of women or men.

Effects on ability to drive and use machines

Besremi can impair the ability to drive and use machines. Patients who experience dizziness, somnolence or hallucinations during therapy with Besremi (see “Undesirable effects”) must not drive or use machines.

Undesirable effects

Summary of the safety profile

The most common adverse reactions are leukopenia (19.1%), thrombocytopenia (18.5%), arthralgia (12.9%), fatigue (12.4%), increased gamma-glutamyltransferase (11.2%), influenza-like illness (10.7%), myalgia (10.7%), pyrexia (8.4%), pruritus (8.4%), increased alanine aminotransferase (8.4%), anaemia (7.9%), pain in the extremities (6.7%), alopecia (6.7%), neutropenia (6.7%), increased aspartate aminotransferase (6.2%), headache (6.2%), diarrhoea (5.6%), chills (5.1%), dizziness (5.1%) and injection site reaction (5.1%).

Serious adverse reactions are depression (1.1%), atrial fibrillation (1.1%) and acute stress disorder (0.6%).

Adverse reactions are listed by system organ class and frequency (very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000) or not known (cannot be estimated from the available data).

The following treatment-related adverse reactions were reported in clinical studies on ropeginterferon alfa-2b with 178 adult patients with polycythaemia vera.

Infections and infestations

Common: respiratory tract infection, rhinitis, fungal skin infection
Uncommon: oral herpes, herpes zoster, oral candidiasis, sinusitis, oesophageal candidiasis, vulvovaginal mycosis, hordeolum, onychomycosis

Blood and lymphatic system disorders

Very common: leukopenia (19.1%), thrombocytopenia (18.5%)
Common: anaemia, neutropenia, pancytopenia, blood lactate dehydrogenase increased
Uncommon: platelet count increased, blood uric acid increased, positive Coombs test

Immune system disorders

Common: thyroid antibodies positive, antinuclear antibodies positive
Uncommon: Basedow's disease, sarcoidosis[#]
Very rare: idiopathic or thrombotic thrombocytopenic purpura[#]
Isolated cases: Vogt-Koyanagi-Harada disease[#], acute hypersensitivity reactions[#**]

Endocrine disorders

Common: hypothyroidism, hyperthyroidism, thyroiditis, blood thyrotropin increased
Uncommon: diabetes mellitus[#]

Metabolism and nutrition disorders

Common: hypertriglyceridaemia, decreased appetite

Psychiatric disorders

Common: depression, aggression[#], insomnia, anxiety, mood altered, mood swings, listlessness
Uncommon: suicide attempt[#], suicidal ideation[#], confusional state[#], acute stress disorder, hallucinations, emotional distress, nervousness, apathy, nightmares, 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 ischaemia[#]

Vascular disorders

Common: microangiopathy
Uncommon: Raynaud’s phenomenon, hypertension, haematoma, sensation of heat (flushing)

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea
Uncommon: pneumonitis, cough, epistaxis, throat irritation
Very rare: lung infiltration[#]
Isolated cases: 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
Isolated cases: tooth disorder[#], gum disease[#]

Hepatobiliary disorders

Very common: gamma-glutamyltransferase increased (11.2%)
Common: liver disorder, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Uncommon: hepatotoxicity, toxic hepatitis, hepatomegaly
Rare: hepatic failure[#]

Skin and subcutaneous tissue disorders

Common: pruritus, alopecia, rash, erythema, psoriasis, xeroderma, acneiform dermatitis, hyperkeratosis, hyperhidrosis, dry skin
Uncommon: photosensitivity reaction, skin exfoliation, nail dystrophy
Isolated cases: skin depigmentation[#]

Musculoskeletal and connective tissue disorders

Very common: arthralgia (12.9%), myalgia (10.7%)
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 (10.7%), tiredness (fatigue) (12.4%)
Common: pyrexia, injection site reaction, asthenia, chills, general physical health deterioration, injection site erythema, body temperature increased
Uncommon: injection site pain, injection site pruritus, sensitivity to weather change, weight decrease
Isolated cases: tongue hyperpigmentation[#]

[#]Reported as an adverse reaction during treatment with other medicinal products containing interferon alfa.
*Mandatory statement for medicinal products containing interferon

**e.g. urticaria, angioedema, bronchoconstriction or anaphylaxis.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

During the clinical study programme, one case of accidental overdose with ropeginterferon alfa 2b was reported. The patient received a 10-times higher starting dose than recommended and developed flu-like symptoms, which were rated as non-serious, for three days. The patient recovered completely after paracetamol administration and temporary discontinuation of therapy with ropeginterferon alfa-2b.
There is no antidote for the medicinal product available. In case of overdose, close medical surveillance of the patient and, if necessary, symptomatic treatment are recommended.

Properties/Effects

ATC code

L03AB15
Ropeginterferon alfa-2b is a recombinant interferon alfa-2b conjugated with a two-arm methoxypolyethylene glycol (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, whose cellular effects are mediated by binding to a transmembrane receptor called interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signalling cascade through the activation of kinases, particularly Janus kinase 1 (JAK1), tyrosine kinase 2 (TYK2) and signal transducer and activator of transcription (STAT) proteins. Through nuclear translocation of STAT proteins, distinct gene-expression programmes are controlled and many cellular effects are induced. Interferon alfa showed an inhibitory effect on the proliferation of haematopoietic and fibroblast progenitor cells in the bone marrow and antagonised the action of growth factors and other cytokines that play a role in the development of myelofibrosis. These effects may contribute to the therapeutic effect of interferon alfa in polycythaemia vera.

Further, it was demonstrated that interferon alfa is able to decrease the *JAK*2V617F-mutated 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).

Pharmacodynamics

Clinical efficacy

In an open-label, randomised phase III study (PROUD-PV), the efficacy and safety of ropeginterferon alfa-2b were investigated in comparison to hydroxycarbamide in 254 adult patients with polycythaemia vera (1:1 randomisation). The main inclusion criteria were: polycythaemia vera diagnosis according to World Health Organisation 2008 criteria, age of ≥ 18 years and either pretreatment with hydroxycarbamide or an indication for cytoreductive therapy. For the indication of cytoreductive therapy, at least one of the following criteria had to be met: age > 60 years, history of a significant, polycythaemia vera-related cardiovascular event, poor response to phlebotomy or poor tolerance of phlebotomy, progressive splenomegaly, platelets > 1000 x 10^9/L or leukocytes > 10 x 10^9/L.

Patients were stratified according to previous administration to hydroxycarbamide, age at screening (≤ 60 or > 60 years) and history of thromboembolic events. The treatment groups were matched at screening for age, gender and ethnicity. In the ropeginterferon alfa-2b treatment arm (n=127) and control treatment arm (n=127), the following mean values (± SD) for patient characteristics were recorded: duration of PV (months) 12.6 ± 24.70 and 15.7 ± 25.65, respectively; JAK2V617F allele burden (%) 41.9 ± 23.49 and 42.8 ± 24.14, respectively; haematocrit (%), 47.8 ± 5.22 and 48.6 ± 5.39, respectively; platelets (10^9/L), 537.7 ± 273.08 and 516.8 ± 254.43, respectively; leukocytes (10^9/L), 11.5 ± 4.76 and 11.9 ± 4.88, respectively. Twelve patients (9.4%) in the ropeginterferon alfa-2b treatment arm and 15 patients (11.8%) in the control treatment arm had pre-existing splenomegaly at screening.

Hydroxycarbamide treatment-naïve (n = 160) and hydroxycarbamide-treated (n = 94) patients were randomised to treatment with either 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 of ropeginterferon alfa-2b.

The haematological response (defined as haematocrit < 45% without phlebotomy [at least 3 months since last phlebotomy], platelets < 400 x 10^9/L and leukocytes < 10 x 10^9/L) after 12 months of treatment was 43.1% [53/123] of patients in the ropeginterferon alfa-2b arm and 45.6% [57/125] of patients in the control treatment arm. For the composite primary endpoint of the PROUD-PV study (haematological response with normal spleen size after 12 months), the non-inferiority of ropeginterferon alfa-2b to control treatment could not be demonstrated (21.3% [26/122] and 27.6% [34/123] response rate; p=0.2), respectively.

In order to evaluate the long-term efficacy and safety of ropeginterferon alfa-2b, 171 adult patients with polycythaemia vera who had previously completed the PROUD-PV study were enrolled in an open-label, phase IIIb extension study (CONTINUATION-PV). As the CONTINUATION-PV study continued the randomly assigned treatment in PROUD-PV, it cannot be called a prospectively randomised study. The extension study did not establish any new null hypothesis; hence, all results are exploratory in nature and no significance is formally possible. In 95 patients, treatment with ropeginterferon alfa-2b (from 50 to 500 micrograms SC every two, three or four weeks) was continued. The mean dose after 36 months of treatment (12-month treatment duration in the PROUD-PV study and 24-month treatment duration in the extension study) was 363 (± 149) micrograms of ropeginterferon alfa-2b.

A complete haematological response with an improvement in disease burden (defined as haematocrit < 45% without phlebotomy in the last 3 months, platelets < 400 x 10^9/L and leukocytes < 10 x 10^9/L, improvement in clinically significant splenomegaly and disease-related symptoms [microvascular disturbances, pruritus, headache]) was shown in 49.5% of patients on treatment with ropeginterferon alfa-2b and 38.0% of patients on control treatment after 24 months of treatment (12 months in the PROUD-PV study and 12 months in the extension study). After 36 months of treatment (12 months in the PROUD-PV study and 24 months in the extension study), the complete haematological response with an improvement in disease burden was 52.6% for treatment with ropeginterferon alfa-2b and 37.8% for the control treatment.

After 36 months of treatment, the patients showed a difference with regard to *JAK2*V617F allele burden (19.7% for treatment with ropeginterferon alfa-2b; 39.3% for the control treatment) and change in *JAK2*V617F allele burden from baseline (-22.9% for treatment with ropeginterferon alfa-2b; -3.5% for the control treatment).

Pharmacokinetics

Absorption

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

The absolute bioavailability of subcutaneously administered ropeginterferon alfa-2b has not been investigated in humans. Thus, no valid statement can be made with regard to absolute bioavailability. Based on data in monkeys, it is approximately 80% and thus similar to that for pegylated interferon alfa-2a.

Distribution

Ropeginterferon alfa-2b is found mainly in the bloodstream and extracellular fluid, as seen by the steady-state volume of distribution (V_d) of 6.6 to 17 litres in patients after subcutaneous administration (dose range 50-450 micrograms). Mean C_{max} in patients after subcutaneous multiple dose

administration was 2.4 ng/mL (at a dose of 50-80 micrograms) to 49 ng/mL (at a dose of 450 micrograms) and AUC_{0-t} ranged between 28.5 ng.h/mL (at a dose of 50-80 micrograms) and 552.6 ng.h/mL (at a dose of 450 micrograms). In healthy volunteers, an interindividual variability of 25-35% for AUC and C_{max} was observed.
Studies on mass balance and tissue distribution, as well as whole-body autoradioluminography studies in rats, showed that a similar medicinal product with interferon alfa (pegylated interferon alfa-2a), in addition to the high concentrations in blood, was distributed to the liver, kidney and bone marrow.

Metabolism

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 elimination compared to unpegylated interferons. Studies in rats with a similar medicinal product containing interferon alfa (pegylated interferon alfa-2a) showed primary elimination via hepatic metabolism. The same elimination route is assumed for ropeginterferon alfa-2b.
Pharmacokinetic interaction studies with pegylated interferon alfa-2a in humans showed a moderate inhibitory effect on substrates metabolised by CYP1A2 and CYP2D6 (see “Interactions”).

Elimination

The elimination of ropeginterferon alfa-2b is not fully characterised. Studies with a similar medicinal product containing interferon alfa (pegylated interferon alfa-2a) have shown 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 than that of unpegylated interferon alfa-2a.
After subcutaneous multiple-dose administration (dose range 50-450 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 0.061 L/h.
The involvement of transport proteins in the absorption, distribution and elimination of ropeginterferon alfa-2b is not known.

Linearity/non-linearity

In a pharmacokinetic study with healthy subjects, the C_{max} of ropeginterferon alfa-2b increased proportionally with the dose. The observed increase in exposure was disproportionately high. The interindividual variability for ropeginterferon alfa-2b was 35% (C_{max}) and 25% (AUC).

Kinetics in specific patient groups

Hepatic impairment

In cirrhotic (Child-Pugh A) and non-cirrhotic patients, similar exposure and a similar pharmacokinetic profile were reported for another medicinal product containing interferon alfa (pegylated interferon alfa-2a). The pharmacokinetics was 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 medicinal products containing pegylated interferon alfa.
The plasma levels in patients with moderate or severe renal impairment receiving 180 micrograms of pegylated interferon alfa-2a once weekly was comparable to or 60% higher than in patients with normal renal function.
In 13 patients with ESRD requiring haemodialysis, administration of 135 micrograms of pegylated interferon alfa-2a once weekly led to a 34% lower drug exposure than in patients with normal renal function.
Patients with renal impairment receiving a single dose of 1.0 microgram/kg pegylated interferon alfa-2b showed an increased relationship of C_{max}, AUC and half-life to the degree of renal impairment. Following multiple dosing of pegylated interferon alfa-2b (1.0 microgram/kg SC weekly over four weeks), the clearance of pegylated interferon alfa-2b in patients with moderate or severe renal impairment was on average 17% and 44% lower, respectively, than in patients with normal renal function. Single-dose data showed that clearance in patients with severe renal impairment not on haemodialysis was comparable to that of patients on haemodialysis.

Elderly patients

The pharmacokinetic data from the use of ropeginterferon alfa-2b in elderly patients are limited. Based on the results from the PROUD-PV and CONTINUATION-PV studies on exposure, pharmacodynamic activity and tolerability, a dose adjustment for ropeginterferon alfa-2b is not considered necessary in elderly patients.

Obese or underweight patients

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

Preclinical data

The toxicity studies were limited to four weeks in most monkeys due to the emergence of anti-interferon antibodies. Preclinical adverse events are consistent with those observed in clinical studies.
Reproductive and developmental studies have not been performed with ropeginterferon alfa-2b. Interferon alfa showed an abortive effect in primates and ropeginterferon alfa-2b is expected to have a similar effect. The effect on fertility has not been investigated.
Ropeginterferon alfa-2b has shown no genotoxic potential.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Shelf life after opening

The pre-filled pen may be stored for up to 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 the contents from light. The pre-filled pen may be used a maximum of two times within these 30 days. Any medicine remaining in the pre-filled pen after the second use and/or after 30 days must be discarded.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for 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 and without visible particles.
Before each administration of the pre-filled pen, the label must always be checked to avoid medication errors due to confusion between Besremi 250 micrograms/0.5 mL solution for injection and Besremi 500 micrograms/0.5 mL solution for injection.
The pre-filled pen with *250 micrograms/0.5 mL* has a *grey push button*.
The pre-filled pen with *500 micrograms/0.5 mL* has a *blue push button*.

Before each injection, a new, sterile needle as provided with the pre-filled pen must be carefully attached onto the pre-filled pen. Needles must be discarded immediately after use.
When the pre-filled pen is used for the first time, the pen is prepared for injection by turning the dose knob until the symbol of a “drop” in the display 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 up towards the needle. Then press the push button until the setting “0” is seen. This may be repeated up to six times. A visible droplet of liquid at the needle tip means that the pre-filled pen and needle are working properly.
The dose can be set in steps of 50 micrograms by rotating the dose knob. If a certain dose cannot be set, there might be an insufficient quantity of medicinal product left in the pen and a new pen must be used.
The needle must be inserted into the skin. The push button must be depressed completely and held down for at least 10 seconds before withdrawing the needle.
To prevent possible transmission of disease or any kind of contamination, the Besremi pre-filled pen must be used only for one 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 first use, regardless of how much medicinal product is remaining in the pre-filled pen.
Empty pens must never be reused and must be properly discarded.

Authorisation number

67488 (Swissmedic)

Packs

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

Each pack contains 1 pre-filled pen and 2 injection needles (A)
The pre-filled pen consists of white polypropylene, with a grey push button. The dose strength “250 µg/0.5 mL” is highlighted in grey on the label. The pen delivers doses of 50 µg, 100 µg, 150 µg, 200 µg and 250 µg.

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

Each pack contains 1 pre-filled pen and 2 injection needles (A)
The pre-filled pen consists of white polypropylene, with a blue push button. The dose strength “500 µg/0.5 mL” is highlighted in blue on the label. The pen delivers doses of 50 µg, 100 µg, 150 µg, 200 µg, 250 µg, 300 µg, 350 µg, 400 µg, 450 µg and 500 µg.

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. One cartridge contains 0.5 mL of solution.

Marketing authorisation holder

OrPha Swiss GmbH, 8700 Küsnacht, Switzerland

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