Part VI: Summary of the risk management plan

Summary of risk management plan for Besremi (Pegylated-Proline-Interferon α-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 dysfunction • 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 and pneumonia • Diabetes mellitus
Important potential risks	• 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-glutamyltransferase, 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	Routine risk communication: SmPC section 4.2, 4.3, 4.4, 4.8, 5.2 PL section 2, 4 Legal status: Prescription only medicine (POM)

Important identified risk: Thyroid dysfunction	
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 communication: SmPC section 4.3, 4.4, 4.8 PL section 2, 4 Legal status: POM

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 signaling 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 communication: SmPC section 4.3, 4.4, 4.7, 4.8 PL section 2, 4 Legal status: POM

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 communication: SmPC section 4.4, 4.8 PL section 2, 4 Legal status: POM

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	Routine risk communication: SmPC section 4.3, 4.4, 4.8 PL section 2, 4

	Legal status: POM

Important identified risk: Pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis and pneumonia	
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	Routine risk communication: SmPC section 4.4, 4.8 PL section 2, 4 Legal status: POM

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	Routine risk communication: SmPC section 4.4, 4.8 PL section 2, 4 Legal status: POM

Important potential risk: Pulmonary arterial hypertension	
Evidence for linking the risk to the medicine	Pulmonary arterial hypertension (PAH) is potential risk associated with IFNα use. PAH is a very rare side effect of IFN treatment but can be life-threatening. Cases of PAH were reported with IFNα treatment notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis).
Risk factors and risk groups	Patients with portal hypertension, HIV infection or cirrhosis are at increased risk.
Risk minimisation measures	Routine risk communication:

	SmPC section 4.4, 4.8 PL section 4 Legal status: POM

Important potential risk: Thrombotic microangiopathy	
Evidence for linking the risk to the medicine	Thrombotic microangiopathy (TMA) is a potential risk associated with IFNα use. Case reports have linked TMA to IFNα treatment. Type I IFN therapies caused direct dose-dependent TMA and the IFN protein itself could directly damage small blood vessels.
Risk factors and risk groups	Patients with deficiency of ADAMTS13 are at risk of developing TMA. Secondary TMAs develop in the setting of various clinical conditions, such as infection, medication, malignancy (especially adenocarcinomas) and various underlying diseases. For instance, acquired TMAs are often associated with connective tissue diseases, and also treatment using several specific drugs. A significant number of drugs have been associated with TMAs, including anti-platelet thienopyridine derivative drugs, antineoplastic drugs such as mitomycin C, and quinine (Fujimura et al., 2010).
Risk minimisation measures	Routine risk communication: SmPC section 4.8 PL section 4 Legal status: POM

Important potential risk: Neoplasms, benign and malignant	
Evidence for linking the risk to the medicine	Neoplasms, benign and malignant, is a potential risk associated with IFNα use. Cases of neoplasms such as glioblastoma and basal cell carcinoma were reported with IFNα treatment. However, a causal relationship could not be determined between these events and the IFNα treatment.
Risk factors and risk groups	Cancer in the family history, genetic predisposition, chronic inflammation, radiation, sunlight, tobacco use, exposure to cancer-causing substances, immunosuppression are risk factors.
Risk minimisation measures	Routine risk communication: SmPC section 4.5 PL section 2 Legal status: POM

Important potential risk: Reproductive toxicity / spontaneous abortions	
Evidence for linking the risk to the medicine	Reproductive toxicity/ spontaneous abortions is a potential risk associated with IFNα use. An abortion-inducing effect was reported in primates receiving IFNα.
Risk factors and risk groups	Women of childbearing potential not using effective contraception during IFN treatment are at increased risk.
Risk minimisation measures	Routine risk communication: SmPC section 4.6 PL section 2 Legal status: POM

Important potential risk: Demyelating disorders	
Evidence for linking the risk to the medicine	Demyelinating disorders is a potential risk associated with IFNα use. Cases of demyelinating disorders in patients with hepatitis C or hepatitis B infection and chronic myelogenous leukemia were reported during INFα treatment.
Risk factors and risk groups	Infection and (auto) immune mechanisms are likely to contribute to the pathogenesis of demyelinating disorders (Reeves et al., 2008).
Risk minimisation measures	Routine risk communication: SmPC section 4.8 PL section 4 Legal status: POM

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

PASS ropegIFN alfa-2b: Safety observational study

Purpose of the study: To further investigate the safety and tolerability of ropegIFN alfa-2b with a special focus on hepatotoxicity to evaluate the effectiveness of risk minimisation measures. Secondary objective: evaluation of cardiovascular events during titration phase.