OrPha Swiss

Summary of the Risk Management Plan (RMP)

for

BESREMI® (Ropeginterferon alfa-2b)

Injektionslösung im Fertigpen

Document Version 1.0

Based on RMP Version number 1.2 (Data lock point 14 Aug 2020)

MAH: OrPha Swiss GmbH, 8700 Küsnacht

Date: 04.02.2021

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Besremi is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Besremi in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. OrPha Swiss GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Besremi.

Part VI: Summary of the risk management plan

Summary of risk management plan for Besremi® (ropeginterferon alfa-2b)

This is a summary of the risk management plan (RMP) for Besremi®. The RMP details important risks of Besremi®, how these risks can be minimised, and how more information will be obtained about Besremi®'s risks and uncertainties (missing information).

Besremi®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Besremi® should be used.

This summary of the RMP for Besremi® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Besremi®'s RMP.

I. The medicine and what it is used for

Besremi® is authorised for treatment of Polycythaemia Vera without symptomatic splenomegaly (see SmPC for the full indication). It contains Pegylated-Proline-Interferon α-2b as the active substance and it is given subcutaneously by pre-filled pen with 250 µg or 500 µg ropeginterferon alfa-2b.

Further information about the evaluation of Besremi®'s benefits can be found in Besremi®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/besremi.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Besremi®, together with measures to minimise such risks for learning more about Besremi®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Besremi® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Besremi® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Besremi®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Hepatotoxicity • Thyroid disorders • Neuropsychiatric adverse effects • Ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal detachment • Cardiac events including cardiomyopathy, myocardial infarction, myocardial ischaemia • Pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis, pneumonia and pulmonary arterial hypertension • Diabetes mellitus
Important potential risks	• None[1)]
Missing information	• None

[1)] Important potential risks in current approved EU RMP (v1.0, dated 27Dec2018): Pulmonary arterial hypertension, Thrombotic microangiopathy, Neoplasms, benign and malignant, Reproductive toxicity/ spontaneous abortions , Demyelating disorders.

II.B Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Hepatotoxicity has been identified as a risk associated with IFNα use. Hepatotoxicity such as increase in gamma-glutamyl transferase, alanine aminotransferase and aspartate aminotransferase or hepatic failure was reported with IFNα treatment.
Risk factors and risk groups	Determination of drug induced liver injury includes an individual susceptibility. This susceptibility is governed by genetic, pre-existing and environmental factors. Predisposing factors consist of ethnicity, CYP polymorphisms, concomitant liver diseases, age, nutritional status and diet, gender and pregnancy (Tarantino *et al.*, 2009)
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections "Special dosage instructions, Patients with impaired hepatic function", "Contraindications" "Warnings and precautions, Liver function", "Undesirable effects" • PL sections "Contraindications", "Precautions for use", "Side effects" • Legal status: Prescription only medicine (POM) <u>Additional risk minimisation measures:</u> • None

Important identified risk: Thyroid disorders	
Evidence for linking the risk to the medicine	Thyroid dysfunction has been identified as a risk associated with IFNα use. Thyroid disorders such as hypothyroidism, hyperthyroidism, thyroiditis or

	increase in thyroid stimulating hormone (TSH) were reported with IFNα treatment.
Risk factors and risk groups	The presence of thyroid peroxidase (TPO) antibodies, has been shown to be a statistically significant risk factor for developing thyroid disease in patients treated with IFN (Tomer *et al.*, 2007). The incidence of thyroid dysfunction is higher in IFN-treated patients with pre-existing thyroid autoimmunity irrespective of the disease being treated (Tovey *et al.*, 2010).
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Contraindications", "Warnings and precautions, "Endocrine system", "Undesirable effects" • PL sections "Contraindications", "Precautions for use", "Side effects" • Legal status: POM Additional risk minimisation measures: • None

Important identified risk: Neuropsychiatric adverse effects	
Evidence for linking the risk to the medicine	Neuropsychiatric adverse effects have been identified as a risk associated with IFNα use. Severe neuropsychiatric adverse effects such as depression, cognitive disturbances, suicidal ideation and psychosis were reported with IFNα treatment.
Risk factors and risk groups	One major risk factor is presence of psychiatric disorders, especially depression in the medical history possibly because of shared biological mechanisms. Genetic variants that have been implicated in depression, like serotonin, or inflammatory pathway related genetic variants increase the risk of developing psychological side effects during IFNα treatment. Several genetic variants throughout the IFNα/β signalling pathway, and genetic variants in the IL-6, IL-1b or nitric oxide synthase-1 (NOS1) genes increase depressive and anxiety symptomatology (Kovacs *et al.*, 2016).
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Contraindications", "Warnings and precautions, Central nervous system", "Effects on ability to drive and use machines", "Undesirable effects" • PL sections "Contraindications", "Precautions for use", "Side effects" • Legal status: POM Additional risk minimisation measures: • None

Important identified risk: Ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal detachment	
Evidence for linking the risk to the medicine	Ocular adverse effects have been identified as a risk associated with IFNα use. Ocular adverse effects such as decreased visual acuity, loss of vision, and retinal detachment were reported with IFNα treatment.
Risk factors and risk groups	Patients with diabetes and hypertension are at increased risk for developing ocular toxicity (PegIntron SmPC).
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections "Warnings and precautions, Visual system", "Undesirable effects" • PL sections "Precautions for use", "Side effects"

Important identified risk: Ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal detachment	
	• Legal status: POM <u>Additional risk minimisation measures:</u> • None

Important identified risk: Cardiac events including cardiomyopathy, myocardial infarction, myocardial ischaemia	
Evidence for linking the risk to the medicine	Cardiac adverse effects have been identified as a risk associated with IFNα use, especially in patients with previous or existing cardiac complications. Severe cardiac adverse effects such as myocardial infarction, congestive heart failure, cardiomyopathy, myocardial ischemia and atrial fibrillation were reported with IFNα treatment.
Risk factors and risk groups	Patients with 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 are at risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections "Contraindications", "Warnings and precautions, Cardiovascular system", "Undesirable effects" • PL sections "Contraindications", "Precautions for use", "Side effects" • Legal status: POM <u>Additional risk minimisation measures:</u> • None

Important identified risk: Pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis, pneumonia, and pulmonary arterial hypertension	
Evidence for linking the risk to the medicine	Pulmonary adverse effects have been identified as a risk associated with IFNα use. Severe pulmonary adverse effects such as pulmonary fibrosis were reported with IFNα treatment. Failure to recognize IFN-associated pulmonary toxicity may result in persistence of pulmonary damage.
Risk factors and risk groups	Patients with lung (respiratory) problems, such as chronic obstructive pulmonary disease (COPD) are at increased risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • SmPC sections "Warnings and precautions, Respiratory system", "Undesirable effects" • PL sections "Precautions for use", "Side effects" • Legal status: POM <u>Additional risk minimisation measures:</u> • None

Important identified risk: Diabetes mellitus	
Evidence for linking the risk to the medicine	Diabetes mellitus has been identified as a risk associated with IFNα use. IFN therapy triggered type 1 diabetes in hepatitis C infected Caucasian and Japanese patients.
Risk factors and risk groups	Patients with genetic predisposition or with other autoimmune diseases are at increased risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u>

Important identified risk: Diabetes mellitus	
	• SmPC sections "Warnings and precautions, Endocrine function", "Undesirable effects" • PL sections "Precautions for use", "Side effects" • Legal status: POM <u>Additional risk minimisation measures:</u> • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Besremi®.

II.C.2 Other studies in post-authorisation development plan

<u>Non-interventional Post-authorisation Safety Study: Besremi-PASS</u>

The objective of the study is to provide further data to characterize the safety and tolerability of ropeginterferon alfa-2b by monitoring the hepatic and cardiovascular safety in patients with polycythaemia vera treated with ropeginterferon alfa-2b in routine post-authorisation use.