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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR

PLEGRIDY (PEGINTERFERON BETA-1A)

RMP version number:	7.0
Data lock point (DLP) for this RMP:	18 Jul 2025
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QPPV name: Jana Hyankova, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

Not applicable - no other versions of Plegridy EU RMP are currently under evaluation.

Details of currently approved RMP

Version number:	6.0
Approved with procedure:	EMEA/H/C/002827/X/0056
Date of approval:	14 December 2020

Rationale for submitting an updated RMP

Version 7.0 of this EU RMP has been created for the following reasons:

- Update study status, objectives and milestones of the category 3 study 105MS404, drug utilization in pregnancy exposure in second and third trimester of pregnancy, in line with the agreed protocol Version 3.0, submitted within Procedure EMA/PAM0000263236
- Update of QPPV details
- Remove post authorization exposure data by country (per guidance on anonymisation of personal data, reference EMA/63692/2025, revision 3)
- Update post authorization exposure estimates based on new data lock point
- Update clinical trial exposure based on new data lock point
- Template changes: Include a row for Section VII in the Summary of Significant Changes, confidentiality statements removed

Summary of significant changes in this RMP

In consideration of the above rationale, a summary of the significant changes implemented in Version 7.0 of this RMP is provided in the table below:

Module	Rationale for update	Summary of significant changes
Part I	Revised from version 6.0 as the proposed IM route is now current	Details of proposed Plegridy IM administration removed from Table 1
Part II Module SI	New treatment options available in the EU since Version 6.0 of this RMP was published	Added treatments to “Main existing treatment options”
Part II Module SII	Not Applicable	Not Applicable
Part II Module SIII	New data lock point for this Version 7.0 RMP	Updates to exposure data due to the new data lock point

Module	Rationale for update	Summary of significant changes
Part II Module SIV	New data lock point for this Version 7.0 RMP available	Revised to include updated data lock point to 19 Jul 2025
Part II Module SV	New data lock point for Version 7.0 RMP available. EU guidance published regarding anonymisation of personal data and assessment of commercially confidential information during the preparation and redaction of risk management plans (EMA/63692/2025).	Post Authorisation Cumulative Exposure estimates updated to 30 Jun 2025. Removal of post-authorisation exposure data by country per EU guidance.
Part II Module SVI	Not Applicable	Not Applicable
Part II Module SVII	The previous version of this RMP is now Version 6.0	Update of the referenced RMP from Version 5.0 to Version 6.0 in SVII.2.1.
Part II Module SVIII	Not Applicable	Not Applicable
Part III	Post authorisation study 105MS404 (drug utilisation in second and third trimester of pregnancy) is active. In Version 6.0 of this RMP, the study was planned. This change was reflected.	Updates to Additional Pharmacovigilance Activities (post authorisation study 105MS404): Added study title, number and name. Updates made to study status from “planned” to “ongoing.” Study milestones were added. Objectives updated in line with protocol.
Part IV	Not Applicable	Not Applicable
Part V	Not Applicable	Not Applicable
Part VI	Post authorisation study 105MS404 (drug utilisation in second and third trimester of pregnancy) is active. In version 6.0, the study was planned. This change was reflected.	Update to additional pharmacovigilance activity category 3 study 105MS304. Addition of study title and number. Updated study status from “planned” to “ongoing.” Added study milestones.

Module	Rationale for update	Summary of significant changes
Part VII	Annexes updated in line with amendments throughout	Annex 2: Updates made to additional pharmacovigilance activity category 3 study 105MS404, drug utilisation in pregnancy study. Changes made to the study status (“planned” to “ongoing”), with study name added and study milestones. Annex 3: Updated Part C. Study 105MS104 INFORM was added (study name and title). Procedure number of the protocol was added. Annex 8: Update to include changes made to the RMP version 7.0.

TABLE OF CONTENTS

PART VII - ANNEXES

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
DIBD	Developmental International Birth Date
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
GCP	Good Clinical Practice
HV	Healthy volunteer
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
IBD	International Birth Date
IFN	Interferon
IM	Intramuscular
INN	International Non-propriety Name
IRR	Incidence Rate Ratio
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NOEL	No Observed Effect Level
PEG	Poly-(ethyleneglycol)
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
ROW	Rest of World
RRMS	Relapsing-remitting Multiple Sclerosis
SC	Subcutaneous
SmPC	Summary of Product Characteristics (EU)
ULN	Upper Limit of Normal
WBC	White Blood Cell

PART I: PRODUCT(S) OVERVIEW

Table 1: Product(s) Overview

Active substance(s) (INN or common name)	Peginterferon beta-1a
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic and immunomodulating agents; immunostimulants; interferons (L03AB13)
Marketing Authorisation Holder	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Plegridy
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Recombinant interferon beta-1a
	Summary of mode of action: A definitive mechanism of action of peginterferon beta-1a in MS is not known. However, it is likely to be consistent with other beta interferons via binding to the type I interferon receptor on the surface of cells and eliciting a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. These genes, and their gene products, are believed to mediate the efficacy of peginterferon beta-1a in MS.
	Important information about its composition: Plegridy is a recombinant interferon beta-1a conjugated to 20,000 Dalton (20 kDa) methoxy poly(ethyleneglycol) [PEG].
Hyperlink to the Product Information	Plegridy | European Medicines Agency (europa.eu)
Indication(s) in the EEA	Indicated in adult patients for the treatment of RRMS
Dosage in the EEA	**Current:** The recommended dose of Plegridy is 125 µg injected subcutaneously or intramuscularly every 2 weeks.

Pharmaceutical form(s) and strengths	**Current *(if applicable)*:** *Form:* Solution for injection in prefilled syringe; Solution for injection in prefilled pen *Strength:* 63 µg, 94 µg, 125 µg
Is the product subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Epidemiology of Multiple Sclerosis

Epidemiology data for the indicated patient population with RRMS is provided in the sections below.

Incidence

The worldwide incidence of multiple sclerosis (MS) is estimated to be 3.6 cases per 100,000 person-years in women (95% confidence interval [CI] 3.0-4.2) and 2.0 cases per 100,000 person years in men (95% CI 1.5-2.4) [Alonso and Hernán 2008].

Prevalence

Worldwide prevalence estimated at 2 to 2.5 million patients. The disease is unevenly distributed throughout the world; its prevalence varies between <5 cases per 100,000 people in tropical areas and Asia and >100 to 200 cases per 100,000 in temperate areas, especially those with large populations of Northern European origin.

Demographics of the population in the authorised indication and risk factors for the disease

MS is approximately twice as common in women as men and predominantly affects adults aged 20 to 60 years.

A genetic predisposition to MS exists, particularly variation involving the HLA-DRB1 locus [Lincoln 2005; Sawcer 2011]. Risk is elevated if a family member has MS [Ebers 2008]. Risk of MS increases with increasing geographic latitude. Vitamin D deficiency has been found to significantly increase the risk of developing MS, so reduced sunlight exposure during childhood at higher latitudes may be an explanation for the geographic phenomenon [Ascherio and Munger 2007].

The main existing treatment options

The main treatment options for MS are beta-interferons (Betaferon, Avonex, and Rebif), glatiramer acetate (GA; Copaxone), fingolimod (Gilenya), teriflunomide (Aubagio), alemtuzumab (Lemtrada), dimethyl fumarate (Tecfidera), natalizumab (Tysabri), ponesimod (Ponvory), diroximel fumarate (Vumerity), and ublituximab (Briumvi).

For more severe disease, main treatment options are anti-neoplastic and immunosuppressant agents, such as ocrelizumab (Ocrevus), mitoxantrone, cyclophosphamide, methotrexate, azathioprine, and cladribine. Furthermore, stem cell transplantation (most commonly autologous haematopoietic stem cell transplantation) may also be used as an experimental therapy for some patients with refractory forms of MS.

Treatment for MS includes various drugs for managing symptoms such as fatigue, depression, and pain, and corticosteroids for acute attacks.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

MS is an inflammatory disease of the brain and spinal cord characterised by focal areas of inflammation that lead to destruction of the myelin sheath and varying degrees of axonal injury.

MS can present with a range of neurological symptoms depending on the category of disease and location of the lesions, but commonly reported symptoms in established, untreated MS are weakness, which is frequently lower limb, sensory symptoms, and bladder problems, and progressive ambulatory decline will affect a sizable proportion of patients with MS. The Expanded Disability Status Scale (EDSS) is the most commonly used outcome measure in MS trials, and it is able to measure changes in ambulatory status even in the upper ranges. The scale extends from 0 (normal neurological examination) to 10 (death from MS complications) in 0.5 unit increments [Marrie 2007]. Observational studies indicate that the course of disability is predictable and irreversible once a certain level of disability is reached. Data from a longitudinal survey in an untreated Nordic population indicated that 15 years after diagnosis 40% of patients needed to use a walking aid and 25% of patients were wheelchair dependent [Myhr 2001]. These results are consistent with a number of studies looking at onset of disability in essentially untreated patients, where irreversible disability in terms of limited walking ability, but without aid or rest for greater than 500 m (EDSS score: 4), was reached after 6 years and the ability to walk with unilateral support for no greater than 100 m (EDSS score: 6) was reached after 20 years [Confavreux and Vukusic 2006] [Einarsson 2006].

A cross-sectional study in Stockholm among 166 MS patients found that, while about half of the patients were able to walk without an aid, only 8% were measured as having normal walking speed compared with the general Swedish population [Einarsson 2006]. The study concludes that, even in the presence of very severe disability, a progressive disease course, and lengthy disease duration, MS may remain relatively benign with regard to cognitive function and manual dexterity, yet less so with regard to walking capacity. Not surprisingly, progression to walking disability is likely to be more rapid in patients with progressive forms of the disease.

Important co-morbidities

Pneumonia

Incidence of pneumonia is estimated to be twice that of the general population. Pulmonary morbidity has been described in MS, especially among patients with more severe disease. Respiratory muscle function is affected by disease severity [Gosselink 1999]. Complications from a respiratory illness are also a common cause of death among patients with MS. A study of the Danish Multiple Sclerosis Registry (1998) found that MS patients were more likely to die from respiratory and infectious diseases than the general population [Koch-Henriksen 1999]. Patients appear to have an increased history of respiratory tract infections prior to MS onset [Marrie 2000]. A crude estimate, based on the MS Danish registry results, suggests that the infection rate in MS patients may be at least 2 times greater than the general population. Reports of pneumonia with interferons-beta are rare and occur primarily in patients using interferons-beta for indications other than MS. Overall, it is reasonable to conclude that the background incidence

of pneumonias and respiratory tract infections in MS patients are likely to be higher than in the general population. At this time, no estimates of pneumonia incidence rates within MS patients were found.

Urinary Symptoms

Urinary symptoms are very common in patients with MS. One in 10 patients may already have urinary symptoms at the time of initial diagnosis of MS. However, on average, symptoms will appear about 6 years after the onset of disease [de Sèze 2007] and are estimated to be present in 64% to 68% of patients with MS as well as incontinence at least weekly in 33% of patients. Symptoms include frequency, urgency, and urinary incontinence, which together are described as overactive bladder syndrome. Urinary tract infections are common in patients with MS and are likely to be present in 30% of MS patients. The incidence of urinary symptoms increases with disease duration. Treatment options for overactive bladder include anticholinergic agents, but none of the newer drugs in this class, which are also likely to be better tolerated, have been specifically studied in patients with MS [Pöllmann and Feneberg 2008]. Infection needs to be excluded in any patients presenting with urinary symptoms.

Pain

An estimated 50% of MS patients visiting an outpatient department are likely to be experiencing pain, which can be directly or indirectly related to MS or MS treatments, or may be coincidental. Depending on the type of pain, treatment options include anti-epileptic drugs and tricyclic antidepressants along with standard pain medication.

Spasticity

Spasticity due to corticospinal tract involvement in MS can result in painful muscle cramps, spasms, and even contractures.

Pain related to spasticity may improve with physiotherapy but can also be treated with muscle relaxants, such as baclofen, tizanidine, or cyclobenzaprine, to prevent painful cramps.

Severe spasticity may be treated with botulinum toxin or intrathecal baclofen pumps may also be implanted due to disabling or painful spasticity [Kumpfel 2008].

Depression and Suicide

The lifetime prevalence of major depression in people with MS is 37% to 54%. The lifetime prevalence of depression in patients with MS is about 2 to 4 times higher than in community based samples [Patten 2005].

MS is associated with a 12% lifetime prevalence of suicide attempts [Patten 2005].

Seizures

The prevalence of epilepsy in MS is probably 2%, and the lifetime risk is in the order of 2% to 3% [Koch 2008]. Both generalised and focal seizures have been attributed to MS. Rarely, status epilepticus and epilepsia partialis continua have been recorded [Warrell 2003]. Literature suggests that incidence of seizures in MS patients is increased about 3 times that of the general population [Nicoletti 2003]; however, estimates of incidence vary. Probably the most relevant estimate is from Eriksson, et al, who estimated in an MS population in Gothenburg that the incidence of seizure (not of a diagnosis of epilepsy) was 3.49/1000 patient-years [Eriksson

2002]. In addition, this publication reports that the risk of seizure also increases with severity of MS and development of the progressive stage of the disease.

Cognitive Dysfunction

The prevalence of cognitive dysfunction is at least 50%. Cognitive dysfunction can include memory loss; impaired attention; difficulties in executive functioning, memory, and problem solving; slowed information processing; and problems shifting between cognitive tasks [Harrison's Principles of Internal Medicine 2011].

Fatigue

Fatigue is experienced by 90% of MS patients. This symptom is the most common reason for work-related disability in MS [Harrison's Principles of Internal Medicine 2011]. Fatigue can be exacerbated by elevated temperatures, by expending exceptional effort to accomplish basic activities of daily living, or by sleep disturbances (such as frequent nocturia). Fatigue may be due to other aetiologies, such as depression or hypothyroidism [Bakshi 2003; Bakshi 2000; Janardhan and Bakshi 2002].

Congestive Heart Failure

The frequency and incidence rate ratio (IRR) was studied in a population-based cohort study of Danish citizens with MS and an age- and sex-matched general population cohort. During the first year of follow-up following a first-time hospital diagnosis of MS, 0.2% of MS patients had heart failure. During 5 years of follow-up, 0.7% of MS patients had heart failure. The cumulative incidence of heart failure 30 years after initial diagnosis of MS was 12%.

In the first year after the initial MS diagnosis, MS was associated with an increased IRR of heart failure (adjusted IRR = 1.92). Patients with MS remained at higher long-term risk of heart failure (adjusted IRR = 1.53) [Christiansen 2010].

Thyroid disorders

The prevalence of thyroid disorders in women with MS is increased 3-fold compared to controls (13.1% vs. 4.3%). This is primarily due to an increase in hypothyroidism (9.4% vs. 2.2%) [Karni and Abramsky 1999]. Symptoms of hypothyroidism, such as fatigue, are also seen with MS and may be mistaken for a worsening of MS.

The prevalence of autoimmune thyroid disease is increased in males with MS (9.4%) vs. controls (1.9%; $p = 0.03$). The prevalence of autoimmune thyroid disease in female patients with MS (8.7%) did not differ from that in female controls (9.2%) [Niederwieser 2003].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Since the non-clinical safety and the clinical safety and efficacy of interferon beta-1a in MS patients are well established (Avonex, Rebif European Public Assessment Report [EPAR]), the object of the non-clinical programme for peginterferon beta-1a (Plegridy) was to establish whether the pharmacology, pharmacokinetic, and safety profile of peginterferon beta-1a was similar to that of interferon beta-1a (Avonex).

Key safety findings from non-clinical studies with potential relevance to human usage are described in Table 2.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity	
Repeat-dose toxicity: A single 5-week, repeat dose toxicology study was conducted with peginterferon beta-1a. Due to the species specificity of human interferon beta-1a, the non-clinical safety studies were conducted in rhesus monkeys. Local tolerance endpoints to evaluate injection site reactions were included in the toxicology study. These endpoints included assessment of erythema, oedema, induration, and histopathological evaluation of tissue collected from post mortem injection sites. A slight increase in body temperature of 1ºF to 3º F (0.55ºC to 1.66º C) was observed within 4 to 8 hours after the first and second doses, but not after subsequent doses. A dose-dependent decrease in lymphocyte count was noted in all peginterferon beta-1a-treated monkeys. None of the effects observed in the 5 week rhesus monkey toxicity study were considered to be adverse; therefore, the no observed adverse effect level (NOAEL) was the highest dose tested (100 µg/kg). Due to the development of neutralising antibodies, the safety margin was determined using exposures following the first dose. The NOAEL provides an approximate 500-fold safety margin over the clinical dose (125 µg) used in Phase 3 studies, based on a comparison of single-dose exposures (area under the serum concentration-time curve from time 0 to 168 hours postdosing [AUC168h]) between rhesus monkeys and humans.	None of the effects observed in the 5 week rhesus monkey toxicity study were considered to be adverse. Peginterferon beta-1a was well tolerated, and there were no treatment-related changes in clinical signs, injection sites, food consumption, body weight, serum chemistry, coagulation, urinalysis, ophthalmology, electrocardiograms, physical evaluations, organ weights, or gross or histological changes. The increase in body temperature and decrease in lymphocytes were reversible, were not considered to be adverse, and were considered to be related to the pharmacological activity of the drug. There were no adverse peginterferon beta-1a related changes at any injection site for any dose tested by either subcutaneous (SC) or intramuscular (IM) route of administration. Refer to SmPC Section 5.3.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Reproductive/developmental toxicity	
The 5-week reproductive toxicity study conducted in rhesus monkeys with peginterferon beta-1a confirmed similar effects on hormones related to abortifacient activity. Consistent with the effects observed with non pegylated interferon beta-1a, weekly administration of peginterferon beta-1a at 70 times the therapeutic dose (on a mg/kg basis and assuming a 70 kg human) to female rhesus monkeys for up to 5 weeks resulted in menstrual irregularities, anovulation, and decreased serum progesterone. These effects were reversible after discontinuation of drug. Thus, peginterferon beta 1a, like the other type I interferons including Avonex, is considered to be abortifacient but not teratogenic in animals.	Since marketing authorisation approval, data have been collected on more than 1000 pregnancy outcomes from pregnancy registries and post-marketing experience, which has indicated no evidence of an increased risk of serious adverse pregnancy outcomes, including spontaneous abortions and major congenital anomalies, after exposure to interferon-beta before and/or during pregnancy as compared to the women with MS who were unexposed to any MS disease modifying drug. Refer to SmPC Section 4.6.
Genotoxicity	
Peginterferon beta-1a did not show evidence of genotoxicity in an in vitro bacterial mutation test (Ames assay) and in an in vitro mammalian chromosome aberration test in human peripheral blood lymphocytes.	<u>Mutagenesis</u> Peginterferon beta‑1a was not mutagenic when tested in an in vitro bacterial reverse mutation (Ames) test and was not clastogenic in an in vitro assay in human lymphocytes. Refer to SmPC Section 5.3
Carcinogenicity	
Peginterferon beta-1a is considered to have a low risk for carcinogenicity in humans based on the mechanism of action of interferon beta-1a, demonstrated anti-tumour efficacy of peginterferon beta-1a in mouse xenograft models, a lack of findings consistent with neoplasia in preclinical safety studies for both interferon beta-1a (Avonex) and peginterferon beta-1a (though limited in study duration), and lack of genotoxicity.	Malignancies are an important potential class effect of interferon-beta products. The malignancy cases reported in the placebo-controlled peginterferon beta-1a experience are consistent with the overall incidence and type of malignancies observed in the general population. Peginterferon beta-1a has not been tested for carcinogenicity in animals. Based on the known pharmacology of interferon beta-1a and clinical experience with interferon-beta, the potential for carcinogenicity is expected to be low. Refer to SmPC Section 5.3

SAFETY FINDING	RELEVANCE TO HUMAN USE
Immunogenicity	
Preclinical safety studies were limited to 5 weeks due to immunogenicity of human interferon in rhesus monkeys and resultant development of neutralising antibodies. The generation of neutralising antibodies was detected after about 2 weeks of treatment, and reduced exposure to interferon beta-1a was detected after 3 to 4 weekly doses.	Development of neutralising antibodies in non-clinical studies with interferon beta-1a was also observed in clinical studies. Three percent of patients (18/681) developed persistent antibodies to the PEG moiety of peginterferon beta-1a. In the clinical study conducted, the development of antibodies against the PEG moiety of peginterferon beta-1a had no discernible impact on safety or clinical efficacy (including annualised relapse rate, magnetic resonance imaging (MRI) lesions, and disability progression). Neutralising antibodies in clinical studies are generally associated with reduced biological activity and may potentially be associated with a reduction in clinical efficacy. The presence of neutralising antibodies has not been associated with adverse events (AEs) or toxicity. Refer to SmPC Section 4.4.
Safety pharmacology	
None	Not applicable
Other toxicity-related information or data	
Dose-dependent reduction in lymphocyte count A dose-dependent decrease in lymphocyte count was noted in all peginterferon beta-1a-treated monkeys. The increase in body temperature and decrease in lymphocytes were reversible, were not considered to be adverse, and were considered to be related to the pharmacological activity of the drug.	Dose-dependent reduction in lymphocyte count with interferon beta-1a are observed in clinical studies with interferon beta-1a. About 4% of patients treated with interferon beta-1a 44 µg SC 3 times per week in clinical trials had persistent decreases in lymphocytes when examined over 6 and 24 months, compared with 1% to 2% of placebo-treated participants [Rieckmann 2004]. Refer to SmPC Section 4.8.[Rieckmann 2004]

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Integrated Clinical Trial Exposure

The evaluations of safety presented in this EU RMP (in support of the overall benefit-risk assessment of Plegridy, formerly known as BIIB017) focuses primarily upon the review of integrated data from three Phase 3 studies (105MS301, 105MS302, 105MS303; plus other studies, n = 1863) of peginterferon beta-1a (administered SC) in the indicated patient population (MS), and seven studies conducted in healthy volunteers (HVs) (comprising both SC and IM routes of administration; 105HV101, 105HV102, 105HV103, 105HV104, 105HV105, 105HV106, and 105RI101; n = 405), from the Developmental International Birthdate (DIBD) for peginterferon beta-1a (23 May 2007) through the data-lock date of the most recent Periodic Safety Update Report (PSUR) 18 Jul 2025.

Exposure data, stratified by duration and dose, age, sex and ethnic origin/race are presented in Table 3, Table 4, and Table 5.

Table 3: Cumulative Participant Exposure to BIIB017 From Clinical Trials In MS Participants By Interval And Dose Frequency Through 18 Jul 2025 (n = 1863)

BIIB017 125 (mcg) SC			
	Every 4 weeks	Every 2 weeks	Total
Number of participants	728	1135	1863
Total number of participant-years exposed to study treatment (a) (b)			
At least one dose	2080.69 (728)	2423.09 (1135)	4503.78 (1863)
≥ 12 weeks	2076.83	2408.96	4485.80
≥ 24 weeks	2072.23	2380.85	4453.08
≥ 36 weeks	2061.60	2352.10	4413.69
≥ 48 weeks (1 year)	2051.08	2313.02	4364.11
≥ 60 weeks	2005.36	2258.40	4263.76
≥ 72 weeks	1982.21	2208.50	4190.72
≥ 84 weeks	1958.60	2181.71	4140.31
≥ 96 weeks (2 years)	1942.08	2068.14	4010.21

BIIB017 125 (mcg) SC			
	Every 4 weeks	Every 2 weeks	Total
Total number of participant-years exposed to study treatment (a) (b)			
≥ 108 weeks	1852.62	1940.94	3793.56
≥ 120 weeks	1831.10	1911.18	3742.28
≥ 132 weeks	1811.66	1880.54	3692.21
≥ 144 weeks (3 years)	1740.06	1813.65	3553.71

Includes completed studies and an ongoing study.
Studies 105MS301, 105MS302, 105MS303, 800MS301, and PRT-PEG-15-10880 are completed.
Study 105MS306 is ongoing.
a Days on study drug is calculated as (date of last dose + 14 days) – (date of first dose) + 1. Weeks on study drug is calculated as (days on study drug)/7.
b Total number of participant-years exposed to study treatment is calculated as the sum of number of days exposed to study treatment/365.25

Table 4: Cumulative Participant Exposure to BIIB017 from Clinical Trials by Age and Sex Through 18 July 2025 (HVs and MS Participants n = 2153)

Age group	**Participants**		**Person-time [a]**	
	Male (n = 729) n%	**Female (n = 1424) n (%)**	**Male**	**Female**
Cumulative for all indications				
<18 years	1	5	1.88	7.00
Adults (18 to 65 years)	720 (99)	1415 (>99)	1276.00	3102.03
66-75 years	8 (1)	4 (<1)	0.33	0.16
>75	0	0	0	0
Total	729 (100)	1424 (100)	1278.21	3109.19

Includes all completed studies: 105HV101, 105HV102, 105HV103, 105HV104, 105HV105, 105HV106, 105RI101, 105MS301, 105MS302, 105MS303, 800MS301, and PRT-PEG-15-10880.
Note: Only participants exposed to BIIB017 are included.
[a] Person-time is calculated as [(date of last treatment dose+14 days) - date of first treatment dose+1]/365.25.

Table 5: Cumulative Participant Exposure to BIIB017 from Clinical Trials by Racial Group Through 18 Jul 2025 (HVs and MS Participants n = 2153)

Race	**Participant**	**Person-time [a]**
Asian	195	415.54

Race	Participant	Person-time [a]
Black	135	25.62
Caucasian	1649	3630.94
Other	98	232.65
Not reported[b]	76	82.66
Missing	0	0
Total	2153	4387.40

Includes all completed studies: 105HV101, 105HV102, 105HV103, 105HV104, 105HV105, 105HV106,105RI101, 105MS301, 105MS302, 105MS303, 800MS301, PRT-PEG-15-10880.
Note: Only participants exposed to BIIB017 are included.
[a] Participant-Years is calculated as [(date of last treatment dose+14 days) - date of first treatment dose+1]/365.25. dose+1]/365.25.
[b] Race was not reported due to local ethics committee requirements.

Exposure to Plegridy IM in Healthy Volunteers (Study 105HV106)

The assessment of the safety of Plegridy in support of the proposed IM route of administration was based on data obtained from Study 105HV106 – a phase 1, open-label, crossover study which evaluated the bioequivalence of Plegridy IM and Plegridy SC in healthy volunteers.

In this study, 136 healthy volunteers received a single dose of Plegridy via both the IM and SC routes of administration. All volunteers were adults (aged between 21 – 55 years); 75 participants (55.1%) were male and 61 were female (44.9%).

Of the 136 volunteers, 70 were black or African American (51.5%), 59 were White (43.3%), 3 were Asian (2.2%), and 4 were reported their race as Other (2.9%).

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The Plegridy clinical development programme has employed specific exclusion criteria which were either related to the evaluation of efficacy (to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), or were related to safety (in order to protect trial patients from potential risks associated with investigational product administration), or were good clinical practice (GCP) related (e.g., to ensure that proper follow-up was possible).

When evaluating the impact of these exclusion criteria in relation to the impact on the safety of patients receiving treatment with Plegridy in the post-marketing setting, key exclusion criteria pertaining to safety from pivotal studies included in the primary pooled safety dataset are addressed by the "Contraindications" and "Warnings and precautions for use" sections of the Plegridy Summary of Product Characteristics (SmPC).

A review of the key exclusion criteria in pivotal studies, and an assessment of their relevance to be considered as areas of missing information are presented in Table 6.

Table 6: Discussion of exclusion criteria in relation to the assessment of missing information

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of hypersensitivity to natural or recombinant interferon or peginterferon, or to any excipients	Avoidance of hypersensitivity reactions	No	Included as a contraindication in SmPC Section 4.3. Considering this contraindication, use in this patient population is not considered relevant for inclusion as missing information.
Patients with current severe depression and/or suicidal ideation	Depression occurs with increased frequency in the multiple sclerosis population and in association with interferon use	No	Depression occurs with increased frequency in the MS population and in association with interferon use. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Therefore, the use of Plegridy in this patient population is contraindicated, and is not considered relevant for inclusion as missing information.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Prior treatment with interferon could not exceed 4 weeks and must have been discontinued for 6 months	In order to study effect in relatively interferon-naïve participants . Additionally, exclusion of participants with prolonged or recent prior interferon treatment would ensure exclusion of patients with anti-interferon neutralising antibody which could confound efficacy assessments.	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.
History of clinically significant disease that would preclude participation in a clinical trial	To identify individuals who are physically and mentally able to complete the rigors of a clinical trial	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.
History of malignant disease	To help ensure that the participant would not develop an unrelated condition that would preclude completing the 2-year study	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of seizure disorder or unexplained blackouts	To avoid confounding the safety assessments of peginterferon beta-1a. Also, interferon beta may be associated with increased risk of seizures.	No	Seizure is listed as an ADR in the SmPC, therefore, the use of Plegridy in this patient population is not considered to be relevant for inclusion as missing information.
Clinically significant abnormal ECG	To avoid confounding the safety assessments of peginterferon beta-1a	No	Worsening of cardiac disease has been reported in patients receiving interferon beta. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease, or arrhythmia, should be monitored for worsening of their cardiac condition, particularly during initiation of treatment. The use of Plegridy in this patient population is not considered relevant for inclusion as missing information.
History of HIV infection	To avoid confounding the safety assessments of peginterferon beta-1a	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.
History of hepatitis C infection or current hepatitis B infection	Interferons may increase the risk of hepatic injury. Participants with history of hepatitis were excluded to avoid confounding the safety assessments of peginterferon beta-1a.	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Abnormal liver tests (ALT or AST >2 × ULN or bilirubin >1.5 × ULN)	Interferon-beta has been associated with elevation in hepatic enzymes. Participants with history of hepatitis were excluded to avoid confounding the safety assessments of peginterferon beta-1a.	No	Elevations in hepatic enzymes and hepatic injury have been observed with the use of peginterferon beta-1a. Patients should be monitored for signs of hepatic injury. The use of Plegridy in this patient population is not considered to be relevant for inclusion as missing information.
Abnormal peripheral blood cell count (WBC <3700, absolute neutrophil count <1500, platelet count <150,000, or haemoglobin <10 (female) or <11 (male)	Interferon-beta has been associated with decrease in peripheral blood cell counts. Participants with history of abnormal peripheral blood cell counts were excluded to avoid confounding the safety assessments of peginterferon beta-1a.	No	Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with peginterferon beta-1a. Patients should be monitored for symptoms or signs of decreased peripheral blood counts. The use of Plegridy in this patient population is not considered to be relevant for inclusion as missing information.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Serum creatinine >ULN	To avoid confounding the safety assessments of peginterferon beta-1a	No	Since the major route of elimination for peginterferon is renal excretion, the effect of renal impairment and the subsequent potential for accumulation of the drug was considered in the clinical development programme Study 105RI101 assessed the pharmacokinetics and safety profile of single-dose peginterferon beta-1a in participants with pre-existing renal impairment and in healthy participants (29 participants with mild, moderate, or severe renal impairment, or with end stage renal disease, and 6 participants with no medical history of renal impairment). No clinically meaningful differences were observed between the type and incidence of AEs reported by participants with renal impairment compared with participants with normal renal function. The incidence, severity, and type of AEs were similar across all study groups. No dosage adjustments are necessary in patients with renal impairment based on study data in mild, moderate, and severe renal impairment and end-stage renal disease. However, due to an increase in AUC and C_{max} (maximum concentration) in patients with severe renal impairment, caution should be used when administering peginterferon beta 1a to this patient population.
Prothrombin time or activated partial thromboplastin time >1.2 × ULN	Interferon beta has been associated with abnormal liver function tests. Participants were excluded to avoid confounding the safety assessments of peginterferon beta-1a	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of hypersensitivity or intolerance to paracetamol, ibuprofen, naproxen, or aspirin	These were the agents chosen for use in mitigating flu-like symptoms in the clinical trial.	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.
Treatment with other agents to treat MS symptoms or underlying disease	To avoid confounding the assessment of safety and efficacy of peginterferon beta-1a.	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.
Treatment with another investigational drug within 6 months	To avoid confounding the assessment of safety and efficacy of peginterferon beta-1a.	No	The exclusion was not due to a specific safety concern with the use of peginterferon beta-1a.
Female patients who are currently breastfeeding	It is not known whether peginterferon beta-1a is secreted in human milk.	No	It is not known whether peginterferon beta-1a is secreted in human milk. Limited information available on the transfer of interferon beta-1a into breast milk suggests that levels of interferon beta excreted in human milk are negligible. No harmful effects in breastfed infants of women treated with interferon beta-1a have been reported. A decision should be made either to discontinue breastfeeding or peginterferon beta-1a therapy, taking into account the benefit of breast- feeding for the child and the benefit of therapy for the woman. The use of Plegridy in this patient population is not considered relevant for inclusion as missing information.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of drug or alcohol abuse within 2 years	To ensure participant compliance with the protocol requirements. Also, concomitant use of potential hepatotoxic agents with peginterferon beta-1a due to potential increased risk of liver injury.	No	Caution should be used and close monitoring considered when administering of peginterferon beta-1a to patients with severe hepatic impairment. Patients should be monitored for signs of hepatic injury and caution exercised when interferons are used concomitantly with other drugs associated with hepatic injury. The use of Plegridy in this patient population is not considered to be relevant for inclusion as missing information.
Initiation of treatment in pregnancy	Non-clinical data indicated that there may be an increased risk of spontaneous abortion	Yes – in relation to drug exposure during the second and third trimester of pregnancy	Since marketing authorisation approval, data have been collected on more than 1000 pregnancy outcomes from pregnancy registries and post-marketing experience. These data indicate no evidence of an increased risk of serious adverse pregnancy outcomes, including spontaneous abortions and major congenital anomalies, after exposure to interferon beta before and/or during pregnancy as compared to the women with MS who were unexposed to any MS disease modifying drug. Nevertheless, in recognition of the paucity of data pertaining to interferon-beta exposure during the second and third trimesters of pregnancy, this is to be retained as missing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 7.

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	Clinical trial 800MS301 was a study in paediatric participants aged 10 through 17 years to evaluate the efficacy and safety of Tecfidera and Plegridy. The study was terminated early due to low recruitment. There were 6 participants exposed to Plegridy in this study. Study 105MS306 (paediatric participants aged 10 to less than 18 years for treatment of relapsing remitting MS) is ongoing.
Elderly participants	• 66-75 years: 12 participants • ≥75 years: 0 patients These data are derived from 2153 participants from completed studies.
Pregnant women	Pregnant women were excluded from the clinical trials; however, from the DIBD through 18 July 2025, a total of 26 pregnancies have been reported from interventional clinical studies. Of these 26 pregnancies, 25 had reported outcomes including 11 live births without congenital anomaly, 8 elective terminations with no known foetal defects, 5 spontaneous abortions, and 1 ectopic pregnancy.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: • Hepatic impairment	Not included in the clinical development programme.
Patients with relevant comorbidities: • Renal impairment	Study 105RI101 assessed the pharmacokinetics and safety profile of single-dose peginterferon beta-1a in participants with pre-existing renal impairment and in healthy participants: 29 participants with mild, moderate, or severe renal impairment, or with end stage renal disease were enrolled in this study.
Patients with relevant comorbidities: • Cardiovascular impairment	Not included in the clinical development programme.

Type of special population	Exposure
Patients with relevant comorbidities: • Immunocompromised patients	Not included in the clinical development programme.
Patients with relevant comorbidities: • Decreased peripheral blood cell counts	Patients with reductions in white blood cells, neutrophils, platelets, or haemoglobin at screening were excluded from clinical trials with peginterferon beta-1a. Decreased peripheral blood cell counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving beta interferons. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with peginterferon beta-1a. Patients should be monitored for symptoms or signs of decreased peripheral blood cell counts.
Patients with relevant different ethnic origin	Cumulative exposure to Plegridy in clinical trials by racial group through 18 July 2025 are presented below: • Asian = 195 participants • Black = 135 participants • Caucasian = 1649 participants • Other = 98 participants • Not reported (due to local ethics committee requirements) = 76 participants These data are derived from 2153 participants in completed studies. No racial or ethnic differences have been identified.
Subpopulations carrying relevant genetic polymorphisms	There are no polymorphisms relevant to the pharmacology of interferon beta-1a.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Exposure to peginterferon beta-1a from marketing experience is calculated using monthly sales data from the International Birth Date (IBD) through 30 June 2025.

For each month, an algorithm is used to calculate on-going and new patients based on the estimated discontinuation percentage applied to the monthly sales patient numbers. These data are then summed across the months for the reporting of new patients for cumulative and/or interval reports. Infusions represents the sum of the amount of therapy equivalent to a single patient's infusion of peginterferon beta-1a regardless of whether new or on-going, in a given time period. Person-years are estimated by dividing the total number of sales patients for a given month by 12, and then summing the person-years for the target time period.

SV.1.2 Exposure

Cumulative post-marketing exposure to Plegridy is presented in Table 8.

Table 8: Exposure table by region

	Cumulative: IBD to 30 June 2025		
	Number of Patients	**Units**	**Person-Years**
EEA	52,382	1,702,140	141,845
ROW (Excluding EEA)	51,086	1,374,519	114.554
Global	**103,468**	**3,076,659**	**256,389**

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Beta-interferons are not associated with abuse potential. AEs reported in peginterferon beta-1a-treated patients were evaluated, and the potential for misuse of peginterferon beta-1a is considered to be very low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.2.1 Newly identified safety concerns

No new safety concerns have been identified since the previous version of this EU RMP (Version 6.0, dated 17 Dec 2020) was approved.

SVII.2.2 Reclassification of existing safety concerns

Not applicable – no safety concerns have been reclassified or removed in the current EU RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

None

SVII.3.2 Presentation of the missing information

Use during second and third trimester of pregnancy

Evidence source

Fertility and developmental studies in rhesus monkeys have been carried out with non-pegylated interferon beta-1a, which reported that at very high doses, anovulatory and abortifacient effects were observed in animals. However, these limited non-clinical data are considered outweighed by human clinical studies data (which provided no reliable evidence to suggest an increased risk of spontaneous abortion following interferon-beta use), and by a large amount of more recently obtained data from the two pregnancy Registry studies (the European Interferon-beta Pregnancy Registry, and the EPID MS Nordic Registers Pregnancy Study [EUPAS13054]). Analysis of the pregnancy outcome data on 948 pregnancy outcomes from these Registry studies indicated that the prevalence of both major congenital anomalies in live births and spontaneous abortions were within the background rate of both the untreated MS population and the general population

Therefore, it is considered that that the benefits of continuing or initiating MS treatment with interferon-beta before and/or during pregnancy outweigh the potential risks from the therapy or from treatment discontinuation, and no new safety concerns were identified.

Nevertheless, it is acknowledged that the number of patients with documented exposure to interferon-beta during second and third trimesters of pregnancy within these Registries and from post-marketed use overall, is low.

Population in need of further characterisation

Women exposed to interferon-beta during their second and third trimesters of pregnancy.

PART II: MODULE SVIII - SUMMARY OF SAFETY CONCERNS

The Plegridy safety specification includes the following important identified risks, important potential risks and areas of missing information (Table 9).

Table 9: Summary of safety concerns

Important identified risks	• None
Important potential risks	• None
Missing information	• Use during second and third trimester of pregnancy

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III: 1 Routine pharmacovigilance activities

Biogen employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

Routine pharmacovigilance of adverse reaction reporting and signal detection is considered sufficient to monitor the risks presented.

III. 2 Additional pharmacovigilance activities

One study in the indicated patient population is currently ongoing in order to provide further characterisation data in regard to the area of missing information of *"Use during second and third trimester of pregnancy*." This study is summarised below:

105MS404 INFORM (Interferon-Beta Exposure in the 2nd and 3rd Trimester of Pregnancy – a Register-Based Drug Utilisation Study in Finland and Sweden: A drug utilisation study in pregnancy (exposure in second and third trimester). This study is a population-based cohort study using register data from 2 Nordic countries (Finland and Sweden), enrolling pregnant women with MS exposed to interferon-beta during their second and third trimesters of pregnancy.

Rationale and study objectives: Analysis of 948 pregnancy outcomes from the EPID MS Pregnancy Study (EUPAS13054) and the European Interferon-beta Pregnancy Registry indicated that the prevalence of major congenital anomalies in live births and spontaneous abortions were within the background rate of both the untreated MS population and the general population. However, most of the available data corresponded to exposure during first trimester of pregnancy, the period of most vulnerability due to organogenesis. To further address the remaining uncertainty pertaining to exposure during second and third trimesters of pregnancy, a first stage study is evaluating interferon-beta use amongst pregnant women in Sweden and Finland using a staggered approach which will comprise:

- Evaluation of interferon-beta utilization among pregnant women with MS in Sweden and Finland at 3 years and, if needed, 5 years following label implementation using aggregate level data; and
- Evaluation of trends in drug utilisation patterns in the target population before and after label implementation.

Aggregate data analysis at 3 and 5 years (if needed) will inform an overall assessment of whether it is appropriate and feasible to proceed with a second stage - a full study on the effect on pregnancy outcomes of interferon exposure during second and third trimester of pregnancy using individual level data, based on the observed pattern of interferon-beta use among pregnant women.

Milestones:

- Protocol Version 3.0 adopted 19 Jun 2025 by the Committee for Medicinal Products for Human Use
- Drug utilisation study at 3 years and 5 years (if needed) following implementation of the updated SmPC

III. 3 Summary table of additional pharmacovigilance activities

A summary of the studies included in the pharmacovigilance plan are summarised in Table 10.

Table 10: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
<u>Category 1</u> – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
• None				
<u>Category 2</u> – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
• None				
<u>Category 3</u> – Required additional pharmacovigilance activities				
INFORM, 105MS404 Interferon-Beta Exposure in the 2nd and 3rd Trimester of Pregnancy- a Register-Based Drug Utilisation Study in Finland and Sweden • **<u>Status:</u>** Ongoing	***<u>Primary objective 1</u>*** To determine the number of pregnancies in women with MS in the following exposure groups not allowing exposure to other MS disease modifying drugs; • Pregnancies exposed to IFN beta only (late pregnancy) • Pregnancies unexposed to IFN beta nor MS disease modifying drugs See protocol for further details ***<u>Primary objective 2</u>*** To determine which level of precision for the risk of pre-defined adverse pregnancy outcomes related to IFN beta exposure in late pregnancy can be obtained with the available exposed and unexposed pregnancies, as in Primary objective 1.	• Use during second and third trimester of pregnancy	Drug utilisation study report 3 years after label implementation	31 Oct 2025
			If needed, Drug utilization study report 5 years after label implementation	31 Oct 2026

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	Primary objective 3 To describe the patterns of IFN beta use during pregnancy in Finland and Sweden 5 years before and 3 years after the label implementation, by describing the annual number of pregnancies of women with MS in the exposure groups defined in Primary objective 1 and in the additional exposure groups not allowing exposure in MS disease modifying drugs. See protocol for further details. ***Secondary objective 1:*** To determine the number of pregnancies of women with MS in Finland and Sweden in exposure groups allowing exposure to other MS disease modifying drugs. See protocol for further details. ***Secondary objective 2:*** To evaluate the pattern in the use of IFN beta among all women with MS of child-bearing age in Finland and Sweden, regardless of being pregnant, by describing the annual number of women with MS in childbearing age, and with dispensed IFN beta in 2015-2022.			

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable - there are no imposed post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V: 1 Routine risk minimisation measures

Routine risk minimisation measures are in place in order to ensure the maintenance of a favourable benefit/risk balance to patients administered Plegridy.

In the post-marketing setting, routine risk minimisation measures are the SmPC and PL, which are the primary tools to communicate information about the benefits and risks associated with the use of Plegridy. These documents provide information to the prescriber and to the patient about the identified safety concerns and relevant potential safety concerns, and how these concerns should be managed in certain circumstances.

A description of the routine risk minimisation measures per safety concern are discussed in Table 11.

Table 11: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
None	None
Important Potential Risks	
None	None
Missing Information	
Use during second and third trimester of pregnancy	***Routine risk communication:*** • Section 4.6 of the SmPC describes the paucity of data in relation to drug exposure during the second and third trimester of pregnancy ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None ***Other routine risk minimisation measures beyond the Product Information:*** Legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of MS.

V. 2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 12: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
None		
Missing information		
Use during second and third trimester of pregnancy	***Routine risk minimisation measures:*** *Information in Section 4.6 of the SmPC describing paucity of data in relation to drug exposure during the second* *Legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of MS.* ***Additional risk minimisation measures:*** *No risk minimisation measures*	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** *None* ***Additional pharmacovigilance activities:*** *105MS404, INFORM, Drug utilisation study in pregnancy (exposure in second and third trimester) 31 Oct 2026*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR PLEGRIDY (PEGINTERFERON BETA-1A)

Summary of Risk Management Plan for Plegridy (PEGINTERFERON BETA-1A)

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

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

This summary of the RMP for Plegridy should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of 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 Plegridy's RMP.

I. The medicine and what it is used for

Plegridy is authorised for use in adult patients for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS). It contains peginterferon beta-1a as the active substance, and it is given by either subcutaneous or intramuscular injection every 2 weeks.

Further information about the evaluation of the benefits of Plegridy can be found in the EPAR for Plegridy, including in its plain-language summary, available on the EMA website, under the medicine's webpage Plegridy | European Medicines Agency (europa.eu).

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

Important risks of Plegridy, together with measures to minimise such risks and the proposed studies for learning more about Plegridy'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 Plegridy is not yet available, it is listed under “missing information” below.

II.A List of important risks and missing information

Important risks of Plegridy 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 Plegridy. 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	• None
Important potential risks	• None
Missing information	• Use during second and third trimester of pregnancy

II.B Summary of important risks

There are no important identified risks or important potential risks with Plegridy treatment. This section presents a summary of missing information.

Missing Information	
Use during second and third trimester of pregnancy	
Risk minimisation measures	***Routine risk minimisation measures:*** • Information in Section 4.6 of the SmPC describing the paucity of data in relation to drug exposure during the second and third trimester of pregnancy. • Legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of MS. ***Additional risk minimisation measures:*** • No risk minimisation measures
Additional pharmacovigilance activities	***Additional pharmacovigilance activities***: • 105MS404 (INFORM) Drug utilisation study in late pregnancy (exposure in second and third trimester) See Section II.C.2. of this summary for an overview of the post-authorisation development plan.

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 Plegridy.

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

Other studies in the post authorisation development plan are as follows:

INFORM:

Purpose of the study: Analysis of 948 pregnancy outcomes from the EPID MS Pregnancy Study (EUPAS13054) and the European Interferon-beta Pregnancy Registry indicated that the prevalence of major congenital anomalies in live births and spontaneous abortions were within the background rate of both the untreated MS population and the general population. However, most of the available data corresponded to exposure during first trimester of pregnancy, the period of most vulnerability due to organogenesis.

To further address the remaining uncertainty pertaining to exposure during second and third trimesters of pregnancy, a first-stage study is currently evaluating interferon-beta use amongst pregnant women in Sweden and Finland using a staggered approach as follows:

- Evaluation of interferon-beta utilization among pregnant women with MS in Sweden and Finland at 3 years and, if needed, 5 years following label implementation using aggregate level data; and
- Evaluation of trends in drug utilisation patterns in the target population before and after label implementation.

Aggregate data analysis at 3 and 5 years (if needed) will inform an overall assessment of whether it is appropriate and feasible to proceed with a second stage – a full study on the effect of pregnancy outcomes of interferon exposure during second and third trimester of pregnancy using individual level data, based on the observed pattern of interferon-beta use among pregnant women.

Milestones:

- Protocol Version 3.0 adopted 19 Jun 2025 by the Committee for Medicinal Products for Human Use
- Interim report due on 31 Oct 2025
- Final report of study on 31 Oct 2026

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.