

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 63 micrograms solution for injection in pre-filled syringe.
Plegridy 94 micrograms solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 63 microgram pre-filled syringe contains 63 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Each 94 microgram pre-filled syringe contains 94 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

The dose indicates the quantity of the interferon beta-1a moiety of peginterferon beta-1a without consideration of the PEG moiety attached.

*The active substance, peginterferon beta-1a, is a covalent conjugate of interferon beta-1a, produced in Chinese Hamster Ovary cells, with 20,000 Dalton (20 kDa) methoxy poly(ethyleneglycol) using an O-2-methylpropionaldehyde linker.

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information see section 5.1.

Excipients with known effect

Each syringe contains 0.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless solution with pH 4.5-5.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

Efficacy of Plegridy has been demonstrated over placebo. Direct comparative data for Plegridy versus non-pegylated interferon beta or data on efficacy of Plegridy after switching from a non-pegylated interferon beta

are not available. This should be considered when switching patients between pegylated and non-pegylated interferons. Please refer also to section 5.1.

Posology

The recommended dosage of Plegridy is 125 micrograms injected subcutaneously every 2 weeks (14 days).

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (on day 0), increasing to 94 micrograms at dose 2 (on day 14), reaching the full dose of 125 micrograms by dose 3 (on day 28) and continuing with the full dose (125 micrograms) every 2 weeks (14 days) thereafter (see Table 1). An Initiation Pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Table 1: Titration schedule at initiation

Dose	Time*	Amount (micrograms)	Syringe label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

*Dosed every 2 weeks (14 days)

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of anti-inflammatory, analgesic and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment (see section 4.8).

If a dose is missed, it should be administered as soon as possible.

- If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.
- If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Plegridy within 7 days of each other.

Special populations

Elderly population

The safety and efficacy of Plegridy in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials.

Renal impairment

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 (see sections 4.4 and 5.2).

Hepatic impairment

Plegridy has not been studied in patients with hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Plegridy in children and adolescents aged 0 to 18 years have not been established in multiple sclerosis. No data are available.

Method of administration

Plegridy is for subcutaneous use.

It is recommended that a healthcare professional trains patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections include abdomen, arm, and thigh.

Each Plegridy pre-filled syringe is provided with the needle pre-attached. Pre-filled syringes are for single use only and should be discarded after use.

Precautions to be taken before handling or administering the medicinal product

Once removed from the refrigerator, Plegridy should be allowed to warm to room temperature (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm Plegridy.

Plegridy pre-filled syringe must not be used if the liquid is coloured, cloudy, or contains floating particles. The liquid in the syringe must be clear and colourless.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or peginterferon or to any of the excipients listed in section 6.1.
- Initiation of treatment in pregnancy (see section 4.6).
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Hepatic injury

Elevated serum hepatic transaminase levels, hepatitis, autoimmune hepatitis and rare cases of severe hepatic failure have been reported with interferon beta medicinal products. Elevations in hepatic enzymes have been observed with the use of Plegridy. Patients should be monitored for signs of hepatic injury (see section 4.8).

Depression

Plegridy should be administered with caution to patients with previous depressive disorders (see section 4.3). Depression occurs with increased frequency in the multiple sclerosis 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.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with Plegridy should be considered (see section 4.8).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a rare complication of treatment with interferon beta, including Plegridy. Peginterferon beta-1a should be discontinued if serious hypersensitivity reactions occur (see section 4.8).

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. To minimise the risk of injection site reactions patients should be instructed in the use of an aseptic injection technique. The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the

skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. One patient treated with Plegridy in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see section 4.8).

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with Plegridy. Patients should be monitored for symptoms or signs of decreased peripheral blood counts (see section 4.8).

Renal and urinary disorders

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Plegridy should be considered.

Severe renal impairment

Caution should be used when administering Plegridy to patients with severe renal impairment.

Thrombotic microangiopathy (TMA)

Cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Plegridy is recommended.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. aspartate aminotransferase (AST), alanine aminotransaminase (ALT)), are recommended prior to initiation and at regular intervals following introduction of Plegridy therapy and then periodically thereafter in the absence of clinical symptoms.

Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

Seizure

Plegridy should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see section 4.8).

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving interferon beta. The incidence of cardiovascular events was similar between Plegridy (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received Plegridy in the ADVANCE study. Nevertheless, 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.

Immunogenicity

Patients may develop antibodies to Plegridy. Data from patients treated up to 2 years with Plegridy suggests that less than 1% (5/715) developed persistent-neutralising antibodies to the interferon beta-1a portion of peginterferon beta-1a. Neutralising antibodies have the potential to reduce clinical efficacy. However, the development of antibodies against the interferon moiety of peginterferon beta-1a had no discernible impact on safety or clinical efficacy, although the analysis was limited by the low immunogenicity incidence.

3% 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, MRI lesions, and disability progression).

Hepatic impairment

Caution should be used and close monitoring considered when administering Plegridy 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 medicinal products associated with hepatic injury (see sections 4.8 and 5.2).

Sodium content

Each syringe contains less than 1 mmol (23 mg) sodium and is therefore considered essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The clinical studies indicate that multiple sclerosis patients can receive Plegridy and corticosteroids during relapses. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential have to take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Plegridy she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before treatment started, the risk of a severe relapse following discontinuation of Plegridy in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy

There is limited information on the use of Plegridy in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether peginterferon beta-1a is secreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants, a decision should be made either to discontinue breast-feeding or Plegridy therapy.

Fertility

There are no data on the effects of peginterferon beta-1a on human fertility. In animals, anovulatory effects were observed at very high doses (see section 5.3). No information is available on the effects of peginterferon beta-1a on male fertility in animals.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions (ADR) (at a higher incidence than placebo) for Plegridy 125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.

The most commonly reported adverse reaction leading to discontinuation in patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Tabulated list of adverse reactions

In clinical studies, a total of 1468 patients received Plegridy for up to 278 weeks with an overall exposure equivalent of 4217 person-years. 1285 patients received at least 1 year, 1124 patients have received at least 2 years, 947 patients received at least 3 years, and 658 patients received at least 4 years of treatment with Plegridy. The experience in the randomised, uncontrolled phase (year 2) of the ADVANCE study and in the extension study ATTAIN (treatment received for up to 4 years) was consistent with the experience in the 1 year placebo-controlled phase of the ADVANCE study.

The table summarizes ADRs (incidence above placebo and with a reasonable possibility of causality) from 512 patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 48 weeks.

The ADRs are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below are expressed according to the following categories:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*	Rare
Immune system disorders	Hypersensitivity reaction	Uncommon
Nervous system disorders	Headache	Very common
	Seizure	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary arterial hypertension [†]	Not known
Gastrointestinal disorders	Nausea	Common
	Vomiting	
Skin and subcutaneous tissue disorders	Pruritus	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Very common
	Arthralgia	
Renal and urinary disorders	Nephrotic syndrome, glomerulosclerosis	Rare
General disorders and administration site conditions	Injection site erythema	Very common
	Influenza like illness	
	Pyrexia	
	Chills	
	Injection site pain	
	Asthenia	
	Injection site pruritus	
	Hyperthermia	Common
	Pain	
	Injection site oedema	
	Injection site warmth	
	Injection site haematoma	
	Injection site rash	
	Injection site swelling	
	Injection site discolouration	
	Injection site inflammation	
	Injection site necrosis	
Investigations	Body temperature increased	Common
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Gamma-glutamyl-transferase increased	
	Haemoglobin decreased	

MedDRA System Organ Class	Adverse reaction	Frequency category
	Platelet count decreased	Uncommon
	Decreases in white blood cell counts	Common
Psychiatric disorders	Depression	Common

*Class label for interferon beta products (see section 4.4).

† Class label for interferon products, see below *Pulmonary arterial hypertension*

Description of selected adverse reactions

Flu-like symptoms

Influenza-like illness was experienced by 47% of patients receiving Plegridy 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest at the initiation of treatment and generally decreased over the first 6 months. Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received Plegridy during the placebo controlled phase of the ADVANCE study discontinued treatment due to flu-like symptoms. An open-label study in patients switching from interferon beta therapy to Plegridy evaluated the onset and duration of prophylactically treated flu-like symptoms. In patients experiencing flu-like symptoms, the median time to onset was 10 hours (interquartile range, 7 to 16 hours) after injection, and the median duration was 17 hours (interquartile range, 12 to 22 hours).

Injection site reactions

Injection site reactions (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received Plegridy 125 micrograms every 2 weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported injection site reaction. Of the patients who experienced injection site reactions 95% reported them as mild or moderate in severity. One patient out of 1468 patients who received Plegridy in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic transaminase abnormalities

The incidence of hepatic transaminase increases was greater in patients receiving Plegridy compared to placebo. The majority of enzyme elevations were <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase (>5 times ULN), were reported in 1% and <1% of placebo-treated patients and 2% and <1% of patients treated with Plegridy respectively. Elevations of serum hepatic transaminases combined with elevated bilirubin were observed in two patients who had pre-existing liver test abnormalities prior to receiving Plegridy in the clinical trials. Both cases resolved following discontinuation of Plegridy.

Haematological disorders

Decreases in white blood cell counts of $<3.0 \times 10^9/L$ were observed in 7% of patients receiving Plegridy and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with Plegridy. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts ($<0.5 \times 10^9/L$) (<1%), neutrophil counts ($\leq 1.0 \times 10^9/L$) (<1%) and platelet counts ($\leq 100 \times 10^9/L$) ($\leq 1\%$) was similar in Plegridy-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with Plegridy: one patient (<1%) experienced severe thrombocytopenia (platelet count $<10 \times 10^9/L$), another patient (<1%) experienced severe neutropenia (neutrophil count $<0.5 \times 10^9/L$). In both patients, cell counts recovered after discontinuation of Plegridy. Slight decreases in mean red blood cell (RBC) counts were observed in Plegridy treated patients. The incidence of potentially clinically significant decreases in RBC counts ($<3.3 \times 10^{12}/L$) was similar in Plegridy-treated patients compared to placebo-treated patients.

Hypersensitivity reactions

Hypersensitivity events were reported in 16% of patients treated with Plegridy 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of Plegridy treated patients experienced a serious hypersensitivity event (e.g. angioedema, urticaria) and they recovered promptly after treatment with anti-histamines and/or corticosteroids.

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both Plegridy 125 micrograms every 2 weeks and placebo groups. The incidence of serious events related to depression and suicidal ideation were similar and low (<1%) in both Plegridy 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

The incidence of seizure events was low and comparable in patients receiving Plegridy (125 micrograms every 2 weeks) and placebo (<1% in each group).

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of over-dose, patients may be hospitalized for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; immunostimulants; interferons
ATC code: L03AB13

Plegridy is an interferon beta-1a conjugated with a single, linear molecule of 20,000 Da methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde (20 kDa mPEG-O-2-methylpropionaldehyde) at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 44 kDa of which the protein moiety constitutes approximately 23 kDa.

Mechanism of action

A definitive mechanism of action of peginterferon beta-1a in multiple sclerosis (MS) is not known. Plegridy binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. Biological effects that may be mediated

by Plegridy include up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN- γ , TNF- α) and inhibiting the migration of activated T cells across the blood brain barrier; however additional mechanisms may be involved. Whether the mechanism of action of Plegridy in MS is mediated by the same pathway(s) as the biological effects described above is not known because the pathophysiology of MS is only partially understood.

Pharmacodynamic effects

Plegridy is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule at the alpha-amino group of the N-terminal amino acid residue.

Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature. The pharmacological properties of Plegridy are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule.

Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2',5'-oligoadenylate synthetase (2',5'-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,-trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for Plegridy compared to non-pegylated interferon beta-1a (IM) when both were given at the same dose by activity (6 MIU). The duration of this response was sustained and prolonged for Plegridy, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with Plegridy, with a sustained and prolonged elevation over 10 days compared to 5 days observed for non-pegylated interferon beta-1a. Neopterin concentrations return to baseline after the two week dosing interval.

Clinical efficacy and safety

The efficacy and safety of Plegridy was assessed from the placebo-controlled first year of a 2 year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). 1512 patients were randomised to and dosed with 125 micrograms Plegridy injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500).

The primary endpoint was the annualised relapse rate (ARR) over 1 year. The study design and patient demographics are presented in Table 2.

No data are available from clinical efficacy/safety studies directly comparing pegylated with non-pegylated interferon beta-1a, or from patients switching between non-pegylated and pegylated interferon.

Table 2: Study design

Study design	
Disease history	Patients with RRMS, with at least 2 relapses within the prior 3 years, and 1 relapse in the prior year, with an EDSS score of ≤ 5.0
Follow-up	1 year
Study population	83% treatment-naïve patients 47% ≥ 2 relapses in prior year 38% at least 1 Gd+ lesion at baseline 92% ≥ 9 T2 lesions baseline 16% EDSS ≥ 4 17% previously treated
Baseline characteristics	
Mean age (years)	37
Mean/Median disease duration (years)	3.6/2.0
Mean number of relapses within the past 3 years	2.5
Mean EDSS score at baseline	2.5

EDSS: Expanded Disability Status Scale

Gd+: Gadolinium-enhancing

Plegridy every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo ($p=0.0007$) at one year (Table 3) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. Plegridy also significantly reduced the risk of relapse by 39% ($p=0.0003$), the risk of sustained disability progression confirmed at 12 weeks by 38% ($p=0.0383$) and at 24 weeks (post-hoc analysis) by 54% ($p=0.0069$), the number of new or newly enlarging T2 lesions by 67% ($p<0.0001$), the number of Gd-enhancing lesions by 86% ($p<0.0001$) and the number of new T1 hypointense lesions compared to placebo by 53% ($p<0.0001$). A treatment effect was observed as early as 6 months, with Plegridy 125 micrograms every 2 weeks demonstrating a 61% reduction ($p<0.0001$) in new or newly enlarging T2 lesions as compared with placebo. Across relapse and MRI endpoints Plegridy 125 micrograms every two weeks showed a numerically greater treatment effect over the Plegridy every four weeks dosing regimen at year 1.

Results over 2 years confirmed that efficacy was maintained beyond the placebo controlled first year of the study. Patients exposed to Plegridy every 2 weeks showed statistically significant reductions compared to patients exposed to Plegridy every 4 weeks over 2 years in a post-hoc analysis for endpoints including ARR (24%, $p=0.0209$), the risk of relapse (24%, $p=0.0212$), the risk of disability progression with 24 week confirmation (36%, $p=0.0459$), and MRI endpoints (new/enlarging T2 60%, Gd+ 71%, and new T1 hypointense lesions 53%; $p<0.0001$ for all). In the ATTAIN extension study, long-term efficacy with Plegridy was maintained with continuous treatment up to 4 years as shown by clinical and MRI measures of MS disease activity. Of a total of 1468 patients, 658 patients continued at least 4 years of treatment with Plegridy.

Results for this study are shown in Table 3.

Table 3: Clinical and MRI results

	Placebo	Plegridy 125 micrograms every 2 weeks	Plegridy 125 micrograms every 4 weeks
Clinical endpoints			
N	500	512	500
Annualised relapse rate	0.397	0.256	0.288
Rate ratio		0.64	0.72
95% CI		0.50 – 0.83	0.56 – 0.93
P-value		p=0.0007	p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR		0.61	0.74
95% CI		0.47 – 0.80	0.57 – 0.95
P-value		p=0.0003	p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR		0.62	0.62
95% CI		0.40 – 0.97	0.40 – 0.97
P-value		p=0.0383	p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR		0.46	0.67
95% CI		(0.26 – 0.81)	(0.41 – 1.10)
P-value		p=0.0069	p=0.1116
MRI endpoints			
N	476	457	462
Mean [Median] no. of new or newly enlarging T2 hyperintense lesions (range)	13.3 [6.0] (0 – 148)	4.1 [1.0] (0 – 69)	9.2 [3.0] (0 – 113)
Lesion mean ratio (95% CI)		0.33 (0.27, 0.40)	0.72 (0.60, 0.87)
P-value		p≤0.0001	p=0.0008
Mean [Median] no. of Gd-enhancing lesions (range)	1.4 [^] [0.0] (0 – 39)	0.2 [0.0] (0 – 13)	0.9 [0.0] (0 – 41)
% reduction vs placebo		86	36
P-value		p<0.0001	p=0.0738
Mean [Median] no. of new T1 hypointense lesions (range)	3.8 [1.0] (0 – 56)	1.8 [0.0] (0 – 39)	3.1 [1.0] (0 – 61)
% reduction vs placebo		53	18
P-value		p<0.0001	0.0815

HR: Hazard ratio

CI: Confidence interval

* Sustained disability progression was defined as at least a 1 point increase from baseline EDSS \geq 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 / 24 weeks.

[^]n=477

Patients who failed previous MS treatment were not included in the study.

Subgroups of patients with higher disease activity were defined by relapse and MRI criteria as reported below, with the following efficacy results:

- For patients with ≥ 1 relapse in the previous year and ≥ 9 T2 lesions or ≥ 1 Gd+ lesion (n=1401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for Plegridy every 4 weeks and 0.25 for Plegridy every 2 weeks.

Results in this subgroup were consistent with those in the overall population.

- For patients with ≥ 2 relapses in the previous year and at least 1 Gd+ lesion (n=273), the annual relapse rate at 1 year was 0.47 for placebo, 0.35 for Plegridy every 4 weeks, and 0.33 for Plegridy every 2 weeks.

Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Plegridy in one or more subsets of the paediatric population in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum half-life of peginterferon beta-1a is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 to 188 micrograms as observed in a single dose and a multiple dose study in healthy subjects. Pharmacokinetics observed in multiple sclerosis patients were consistent with those seen in healthy subjects.

Absorption

Following subcutaneous administration of peginterferon beta-1a in multiple sclerosis patients, the peak concentration was reached between 1 to 1.5 days post-dose. The observed C_{max} (mean \pm SE) was 280 ± 79 pg/mL following repeat dosing of 125 micrograms every two weeks. Subcutaneous peginterferon beta-1a resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2-, 3.5- and 5-fold higher C_{max} , following single doses of 63 (6 MIU), 125 (12 MIU), and 188 (18 MIU) micrograms respectively, compared to intramuscular administration of 30 (6 MIU) micrograms non-pegylated beta-1a.

Distribution

Following repeat dosing of 125 micrograms doses every two weeks by subcutaneous administration, the volume of distribution uncorrected for bioavailability (mean \pm SE) was 481 ± 105 L.

Biotransformation and elimination

Urinary (renal) clearance is postulated to be a major excretory pathway for Plegridy. The process of covalently conjugating a PEG moiety to a protein can alter the in vivo properties of the unmodified protein, including decreased renal clearance and decreased proteolysis thus extending the circulating half-life. Accordingly, the half-life ($t_{1/2}$) of peginterferon beta-1a is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean \pm SE) of peginterferon beta-1a was 78 ± 15 hours at steady state. The mean steady state clearance of peginterferon beta-1a was 4.1 ± 0.4 L/hr.

Special populations

Renal impairment

A single-dose study in healthy subjects and subjects with various degrees of renal impairment (mild, moderate, and severe renal impairment as well as subjects with end state renal disease) showed a fractional increase in AUC (13-62%) and C_{max} (42-71%) in subjects with mild (estimated glomerular filtration rate 50 to ≤ 80 mL/min/1.73m²), moderate (estimated glomerular filtration rate 30 to < 50 mL/min/1.73m²), and severe (estimated glomerular filtration rate < 30 mL/min/1.73m²) renal impairment, compared to subjects with normal renal function (estimated glomerular filtration rate > 80 mL/min/1.73m²). Subjects with end stage renal disease requiring 2-3 times haemodialysis weekly showed similar AUC and C_{max} as compared to subjects with normal renal function. Each haemodialysis reduced peginterferon beta-1a concentration by approximately 24%, suggesting that haemodialysis partially removes peginterferon beta-1a from systemic circulation.

Hepatic function

The pharmacokinetics of peginterferon beta-1a has not been evaluated in patients with hepatic insufficiency.

Elderly patients

Clinical experience in patients aged above 65 years is limited. However, results from a population pharmacokinetic analysis (in patients up to 65 years) suggest that age does not impact peginterferon beta-1a clearance.

Gender

No gender effect on the pharmacokinetics of peginterferon beta-1a was found in a population pharmacokinetic analysis.

Race

Race had no effect on the pharmacokinetics of peginterferon beta-1a in a population pharmacokinetic analysis.

5.3 Preclinical safety data

Toxicity

Following repeated subcutaneous administration of peginterferon beta-1a in rhesus monkeys at doses up to 400-fold (based on exposure, AUC) the recommended therapeutic dose; no effects other than the known mild pharmacological responses by rhesus monkeys to interferon beta-1a were observed after the first and second weekly dose. Repeated dose toxicology studies were limited to 5 weeks as exposure was greatly diminished from 3 weeks onwards, due to the formation of anti-drug antibodies by rhesus monkeys to human interferon beta-1a. Therefore, the long-term safety of chronic administration of Plegridy to patients cannot be assessed on the basis of these studies.

Mutagenesis

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.

Carcinogenesis

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.

Reproductive Toxicity

Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Fertility and developmental studies in rhesus monkeys have been carried out with non-pegylated interferon beta-1a. At very high doses, anovulatory and abortifacient effects were observed in animals. No information is available on the potential effects of peginterferon beta-1a on male fertility. Upon repeated dosing with peginterferon beta-1a of sexually mature female monkeys, effects on menstrual cycle length and progesterone levels were observed. Reversibility of the effects on menstrual cycle length was demonstrated. The validity of extrapolating these non-clinical data to humans is unknown.

Data from studies with other interferon beta compounds did not show teratogenic potential. The available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
L-Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Plegridy can be stored at room temperature (up to 25°C) for up to 30 days as long as it is stored away from light. If Plegridy is at room temperature for a total of 30 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 30 days or more, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

See section 6.3 for additional information on storage at room temperature (up to 25°C).

6.5 Nature and contents of container

1 mL pre-filled syringe made of glass (Type I) with a bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield, containing 0.5 mL of solution.

The Plegridy Initiation Pack contains 1x 63 micrograms pre-filled syringe (orange labelled syringe, 1st dose) and 1x 94 micrograms pre-filled syringe (blue labelled syringe, 2nd dose) in sealed plastic trays.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOGEN IDEC LIMITED

Innovation House

70 Norden Road

Maidenhead

Berkshire

SL6 4AY

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 125 microgram pre-filled syringe contains 125 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

The dose indicates the quantity of the interferon beta-1a moiety of peginterferon beta-1a without consideration of the PEG moiety attached.

*The active substance, peginterferon beta-1a, is a covalent conjugate of interferon beta-1a, produced in Chinese Hamster Ovary cells, with 20,000 Dalton (20 kDa) methoxy poly(ethyleneglycol) using an O-2-methylpropionaldehyde linker.

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information see section 5.1.

Excipients with known effect

Each syringe contains 0.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless solution with pH 4.5-5.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

Efficacy of Plegridy has been demonstrated over placebo. Direct comparative data for Plegridy versus non-pegylated interferon beta or data on efficacy of Plegridy after switching from a non-pegylated interferon beta are not available. This should be considered when switching patients between pegylated and non-pegylated interferons. Please refer also to section 5.1.

Posology

The recommended dosage of Plegridy is 125 micrograms injected subcutaneously every 2 weeks (14 days).

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (on day 0), increasing to 94 micrograms at dose 2 (on day 14), reaching the full dose of 125 micrograms by dose 3 (on day 28) and continuing with the full dose (125 micrograms) every 2 weeks (14 days) thereafter (see Table 1). An Initiation Pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Table 1: Titration schedule at initiation

Dose	Time*	Amount (micrograms)	Syringe label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

*Dosed every 2 weeks (14 days)

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of anti-inflammatory, analgesic and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment (see section 4.8).

If a dose is missed, it should be administered as soon as possible.

- If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.
- If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Plegridy within 7 days of each other.

Special populations

Elderly population

The safety and efficacy of Plegridy in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials.

Renal impairment

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 (see sections 4.4 and 5.2).

Hepatic impairment

Plegridy has not been studied in patients with hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Plegridy in children and adolescents aged 0 to 18 years have not been established in multiple sclerosis. No data are available.

Method of administration

Plegridy is for subcutaneous use.

It is recommended that a healthcare professional trains patients in the proper technique for self-administering

subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections include abdomen, arm, and thigh.

Each Plegridy pre-filled syringe is provided with the needle pre-attached. Pre-filled syringes are for single use only and should be discarded after use.

Precautions to be taken before handling or administering the medicinal product

Once removed from the refrigerator, Plegridy should be allowed to warm to room temperature (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm Plegridy.

Plegridy pre-filled syringe must not be used if the liquid is coloured, cloudy, or contains floating particles. The liquid in the syringe must be clear and colourless.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or peginterferon or to any of the excipients listed in section 6.1.
- Initiation of treatment in pregnancy (see section 4.6).
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Hepatic injury

Elevated serum hepatic transaminase levels, hepatitis, autoimmune hepatitis and rare cases of severe hepatic failure have been reported with interferon beta medicinal products. Elevations in hepatic enzymes have been observed with the use of Plegridy. Patients should be monitored for signs of hepatic injury (see section 4.8).

Depression

Plegridy should be administered with caution to patients with previous depressive disorders (see section 4.3). Depression occurs with increased frequency in the multiple sclerosis 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.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with Plegridy should be considered (see section 4.8).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a rare complication of treatment with interferon beta, including Plegridy. Peginterferon beta-1a should be discontinued if serious hypersensitivity reactions occur (see section 4.8).

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. To minimise the risk of injection site reactions patients should be instructed in the use of an aseptic injection technique. The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. One patient treated with Plegridy in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see section 4.8).

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with Plegridy. Patients should be monitored for symptoms or signs of decreased peripheral blood counts (see section 4.8).

Renal and urinary disorders

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Plegridy should be considered.

Severe renal impairment

Caution should be used when administering Plegridy to patients with severe renal impairment.

Thrombotic microangiopathy (TMA)

Cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Plegridy is recommended.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. aspartate aminotransferase (AST), alanine aminotransaminase (ALT)), are recommended prior to initiation and at regular intervals following introduction of Plegridy therapy and then periodically thereafter in the absence of clinical symptoms.

Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

Seizure

Plegridy should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see section 4.8).

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving interferon beta. The incidence of cardiovascular events was similar between Plegridy (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received Plegridy in the ADVANCE study. Nevertheless, 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.

Immunogenicity

Patients may develop antibodies to Plegridy. Data from patients treated up to 2 years with Plegridy suggests that less than 1% (5/715) developed persistent-neutralising antibodies to the interferon beta-1a portion of peginterferon beta-1a. Neutralising antibodies have the potential to reduce clinical efficacy. However, the development of antibodies against the interferon moiety of peginterferon beta-1a had no discernible impact on safety or clinical efficacy, although the analysis was limited by the low immunogenicity incidence.

3% 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, MRI lesions, and disability progression).

Hepatic impairment

Caution should be used and close monitoring considered when administering Plegridy 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 medicinal products associated with hepatic injury (see sections 4.8 and 5.2).

Sodium content

Each syringe contains less than 1 mmol (23 mg) sodium and is therefore considered essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The clinical studies indicate that multiple sclerosis patients can receive Plegridy and corticosteroids during relapses. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential have to take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Plegridy she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate

before treatment started, the risk of a severe relapse following discontinuation of Plegridy in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy

There is limited information on the use of Plegridy in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether peginterferon beta-1a is secreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants, a decision should be made either to discontinue breast-feeding or Plegridy therapy.

Fertility

There are no data on the effects of peginterferon beta-1a on human fertility. In animals, anovulatory effects were observed at very high doses (see section 5.3). No information is available on the effects of peginterferon beta-1a on male fertility in animals.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions (ADR) (at a higher incidence than placebo) for Plegridy 125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia. The most commonly reported adverse reaction leading to discontinuation in patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Tabulated list of adverse reactions

In clinical studies, a total of 1468 patients received Plegridy for up to 278 weeks with an overall exposure equivalent of 4217 person-years. 1285 patients received at least 1 year, 1124 patients have received at least 2 years, 947 patients received at least 3 years, and 658 patients received at least 4 years of treatment with Plegridy. The experience in the randomised, uncontrolled phase (year 2) of the ADVANCE study and in the extension study ATTAIN (treatment received for up to 4 years) was consistent with the experience in the 1 year placebo-controlled phase of the ADVANCE study.

The table summarizes ADRs (incidence above placebo and with a reasonable possibility of causality) from 512 patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 48 weeks.

The ADRs are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below are expressed according to the following categories:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*	Rare
Immune system disorders	Hypersensitivity reaction	Uncommon
Nervous system disorders	Headache	Very common
	Seizure	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary arterial hypertension [†]	Not known
Gastrointestinal disorders	Nausea	Common
	Vomiting	
Skin and subcutaneous tissue disorders	Pruritus	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Very common
	Arthralgia	
Renal and urinary disorders	Nephrotic syndrome, glomerulosclerosis	Rare
General disorders and administration site conditions	Injection site erythema	Very common
	Influenza like illness	
	Pyrexia	
	Chills	
	Injection site pain	
	Asthenia	
	Injection site pruritus	
	Hyperthermia	
	Pain	
	Injection site oedema	
	Injection site warmth	
	Injection site haematoma	
	Injection site rash	
	Injection site swelling	
	Injection site discolouration	
	Injection site inflammation	Rare
	Injection site necrosis	
	Investigations	Body temperature increased
Alanine aminotransferase increased		
Aspartate aminotransferase increased		
Gamma-glutamyl-transferase increased		
Haemoglobin decreased		
Platelet count decreased		Uncommon
Decreases in white blood cell counts		Common
Psychiatric disorders	Depression	Common

*Class label for interferon beta products (see section 4.4).

[†] Class label for interferon products, see below *Pulmonary arterial hypertension*.

Description of selected adverse reactions

Flu-like symptoms

Influenza-like illness was experienced by 47% of patients receiving Plegridy 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest at the initiation of treatment and generally decreased over the first 6 months. Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received Plegridy during the placebo controlled phase of the ADVANCE study discontinued treatment due to flu-like symptoms. An open-label study in patients switching from interferon beta therapy to Plegridy evaluated the onset and duration of prophylactically treated flu-like symptoms. In patients experiencing flu-like symptoms, the median time to onset was 10 hours (interquartile range, 7 to 16 hours) after injection, and the median duration was 17 hours (interquartile range, 12 to 22 hours).

Injection site reactions

Injection site reactions (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received Plegridy 125 micrograms every 2 weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported injection site reaction. Of the patients who experienced injection site reactions 95% reported them as mild or moderate in severity. One patient out of 1468 patients who received Plegridy in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic transaminase abnormalities

The incidence of hepatic transaminase increases was greater in patients receiving Plegridy compared to placebo. The majority of enzyme elevations were <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase (>5 times ULN), were reported in 1% and <1% of placebo-treated patients and 2% and <1% of patients treated with Plegridy respectively. Elevations of serum hepatic transaminases combined with elevated bilirubin were observed in two patients who had pre-existing liver test abnormalities prior to receiving Plegridy in the clinical trials. Both cases resolved following discontinuation of Plegridy.

Haematological disorders

Decreases in white blood cell counts of $<3.0 \times 10^9/L$ were observed in 7% of patients receiving Plegridy and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with Plegridy. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts ($<0.5 \times 10^9/L$) (<1%), neutrophil counts ($\leq 1.0 \times 10^9/L$) (<1%) and platelet counts ($\leq 100 \times 10^9/L$) ($\leq 1\%$) was similar in Plegridy-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with Plegridy: one patient (<1%) experienced severe thrombocytopenia (platelet count $<10 \times 10^9/L$), another patient (<1%) experienced severe neutropenia (neutrophil count $<0.5 \times 10^9/L$). In both patients, cell counts recovered after discontinuation of Plegridy. Slight decreases in mean red blood cell (RBC) counts were observed in Plegridy treated patients. The incidence of potentially clinically significant decreases in RBC counts ($<3.3 \times 10^{12}/L$) was similar in Plegridy-treated patients compared to placebo-treated patients.

Hypersensitivity reactions

Hypersensitivity events were reported in 16% of patients treated with Plegridy 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of Plegridy treated patients experienced a serious hypersensitivity event (e.g. angioedema, urticaria) and they recovered promptly after treatment with anti-histamines and/or corticosteroids.

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both Plegridy 125 micrograms every 2 weeks and placebo groups. The incidence of serious events related to depression and suicidal ideation were similar and low (<1%) in both Plegridy 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

The incidence of seizure events was low and comparable in patients receiving Plegridy (125 micrograms every 2 weeks) and placebo (<1% in each group).

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of over-dose, patients may be hospitalized for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; immunostimulants; interferons
ATC code: L03AB13

Plegridy is an interferon beta-1a conjugated with a single, linear molecule of 20,000 Da methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde (20 kDa mPEG-O-2-methylpropionaldehyde) at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 44 kDa of which the protein moiety constitutes approximately 23 kDa.

Mechanism of action

A definitive mechanism of action of peginterferon beta-1a in multiple sclerosis (MS) is not known. Plegridy binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. Biological effects that may be mediated by Plegridy include up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN- γ , TNF- α) and inhibiting the migration of activated T cells across the blood brain barrier; however additional mechanisms may be involved. Whether the mechanism of action of Plegridy in MS is mediated by the same pathway(s) as the biological effects described above is not known because the pathophysiology of MS is only partially understood.

Pharmacodynamic effects

Plegridy is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule at the alpha-amino group of the N-terminal amino acid residue.

Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature. The pharmacological properties of Plegridy are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule.

Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2',5'-oligoadenylate synthetase (2',5'-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,-trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for Plegridy compared to non-pegylated interferon beta-1a (IM) when both were given at the same dose by activity (6 MIU). The duration of this response was sustained and prolonged for Plegridy, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with Plegridy, with a sustained and prolonged elevation over 10 days compared to 5 days observed for non-pegylated interferon beta-1a. Neopterin concentrations return to baseline after the two week dosing interval.

Clinical efficacy and safety

The efficacy and safety of Plegridy was assessed from the placebo-controlled first year of a 2 year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). 1512 patients were randomised to and dosed with 125 micrograms Plegridy injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500).

The primary endpoint was the annualised relapse rate (ARR) over 1 year. The study design and patient demographics are presented in Table 2.

No data are available from clinical efficacy/safety studies directly comparing pegylated with non-pegylated interferon beta-1a, or from patients switching between non-pegylated and pegylated interferon.

Table 2: Study design

Study design	
Disease history	Patients with RRMS, with at least 2 relapses within the prior 3 years, and 1 relapse in the prior year, with an EDSS score of ≤ 5.0
Follow-up	1 year
Study population	83% treatment-naïve patients 47% ≥ 2 relapses in prior year 38% at least 1 Gd+ lesion at baseline 92% ≥ 9 T2 lesions baseline 16% EDSS ≥ 4 17% previously treated
Baseline characteristics	
Mean age (years)	37
Mean/Median disease duration (years)	3.6/2.0
Mean number of relapses within the past 3 years	2.5
Mean EDSS score at baseline	2.5

EDSS: Expanded Disability Status Scale

Gd+: Gadolinium-enhancing

Plegridy every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo ($p=0.0007$) at one year (Table 3) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. Plegridy also significantly reduced the risk of relapse by 39% ($p=0.0003$), the risk of sustained disability progression confirmed at 12 weeks by 38% ($p=0.0383$) and at 24 weeks (post-hoc analysis) by 54% ($p=0.0069$), the number of new or newly enlarging T2 lesions by 67% ($p<0.0001$), the number of Gd-enhancing lesions by 86% ($p<0.0001$) and the number of new T1 hypointense lesions compared to placebo by 53% ($p<0.0001$). A treatment effect was observed as early as 6 months, with Plegridy 125 micrograms every 2 weeks demonstrating a 61% reduction ($p<0.0001$) in new or newly enlarging T2 lesions as compared with placebo. Across relapse and MRI endpoints Plegridy 125 micrograms every two weeks showed a numerically greater treatment effect over the Plegridy every four weeks dosing regimen at year 1.

Results over 2 years confirmed that efficacy was maintained beyond the placebo controlled first year of the study. Patients exposed to Plegridy every 2 weeks showed statistically significant reductions compared to patients exposed to Plegridy every 4 weeks over 2 years in a post-hoc analysis for endpoints including ARR (24%, $p=0.0209$), the risk of relapse (24%, $p=0.0212$), the risk of disability progression with 24 week confirmation (36%, $p=0.0459$), and MRI endpoints (new/enlarging T2 60%, Gd+ 71%, and new T1 hypointense lesions 53%; $p<0.0001$ for all). In the ATTAIN extension study, long-term efficacy with Plegridy was maintained with continuous treatment up to 4 years as shown by clinical and MRI measures of MS disease activity. Of a total of 1468 patients, 658 patients continued at least 4 years of treatment with Plegridy.

Results for this study are shown in Table 3.

Table 3: Clinical and MRI results

	Placebo	Plegridy 125 micrograms every 2 weeks	Plegridy 125 micrograms every 4 weeks
Clinical endpoints			
N	500	512	500
Annualised relapse rate	0.397	0.256	0.288
Rate ratio		0.64	0.72
95% CI		0.50 – 0.83	0.56 – 0.93
P-value		p=0.0007	p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR		0.61	0.74
95% CI		0.47 – 0.80	0.57 – 0.95
P-value		p=0.0003	p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR		0.62	0.62
95% CI		0.40 – 0.97	0.40 – 0.97
P-value		p=0.0383	p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR		0.46	0.67
95% CI		(0.26 – 0.81)	(0.41 – 1.10)
P-value		p=0.0069	p=0.1116
MRI endpoints			
N	476	457	462
Mean [Median] no. of new or newly enlarging T2 hyperintense lesions (range)	13.3 [6.0] (0 – 148)	4.1 [1.0] (0 – 69)	9.2 [3.0] (0 – 113)
Lesion mean ratio (95% CI)		0.33 (0.27, 0.40)	0.72 (0.60, 0.87)
P-value		p≤0.0001	p=0.0008
Mean [Median] no. of Gd-enhancing lesions (range)	1.4 [^] [0.0] (0 – 39)	0.2 [0.0] (0 – 13)	0.9 [0.0] (0 – 41)
% reduction vs placebo		86	36
P-value		p<0.0001	p=0.0738
Mean [Median] no. of new T1 hypointense lesions (range)	3.8 [1.0] (0 – 56)	1.8 [0.0] (0 – 39)	3.1 [1.0] (0 – 61)
% reduction vs placebo		53	18
P-value		p<0.0001	0.0815

HR: Hazard ratio

CI: Confidence interval

* Sustained disability progression was defined as at least a 1 point increase from baseline EDSS \geq 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 / 24 weeks.

[^]n=477

Patients who failed previous MS treatment were not included in the study.

Subgroups of patients with higher disease activity were defined by relapse and MRI criteria as reported below, with the following efficacy results:

- For patients with ≥ 1 relapse in the previous year and ≥ 9 T2 lesions or ≥ 1 Gd+ lesion (n=1401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for Plegridy every 4 weeks and 0.25 for Plegridy every 2 weeks.

Results in this subgroup were consistent with those in the overall population.

- For patients with ≥ 2 relapses in the previous year and at least 1 Gd+ lesion (n=273), the annual relapse rate at 1 year was 0.47 for placebo, 0.35 for Plegridy every 4 weeks, and 0.33 for Plegridy every 2 weeks.

Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Plegridy in one or more subsets of the paediatric population in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum half-life of peginterferon beta-1a is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 to 188 micrograms as observed in a single dose and a multiple dose study in healthy subjects. Pharmacokinetics observed in multiple sclerosis patients were consistent with those seen in healthy subjects.

Absorption

Following subcutaneous administration of peginterferon beta-1a in multiple sclerosis patients, the peak concentration was reached between 1 to 1.5 days post-dose. The observed C_{max} (mean \pm SE) was 280 ± 79 pg/mL following repeat dosing of 125 micrograms every two weeks. Subcutaneous peginterferon beta-1a resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2-, 3.5- and 5-fold higher C_{max} , following single doses of 63 (6 MIU), 125 (12 MIU), and 188 (18 MIU) micrograms respectively, compared to intramuscular administration of 30 (6 MIU) micrograms non-pegylated beta-1a.

Distribution

Following repeat dosing of 125 micrograms doses every two weeks by subcutaneous administration, the volume of distribution uncorrected for bioavailability (mean \pm SE) was 481 ± 105 L.

Biotransformation and elimination

Urinary (renal) clearance is postulated to be a major excretory pathway for Plegridy. The process of covalently conjugating a PEG moiety to a protein can alter the in vivo properties of the unmodified protein, including decreased renal clearance and decreased proteolysis thus extending the circulating half-life. Accordingly, the half-life ($t_{1/2}$) of peginterferon beta-1a is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean \pm SE) of peginterferon beta-1a was 78 ± 15 hours at steady state. The mean steady state clearance of peginterferon beta-1a was 4.1 ± 0.4 L/hr.

Special populations

Renal impairment

A single-dose study in healthy subjects and subjects with various degrees of renal impairment (mild, moderate, and severe renal impairment as well as subjects with end state renal disease) showed a fractional increase in AUC (13-62%) and C_{max} (42-71%) in subjects with mild (estimated glomerular filtration rate 50 to ≤ 80 mL/min/1.73m²), moderate (estimated glomerular filtration rate 30 to < 50 mL/min/1.73m²), and severe (estimated glomerular filtration rate < 30 mL/min/1.73m²) renal impairment, compared to subjects with normal renal function (estimated glomerular filtration rate > 80 mL/min/1.73m²). Subjects with end stage renal disease requiring 2-3 times haemodialysis weekly showed similar AUC and C_{max} as compared to subjects with normal renal function. Each haemodialysis reduced peginterferon beta-1a concentration by approximately 24%, suggesting that haemodialysis partially removes peginterferon beta-1a from systemic circulation.

Hepatic function

The pharmacokinetics of peginterferon beta-1a has not been evaluated in patients with hepatic insufficiency.

Elderly patients

Clinical experience in patients aged above 65 years is limited. However, results from a population pharmacokinetic analysis (in patients up to 65 years) suggest that age does not impact peginterferon beta-1a clearance.

Gender

No gender effect on the pharmacokinetics of peginterferon beta-1a was found in a population pharmacokinetic analysis.

Race

Race had no effect on the pharmacokinetics of peginterferon beta-1a in a population pharmacokinetic analysis.

5.3 Preclinical safety data

Toxicity

Following repeated subcutaneous administration of peginterferon beta-1a in rhesus monkeys at doses up to 400-fold (based on exposure, AUC) the recommended therapeutic dose; no effects other than the known mild pharmacological responses by rhesus monkeys to interferon beta-1a were observed after the first and second weekly dose. Repeated dose toxicology studies were limited to 5 weeks as exposure was greatly diminished from 3 weeks onwards, due to the formation of anti-drug antibodies by rhesus monkeys to human interferon beta-1a. Therefore, the long-term safety of chronic administration of Plegridy to patients cannot be assessed on the basis of these studies.

Mutagenesis

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.

Carcinogenesis

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.

Reproductive Toxicity

Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Fertility and developmental studies in rhesus monkeys have been carried out with non-pegylated interferon beta-1a. At very high doses, anovulatory and abortifacient effects were observed in animals. No information is available on the potential effects of peginterferon beta-1a on male fertility. Upon repeated dosing with peginterferon beta-1a of sexually mature female monkeys, effects on menstrual cycle length and progesterone levels were observed. Reversibility of the effects on menstrual cycle length was demonstrated. The validity of extrapolating these non-clinical data to humans is unknown.

Data from studies with other interferon beta compounds did not show teratogenic potential. The available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
L-Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Plegridy can be stored at room temperature (up to 25°C) for up to 30 days as long as it is stored away from light. If Plegridy is at room temperature for a total of 30 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 30 days or more, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

See section 6.3 for additional information on storage at room temperature (up to 25°C).

6.5 Nature and contents of container

1 mL pre-filled syringe made of glass (Type I) with a bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield, containing 0.5 mL of solution.

Pack sizes: Box of two or six 125 microgram pre-filled syringes (grey labelled syringes) in sealed plastic trays.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOGEN IDEC LIMITED

Innovation House

70 Norden Road

Maidenhead

Berkshire

SL6 4AY

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/003

EU/1/14/934/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 63 micrograms solution for injection in pre-filled pen.
Plegridy 94 micrograms solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 63 microgram pre-filled pen contains 63 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Each 94 microgram pre-filled pen contains 94 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

The dose indicates the quantity of the interferon beta-1a moiety of peginterferon beta-1a without consideration of the PEG moiety attached.

*The active substance, peginterferon beta-1a, is a covalent conjugate of interferon beta-1a, produced in Chinese Hamster Ovary cells, with 20,000 Dalton (20 kDa) methoxy poly(ethyleneglycol) using an O-2-methylpropionaldehyde linker.

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information see section 5.1.

Excipients with known effect

Each pen contains 0.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless solution with pH 4.5-5.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

Efficacy of Plegridy has been demonstrated over placebo. Direct comparative data for Plegridy versus non-pegylated interferon beta or data on efficacy of Plegridy after switching from a non-pegylated interferon beta

are not available. This should be considered when switching patients between pegylated and non-pegylated interferons. Please refer also to section 5.1.

Posology

The recommended dosage of Plegridy is 125 micrograms injected subcutaneously every 2 weeks (14 days).

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (on day 0), increasing to 94 micrograms at dose 2 (on day 14), reaching the full dose of 125 micrograms by dose 3 (on day 28) and continuing with the full dose (125 micrograms) every 2 weeks (14 days) thereafter (see Table 1). An Initiation Pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Table 1: Titration schedule at initiation

Dose	Time*	Amount (micrograms)	Pen label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

*Dosed every 2 weeks (14 days)

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of anti-inflammatory, analgesic and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment (see section 4.8).

If a dose is missed, it should be administered as soon as possible.

- If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.
- If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Plegridy within 7 days of each other.

Special populations

Elderly population

The safety and efficacy of Plegridy in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials.

Renal impairment

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 (see sections 4.4 and 5.2).

Hepatic impairment

Plegridy has not been studied in patients with hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Plegridy in children and adolescents aged 0 to 18 years have not been established in multiple sclerosis. No data are available.

Method of administration

Plegridy is for subcutaneous use.

It is recommended that a healthcare professional trains patients in the proper technique for self-administering subcutaneous injections using the pre-filled pen. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections include abdomen, arm, and thigh.

Each Plegridy pre-filled pen is provided with the needle pre-attached. Pre-filled pens are for single use only and should be discarded after use.

Precautions to be taken before handling or administering the medicinal product

Once removed from the refrigerator, Plegridy should be allowed to warm to room temperature (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm Plegridy.

Plegridy pre-filled pen must not be used unless green stripes are visible in the Plegridy pre-filled pen injection status window. Plegridy pre-filled pen must not be used if the liquid is coloured, cloudy, or contains floating particles. The liquid in the medication window must be clear and colourless.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or peginterferon or to any of the excipients listed in section 6.1.
- Initiation of treatment in pregnancy (see section 4.6).
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Hepatic injury

Elevated serum hepatic transaminase levels, hepatitis, autoimmune hepatitis and rare cases of severe hepatic failure have been reported with interferon beta medicinal products. Elevations in hepatic enzymes have been observed with the use of Plegridy. Patients should be monitored for signs of hepatic injury (see section 4.8).

Depression

Plegridy should be administered with caution to patients with previous depressive disorders (see section 4.3). Depression occurs with increased frequency in the multiple sclerosis 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.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with Plegridy should be considered (see section 4.8).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a rare complication of treatment with interferon beta, including Plegridy. Peginterferon beta-1a should be discontinued if serious hypersensitivity reactions occur (see section 4.8).

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. To minimise the risk of injection site reactions patients should be instructed in the use of an aseptic injection technique. The procedure for the self-administration by the patient should be reviewed

periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. One patient treated with Plegridy in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see section 4.8).

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with Plegridy. Patients should be monitored for symptoms or signs of decreased peripheral blood counts (see section 4.8).

Renal and urinary disorders

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Plegridy should be considered.

Severe renal impairment

Caution should be used when administering Plegridy to patients with severe renal impairment.

Thrombotic microangiopathy (TMA)

Cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Plegridy is recommended.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. aspartate aminotransferase (AST), alanine aminotransaminase (ALT)), are recommended prior to initiation and at regular intervals following introduction of Plegridy therapy and then periodically thereafter in the absence of clinical symptoms.

Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

Seizure

Plegridy should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see section 4.8).

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving interferon beta. The incidence of cardiovascular events was similar between Plegridy (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received Plegridy in the ADVANCE study. Nevertheless, 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.

Immunogenicity

Patients may develop antibodies to Plegridy. Data from patients treated up to 2 years with Plegridy suggests that less than 1% (5/715) developed persistent-neutralising antibodies to the interferon beta-1a portion of peginterferon beta-1a. Neutralising antibodies have the potential to reduce clinical efficacy. However, the development of antibodies against the interferon moiety of peginterferon beta-1a had no discernible impact on safety or clinical efficacy, although the analysis was limited by the low immunogenicity incidence.

3% 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, MRI lesions, and disability progression).

Hepatic impairment

Caution should be used and close monitoring considered when administering Plegridy 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 medicinal products associated with hepatic injury (see sections 4.8 and 5.2).

Sodium content

Each pen contains less than 1 mmol (23 mg) sodium and is therefore considered essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The clinical studies indicate that multiple sclerosis patients can receive Plegridy and corticosteroids during relapses. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential have to take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Plegridy she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before treatment started, the risk of a severe relapse following discontinuation of Plegridy in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy

There is limited information on the use of Plegridy in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether peginterferon beta-1a is secreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants, a decision should be made either to discontinue breast-feeding or Plegridy therapy.

Fertility

There are no data on the effects of peginterferon beta-1a on human fertility. In animals, anovulatory effects were observed at very high doses (see section 5.3). No information is available on the effects of peginterferon beta-1a on male fertility in animals.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions (ADR) (at a higher incidence than placebo) for Plegridy 125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.

The most commonly reported adverse reaction leading to discontinuation in patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Tabulated list of adverse reactions

In clinical studies, a total of 1468 patients received Plegridy for up to 278 weeks with an overall exposure equivalent of 4217 person-years. 1285 patients received at least 1 year, 1124 patients have received at least 2 years, 947 patients received at least 3 years, and 658 patients received at least 4 years of treatment with Plegridy. The experience in the randomised, uncontrolled phase (year 2) of the ADVANCE study and in the extension study ATTAIN (treatment received for up to 4 years) was consistent with the experience in the 1 year placebo-controlled phase of the ADVANCE study.

The table summarizes ADRs (incidence above placebo and with a reasonable possibility of causality) from 512 patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 48 weeks.

The ADRs are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below are expressed according to the following categories:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*	Rare
Immune system disorders	Hypersensitivity reaction	Uncommon
Nervous system disorders	Headache	Very common
	Seizure	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary arterial hypertension [†]	Not known
Gastrointestinal disorders	Nausea	Common
	Vomiting	
Skin and subcutaneous tissue disorders	Pruritus	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Very common
	Arthralgia	
Renal and urinary disorders	Nephrotic syndrome, glomerulosclerosis	Rare
General disorders and administration site conditions	Injection site erythema	Very common
	Influenza like illness	
	Pyrexia	
	Chills	
	Injection site pain	
	Asthenia	
	Injection site pruritus	
	Hyperthermia	Common
	Pain	
	Injection site oedema	
	Injection site warmth	
	Injection site haematoma	
	Injection site rash	
	Injection site swelling	
	Injection site discolouration	
	Injection site inflammation	
	Injection site necrosis	
Investigations	Body temperature increased	Common
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Gamma-glutamyl-transferase increased	
	Haemoglobin decreased	

MedDRA System Organ Class	Adverse reaction	Frequency category
	Platelet count decreased	Uncommon
	Decreases in white blood cell counts	Common
Psychiatric disorders	Depression	Common

*Class label for interferon beta products (see section 4.4).

† Class label for interferon products, see below *Pulmonary arterial hypertension*.

Description of selected adverse reactions

Flu-like symptoms

Influenza-like illness was experienced by 47% of patients receiving Plegridy 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest at the initiation of treatment and generally decreased over the first 6 months. Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received Plegridy during the placebo controlled phase of the ADVANCE study discontinued treatment due to flu-like symptoms. An open-label study in patients switching from interferon beta therapy to Plegridy evaluated the onset and duration of prophylactically treated flu-like symptoms. In patients experiencing flu-like symptoms, the median time to onset was 10 hours (interquartile range, 7 to 16 hours) after injection, and the median duration was 17 hours (interquartile range, 12 to 22 hours).

Injection site reactions

Injection site reactions (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received Plegridy 125 micrograms every 2 weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported injection site reaction. Of the patients who experienced injection site reactions 95% reported them as mild or moderate in severity. One patient out of 1468 patients who received Plegridy in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic transaminase abnormalities

The incidence of hepatic transaminase increases was greater in patients receiving Plegridy compared to placebo. The majority of enzyme elevations were <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase (>5 times ULN), were reported in 1% and <1% of placebo-treated patients and 2% and <1% of patients treated with Plegridy respectively. Elevations of serum hepatic transaminases combined with elevated bilirubin were observed in two patients who had pre-existing liver test abnormalities prior to receiving Plegridy in the clinical trials. Both cases resolved following discontinuation of Plegridy.

Haematological disorders

Decreases in white blood cell counts of $<3.0 \times 10^9/L$ were observed in 7% of patients receiving Plegridy and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with Plegridy. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts ($<0.5 \times 10^9/L$) (<1%), neutrophil counts ($\leq 1.0 \times 10^9/L$) (<1%) and platelet counts ($\leq 100 \times 10^9/L$) ($\leq 1\%$) was similar in Plegridy-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with Plegridy: one patient (<1%) experienced severe thrombocytopenia (platelet count $<10 \times 10^9/L$), another patient (<1%) experienced severe neutropenia (neutrophil count $<0.5 \times 10^9/L$). In both patients, cell counts recovered after discontinuation of Plegridy. Slight decreases in mean red blood cell (RBC) counts were observed in Plegridy treated patients. The incidence of potentially clinically significant decreases in RBC counts ($<3.3 \times 10^{12}/L$) was similar in Plegridy-treated patients compared to placebo-treated patients.

Hypersensitivity reactions

Hypersensitivity events were reported in 16% of patients treated with Plegridy 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of Plegridy treated patients experienced a serious hypersensitivity event (e.g. angioedema, urticaria) and they recovered promptly after treatment with anti-histamines and/or corticosteroids.

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both Plegridy 125 micrograms every 2 weeks and placebo groups. The incidence of serious events related to depression and suicidal ideation were similar and low (<1%) in both Plegridy 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

The incidence of seizure events was low and comparable in patients receiving Plegridy (125 micrograms every 2 weeks) and placebo (<1% in each group).

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of over-dose, patients may be hospitalized for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; immunostimulants; interferons
ATC code: L03AB13

Plegridy is an interferon beta-1a conjugated with a single, linear molecule of 20,000 Da methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde (20 kDa mPEG-O-2-methylpropionaldehyde) at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 44 kDa of which the protein moiety constitutes approximately 23 kDa.

Mechanism of action

A definitive mechanism of action of peginterferon beta-1a in multiple sclerosis (MS) is not known. Plegridy binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. Biological effects that may be mediated by Plegridy include up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN- γ , TNF- α) and inhibiting the migration of activated T

cells across the blood brain barrier; however additional mechanisms may be involved. Whether the mechanism of action of Plegridy in MS is mediated by the same pathway(s) as the biological effects described above is not known because the pathophysiology of MS is only partially understood.

Pharmacodynamic effects

Plegridy is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule at the alpha-amino group of the N-terminal amino acid residue.

Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature. The pharmacological properties of Plegridy are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule.

Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2',5'-oligoadenylate synthetase (2',5'-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,-trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for Plegridy compared to non-pegylated interferon beta-1a (IM) when both were given at the same dose by activity (6 MIU). The duration of this response was sustained and prolonged for Plegridy, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with Plegridy, with a sustained and prolonged elevation over 10 days compared to 5 days observed for non-pegylated interferon beta-1a. Neopterin concentrations return to baseline after the two week dosing interval.

Clinical efficacy and safety

The efficacy and safety of Plegridy was assessed from the placebo-controlled first year of a 2 year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). 1512 patients were randomised to and dosed with 125 micrograms Plegridy injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500).

The primary endpoint was the annualised relapse rate (ARR) over 1 year. The study design and patient demographics are presented in Table 2.

No data are available from clinical efficacy/safety studies directly comparing pegylated with non-pegylated interferon beta-1a, or from patients switching between non-pegylated and pegylated interferon.

Table 2: Study design

Study design	
Disease history	Patients with RRMS, with at least 2 relapses within the prior 3 years, and 1 relapse in the prior year, with an EDSS score of ≤ 5.0
Follow-up	1 year
Study population	83% treatment-naïve patients 47% ≥ 2 relapses in prior year 38% at least 1 Gd+ lesion at baseline 92% ≥ 9 T2 lesions baseline 16% EDSS ≥ 4 17% previously treated
Baseline characteristics	
Mean age (years)	37
Mean/Median disease duration (years)	3.6/2.0
Mean number of relapses within the past 3 years	2.5
Mean EDSS score at baseline	2.5

EDSS: Expanded Disability Status Scale

Gd+: Gadolinium-enhancing

Plegridy every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo ($p=0.0007$) at one year (Table 3) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. Plegridy also significantly reduced the risk of relapse by 39% ($p=0.0003$), the risk of sustained disability progression confirmed at 12 weeks by 38% ($p=0.0383$) and at 24 weeks (post-hoc analysis) by 54% ($p=0.0069$), the number of new or newly enlarging T2 lesions by 67% ($p<0.0001$), the number of Gd-enhancing lesions by 86% ($p<0.0001$) and the number of new T1 hypointense lesions compared to placebo by 53% ($p<0.0001$). A treatment effect was observed as early as 6 months, with Plegridy 125 micrograms every 2 weeks demonstrating a 61% reduction ($p<0.0001$) in new or newly enlarging T2 lesions as compared with placebo. Across relapse and MRI endpoints Plegridy 125 micrograms every two weeks showed a numerically greater treatment effect over the Plegridy every four weeks dosing regimen at year 1.

Results over 2 years confirmed that efficacy was maintained beyond the placebo controlled first year of the study. Patients exposed to Plegridy every 2 weeks showed statistically significant reductions compared to patients exposed to Plegridy every 4 weeks over 2 years in a post-hoc analysis for endpoints including ARR (24%, $p=0.0209$), the risk of relapse (24%, $p=0.0212$), the risk of disability progression with 24 week confirmation (36%, $p=0.0459$), and MRI endpoints (new/enlarging T2 60%, Gd+ 71%, and new T1 hypointense lesions 53%; $p<0.0001$ for all). In the ATTAIN extension study, long-term efficacy with Plegridy was maintained with continuous treatment up to 4 years as shown by clinical and MRI measures of MS disease activity. Of a total of 1468 patients, 658 patients continued at least 4 years of treatment with Plegridy.

Results for this study are shown in Table 3.

Table 3: Clinical and MRI results

	Placebo	Plegridy 125 micrograms every 2 weeks	Plegridy 125 micrograms every 4 weeks
Clinical endpoints			
N	500	512	500
Annualised relapse rate	0.397	0.256	0.288
Rate ratio		0.64	0.72
95% CI		0.50 – 0.83	0.56 – 0.93
P-value		p=0.0007	p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR		0.61	0.74
95% CI		0.47 – 0.80	0.57 – 0.95
P-value		p=0.0003	p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR		0.62	0.62
95% CI		0.40 – 0.97	0.40 – 0.97
P-value		p=0.0383	p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR		0.46	0.67
95% CI		(0.26 – 0.81)	(0.41 – 1.10)
P-value		p=0.0069	p=0.1116
MRI endpoints			
N	476	457	462
Mean [Median] no. of new or newly enlarging T2 hyperintense lesions (range)	13.3 [6.0] (0 – 148)	4.1 [1.0] (0 – 69)	9.2 [3.0] (0 – 113)
Lesion mean ratio (95% CI)		0.33 (0.27, 0.40)	0.72 (0.60, 0.87)
P-value		p≤0.0001	p=0.0008
Mean [Median] no. of Gd-enhancing lesions (range)	1.4 [^] [0.0] (0 – 39)	0.2 [0.0] (0 – 13)	0.9 [0.0] (0 – 41)
% reduction vs placebo		86	36
P-value		p<0.0001	p=0.0738
Mean [Median] no. of new T1 hypointense lesions (range)	3.8 [1.0] (0 – 56)	1.8 [0.0] (0 – 39)	3.1 [1.0] (0 – 61)
% reduction vs placebo		53	18
P-value		p<0.0001	0.0815

HR: Hazard ratio

CI: Confidence interval

* Sustained disability progression was defined as at least a 1 point increase from baseline EDSS \geq 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 / 24 weeks.

[^]n=477

Patients who failed previous MS treatment were not included in the study.

Subgroups of patients with higher disease activity were defined by relapse and MRI criteria as reported below, with the following efficacy results:

- For patients with ≥ 1 relapse in the previous year and ≥ 9 T2 lesions or ≥ 1 Gd+ lesion (n=1401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for Plegridy every 4 weeks and 0.25 for Plegridy every 2 weeks.

Results in this subgroup were consistent with those in the overall population.

- For patients with ≥ 2 relapses in the previous year and at least 1 Gd+ lesion (n=273), the annual relapse rate at 1 year was 0.47 for placebo, 0.35 for Plegridy every 4 weeks, and 0.33 for Plegridy every 2 weeks.

Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Plegridy in one or more subsets of the paediatric population in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum half-life of peginterferon beta-1a is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 to 188 micrograms as observed in a single dose and a multiple dose study in healthy subjects. Pharmacokinetics observed in multiple sclerosis patients were consistent with those seen in healthy subjects.

Absorption

Following subcutaneous administration of peginterferon beta-1a in multiple sclerosis patients, the peak concentration was reached between 1 to 1.5 days post-dose. The observed C_{max} (mean \pm SE) was 280 ± 79 pg/mL following repeat dosing of 125 micrograms every two weeks. Subcutaneous peginterferon beta-1a resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2-, 3.5- and 5-fold higher C_{max} , following single doses of 63 (6 MIU), 125 (12 MIU), and 188 (18 MIU) micrograms respectively, compared to intramuscular administration of 30 (6 MIU) micrograms non-pegylated beta-1a.

Distribution

Following repeat dosing of 125 micrograms doses every two weeks by subcutaneous administration, the volume of distribution uncorrected for bioavailability (mean \pm SE) was 481 ± 105 L.

Biotransformation and elimination

Urinary (renal) clearance is postulated to be a major excretory pathway for Plegridy. The process of covalently conjugating a PEG moiety to a protein can alter the in vivo properties of the unmodified protein, including decreased renal clearance and decreased proteolysis thus extending the circulating half-life. Accordingly, the half-life ($t_{1/2}$) of peginterferon beta-1a is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean \pm SE) of peginterferon beta-1a was 78 ± 15 hours at steady state. The mean steady state clearance of peginterferon beta-1a was 4.1 ± 0.4 L/hr.

Special populations

Renal impairment

A single-dose study in healthy subjects and subjects with various degrees of renal impairment (mild, moderate, and severe renal impairment as well as subjects with end state renal disease) showed a fractional increase in AUC (13-62%) and C_{max} (42-71%) in subjects with mild (estimated glomerular filtration rate 50 to ≤ 80 mL/min/1.73m²), moderate (estimated glomerular filtration rate 30 to < 50 mL/min/1.73m²), and severe (estimated glomerular filtration rate < 30 mL/min/1.73m²) renal impairment, compared to subjects with normal renal function (estimated glomerular filtration rate > 80 mL/min/1.73m²). Subjects with end stage renal disease requiring 2-3 times haemodialysis weekly showed similar AUC and C_{max} as compared to subjects with normal renal function. Each haemodialysis reduced peginterferon beta-1a concentration by approximately 24%, suggesting that haemodialysis partially removes peginterferon beta-1a from systemic circulation.

Hepatic function

The pharmacokinetics of peginterferon beta-1a has not been evaluated in patients with hepatic insufficiency.

Elderly patients

Clinical experience in patients aged above 65 years is limited. However, results from a population pharmacokinetic analysis (in patients up to 65 years) suggest that age does not impact peginterferon beta-1a clearance.

Gender

No gender effect on the pharmacokinetics of peginterferon beta-1a was found in a population pharmacokinetic analysis.

Race

Race had no effect on the pharmacokinetics of peginterferon beta-1a in a population pharmacokinetic analysis.

5.3 Preclinical safety data

Toxicity

Following repeated subcutaneous administration of peginterferon beta-1a in rhesus monkeys at doses up to 400-fold (based on exposure, AUC) the recommended therapeutic dose; no effects other than the known mild pharmacological responses by rhesus monkeys to interferon beta-1a were observed after the first and second weekly dose. Repeated dose toxicology studies were limited to 5 weeks as exposure was greatly diminished from 3 weeks onwards, due to the formation of anti-drug antibodies by rhesus monkeys to human interferon beta-1a. Therefore, the long-term safety of chronic administration of Plegridy to patients cannot be assessed on the basis of these studies.

Mutagenesis

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.

Carcinogenesis

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.

Reproductive Toxicity

Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Fertility and developmental studies in rhesus monkeys have been carried out with non-pegylated interferon beta-1a. At very high doses, anovulatory and abortifacient effects were observed in animals. No information is available on the potential effects of peginterferon beta-1a on male fertility. Upon repeated dosing with peginterferon beta-1a of sexually mature female monkeys, effects on menstrual cycle length and progesterone levels were observed. Reversibility of the effects on menstrual cycle length was demonstrated. The validity of extrapolating these non-clinical data to humans is unknown.

Data from studies with other interferon beta compounds did not show teratogenic potential. The available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
L-Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Plegridy can be stored at room temperature (up to 25°C) for up to 30 days as long as it is stored away from light. If Plegridy is at room temperature for a total of 30 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 30 days or more, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

See section 6.3 for additional information on storage at room temperature (up to 25°C).

6.5 Nature and contents of container

A pre-filled syringe of Plegridy is contained within a single-use, disposable, spring-powered pen injector called Plegridy Pen. The syringe inside the pen is a 1 mL pre-filled syringe made of glass (Type I) with a bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield, containing 0.5 mL of solution.

The Plegridy Pen Initiation Pack contains 1x 63 micrograms pre-filled pen (orange labelled pen, 1st dose) and 1x 94 micrograms pre-filled pen (blue labelled pen, 2nd dose) in a protective plastic tray.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOGEN IDEC LIMITED

Innovation House

70 Norden Road

Maidenhead

Berkshire

SL6 4AY

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 125 microgram pre-filled pen contains 125 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

The dose indicates the quantity of the interferon beta-1a moiety of peginterferon beta-1a without consideration of the PEG moiety attached.

*The active substance, peginterferon beta-1a, is a covalent conjugate of interferon beta-1a, produced in Chinese Hamster Ovary cells, with 20,000 Dalton (20 kDa) methoxy poly(ethyleneglycol) using an O-2-methylpropionaldehyde linker.

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information see section 5.1.

Excipients with known effect

Each pen contains 0.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless solution with pH 4.5-5.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

Efficacy of Plegridy has been demonstrated over placebo. Direct comparative data for Plegridy versus non-pegylated interferon beta or data on efficacy of Plegridy after switching from a non-pegylated interferon beta are not available. This should be considered when switching patients between pegylated and non-pegylated interferons. Please refer also to section 5.1.

Posology

The recommended dosage of Plegridy is 125 micrograms injected subcutaneously every 2 weeks (14 days).

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (on day 0), increasing to 94 micrograms at dose 2 (on day 14), reaching the full dose of 125 micrograms by dose 3 (on day 28) and continuing with the full dose (125 micrograms) every 2 weeks (14 days) thereafter (see Table 1). An Initiation Pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Table 1: Titration schedule at initiation

Dose	Time*	Amount (micrograms)	Pen label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

*Dosed every 2 weeks (14 days)

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of anti-inflammatory, analgesic and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment (see section 4.8).

If a dose is missed, it should be administered as soon as possible.

- If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.
- If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Plegridy within 7 days of each other.

Special populations

Elderly population

The safety and efficacy of Plegridy in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials.

Renal impairment

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 (see sections 4.4 and 5.2).

Hepatic impairment

Plegridy has not been studied in patients with hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Plegridy in children and adolescents aged 0 to 18 years have not been established in multiple sclerosis. No data are available.

Method of administration

Plegridy is for subcutaneous use.

It is recommended that a healthcare professional trains patients in the proper technique for self-administering subcutaneous injections using the pre-filled pen. Patients should be advised to rotate sites for subcutaneous

injections. The usual sites for subcutaneous injections include abdomen, arm, and thigh.

Each Plegridy pre-filled pen is provided with the needle pre-attached. Pre-filled pens are for single use only and should be discarded after use.

Precautions to be taken before handling or administering the medicinal product

Once removed from the refrigerator, Plegridy should be allowed to warm to room temperature (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm Plegridy.

Plegridy pre-filled pen must not be used unless green stripes are visible in the Plegridy pre-filled pen injection status window. Plegridy pre-filled pen must not be used if the liquid is coloured, cloudy, or contains floating particles. The liquid in the medication window must be clear and colourless.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or peginterferon or to any of the excipients listed in section 6.1.
- Initiation of treatment in pregnancy (see section 4.6).
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Hepatic injury

Elevated serum hepatic transaminase levels, hepatitis, autoimmune hepatitis and rare cases of severe hepatic failure have been reported with interferon beta medicinal products. Elevations in hepatic enzymes have been observed with the use of Plegridy. Patients should be monitored for signs of hepatic injury (see section 4.8).

Depression

Plegridy should be administered with caution to patients with previous depressive disorders (see section 4.3). Depression occurs with increased frequency in the multiple sclerosis 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.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with Plegridy should be considered (see section 4.8).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a rare complication of treatment with interferon beta, including Plegridy. Peginterferon beta-1a should be discontinued if serious hypersensitivity reactions occur (see section 4.8).

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. To minimise the risk of injection site reactions patients should be instructed in the use of an aseptic injection technique. The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. One patient treated with Plegridy in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see section 4.8).

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with Plegridy. Patients should be monitored for symptoms or signs of decreased peripheral blood counts (see section 4.8).

Renal and urinary disorders

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Plegridy should be considered.

Severe renal impairment

Caution should be used when administering Plegridy to patients with severe renal impairment.

Thrombotic microangiopathy (TMA)

Cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Plegridy is recommended.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. aspartate aminotransferase (AST), alanine aminotransaminase (ALT)), are recommended prior to initiation and at regular intervals following introduction of Plegridy therapy and then periodically thereafter in the absence of clinical symptoms.

Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

Seizure

Plegridy should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see section 4.8).

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving interferon beta. The incidence of cardiovascular events was similar between Plegridy (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received Plegridy in the ADVANCE study. Nevertheless, 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.

Immunogenicity

Patients may develop antibodies to Plegridy. Data from patients treated up to 2 years with Plegridy suggests that less than 1% (5/715) developed persistent-neutralising antibodies to the interferon beta-1a portion of peginterferon beta-1a. Neutralising antibodies have the potential to reduce clinical efficacy. However, the development of antibodies against the interferon moiety of peginterferon beta-1a had no discernible impact on safety or clinical efficacy, although the analysis was limited by the low immunogenicity incidence.

3% 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, MRI lesions, and disability progression).

Hepatic impairment

Caution should be used and close monitoring considered when administering Plegridy 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 medicinal products associated with hepatic injury (see sections 4.8 and 5.2).

Sodium content

Each pen contains less than 1 mmol (23 mg) sodium and is therefore considered essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The clinical studies indicate that multiple sclerosis patients can receive Plegridy and corticosteroids during relapses. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential have to take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Plegridy she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before treatment started, the risk of a severe relapse following discontinuation of Plegridy in the event of

pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy

There is limited information on the use of Plegridy in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether peginterferon beta-1a is secreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants, a decision should be made either to discontinue breast-feeding or Plegridy therapy.

Fertility

There are no data on the effects of peginterferon beta-1a on human fertility. In animals, anovulatory effects were observed at very high doses (see section 5.3). No information is available on the effects of peginterferon beta-1a on male fertility in animals.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions (ADR) (at a higher incidence than placebo) for Plegridy 125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.

The most commonly reported adverse reaction leading to discontinuation in patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Tabulated list of adverse reactions

In clinical studies, a total of 1468 patients received Plegridy for up to 278 weeks with an overall exposure equivalent of 4217 person-years. 1285 patients received at least 1 year, 1124 patients have received at least 2 years, 947 patients received at least 3 years, and 658 patients received at least 4 years of treatment with Plegridy. The experience in the randomised, uncontrolled phase (year 2) of the ADVANCE study and in the extension study ATTAIN (treatment received for up to 4 years) was consistent with the experience in the 1 year placebo-controlled phase of the ADVANCE study.

The table summarizes ADRs (incidence above placebo and with a reasonable possibility of causality) from 512 patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 48 weeks.

The ADRs are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below are expressed according to the following categories:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*	Rare
Immune system disorders	Hypersensitivity reaction	Uncommon
Nervous system disorders	Headache	Very common
	Seizure	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary arterial hypertension [†]	Not known
Gastrointestinal disorders	Nausea	Common
	Vomiting	
Skin and subcutaneous tissue disorders	Pruritus	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Very common
	Arthralgia	
Renal and urinary disorders	Nephrotic syndrome, glomerulosclerosis	Rare
General disorders and administration site conditions	Injection site erythema	Very common
	Influenza like illness	
	Pyrexia	
	Chills	
	Injection site pain	
	Asthenia	
	Injection site pruritus	
	Hyperthermia	Common
	Pain	
	Injection site oedema	
	Injection site warmth	
	Injection site haematoma	
	Injection site rash	
	Injection site swelling	
	Injection site discolouration	
	Injection site inflammation	
	Injection site necrosis	
Investigations	Body temperature increased	Common
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Gamma-glutamyl-transferase increased	
	Haemoglobin decreased	
	Platelet count decreased	Uncommon
	Decreases in white blood cell counts	Common
Psychiatric disorders	Depression	Common

*Class label for interferon beta products (see section 4.4).

[†] Class label for interferon products, see below *Pulmonary arterial hypertension*.

Description of selected adverse reactions

Flu-like symptoms

Influenza-like illness was experienced by 47% of patients receiving Plegridy 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest at the initiation of treatment and generally decreased over the first 6 months. Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received Plegridy during the placebo controlled phase of the ADVANCE study discontinued treatment due to flu-like symptoms. An open-label study in patients switching from interferon beta therapy to Plegridy evaluated the onset and duration of prophylactically treated flu-like symptoms. In patients experiencing flu-like symptoms, the median time to onset was 10 hours (interquartile range, 7 to 16 hours) after injection, and the median duration was 17 hours (interquartile range, 12 to 22 hours).

Injection site reactions

Injection site reactions (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received Plegridy 125 micrograms every 2 weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported injection site reaction. Of the patients who experienced injection site reactions 95% reported them as mild or moderate in severity. One patient out of 1468 patients who received Plegridy in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic transaminase abnormalities

The incidence of hepatic transaminase increases was greater in patients receiving Plegridy compared to placebo. The majority of enzyme elevations were <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase (>5 times ULN), were reported in 1% and <1% of placebo-treated patients and 2% and <1% of patients treated with Plegridy respectively. Elevations of serum hepatic transaminases combined with elevated bilirubin were observed in two patients who had pre-existing liver test abnormalities prior to receiving Plegridy in the clinical trials. Both cases resolved following discontinuation of Plegridy.

Haematological disorders

Decreases in white blood cell counts of $<3.0 \times 10^9/L$ were observed in 7% of patients receiving Plegridy and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with Plegridy. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts ($<0.5 \times 10^9/L$) (<1%), neutrophil counts ($\leq 1.0 \times 10^9/L$) (<1%) and platelet counts ($\leq 100 \times 10^9/L$) ($\leq 1\%$) was similar in Plegridy-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with Plegridy: one patient (<1%) experienced severe thrombocytopenia (platelet count $<10 \times 10^9/L$), another patient (<1%) experienced severe neutropenia (neutrophil count $<0.5 \times 10^9/L$). In both patients, cell counts recovered after discontinuation of Plegridy. Slight decreases in mean red blood cell (RBC) counts were observed in Plegridy treated patients. The incidence of potentially clinically significant decreases in RBC counts ($<3.3 \times 10^{12}/L$) was similar in Plegridy-treated patients compared to placebo-treated patients.

Hypersensitivity reactions

Hypersensitivity events were reported in 16% of patients treated with Plegridy 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of Plegridy treated patients experienced a serious hypersensitivity event (e.g. angioedema, urticaria) and they recovered promptly after treatment with anti-histamines and/or corticosteroids.

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both Plegridy 125 micrograms every 2 weeks and placebo groups. The incidence of serious events related to depression and suicidal ideation were similar and low (<1%) in both Plegridy 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

The incidence of seizure events was low and comparable in patients receiving Plegridy (125 micrograms every 2 weeks) and placebo (<1% in each group).

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of over-dose, patients may be hospitalized for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; immunostimulants; interferons
ATC code: L03AB13

Plegridy is an interferon beta-1a conjugated with a single, linear molecule of 20,000 Da methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde (20 kDa mPEG-O-2-methylpropionaldehyde) at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 44 kDa of which the protein moiety constitutes approximately 23 kDa.

Mechanism of action

A definitive mechanism of action of peginterferon beta-1a in multiple sclerosis (MS) is not known. Plegridy binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. Biological effects that may be mediated by Plegridy include up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN- γ , TNF- α) and inhibiting the migration of activated T cells across the blood brain barrier; however additional mechanisms may be involved. Whether the mechanism of action of Plegridy in MS is mediated by the same pathway(s) as the biological effects described above is not known because the pathophysiology of MS is only partially understood.

Pharmacodynamic effects

Plegridy is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule

at the alpha-amino group of the N-terminal amino acid residue.

Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature. The pharmacological properties of Plegridy are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule.

Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2',5'-oligoadenylate synthetase (2',5'-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,- trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for Plegridy compared to non-pegylated interferon beta-1a (IM) when both were given at the same dose by activity (6 MIU). The duration of this response was sustained and prolonged for Plegridy, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with Plegridy, with a sustained and prolonged elevation over 10 days compared to 5 days observed for non-pegylated interferon beta-1a. Neopterin concentrations return to baseline after the two week dosing interval.

Clinical efficacy and safety

The efficacy and safety of Plegridy was assessed from the placebo-controlled first year of a 2 year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). 1512 patients were randomised to and dosed with 125 micrograms Plegridy injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500).

The primary endpoint was the annualised relapse rate (ARR) over 1 year. The study design and patient demographics are presented in Table 2.

No data are available from clinical efficacy/safety studies directly comparing pegylated with non-pegylated interferon beta-1a, or from patients switching between non-pegylated and pegylated interferon.

Table 2: Study design

Study design	
Disease history	Patients with RRMS, with at least 2 relapses within the prior 3 years, and 1 relapse in the prior year, with an EDSS score of ≤ 5.0
Follow-up	1 year
Study population	83% treatment-naïve patients 47% ≥ 2 relapses in prior year 38% at least 1 Gd+ lesion at baseline 92% ≥ 9 T2 lesions baseline 16% EDSS ≥ 4 17% previously treated
Baseline characteristics	
Mean age (years)	37
Mean/Median disease duration (years)	3.6/2.0
Mean number of relapses within the past 3 years	2.5
Mean EDSS score at baseline	2.5

EDSS: Expanded Disability Status Scale

Gd+: Gadolinium-enhancing

Plegridy every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo (p=0.0007) at one year (Table 3) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. Plegridy also significantly reduced the risk of relapse by

39% ($p=0.0003$), the risk of sustained disability progression confirmed at 12 weeks by 38% ($p=0.0383$) and at 24 weeks (post-hoc analysis) by 54% ($p=0.0069$), the number of new or newly enlarging T2 lesions by 67% ($p<0.0001$), the number of Gd-enhancing lesions by 86% ($p<0.0001$) and the number of new T1 hypointense lesions compared to placebo by 53% ($p<0.0001$). A treatment effect was observed as early as 6 months, with Plegridy 125 micrograms every 2 weeks demonstrating a 61% reduction ($p<0.0001$) in new or newly enlarging T2 lesions as compared with placebo. Across relapse and MRI endpoints Plegridy 125 micrograms every two weeks showed a numerically greater treatment effect over the Plegridy every four weeks dosing regimen at year 1.

Results over 2 years confirmed that efficacy was maintained beyond the placebo controlled first year of the study. Patients exposed to Plegridy every 2 weeks showed statistically significant reductions compared to patients exposed to Plegridy every 4 weeks over 2 years in a post-hoc analysis for endpoints including ARR (24%, $p=0.0209$), the risk of relapse (24%, $p=0.0212$), the risk of disability progression with 24 week confirmation (36%, $p=0.0459$), and MRI endpoints (new/enlarging T2 60%, Gd+ 71%, and new T1 hypointense lesions 53%; $p<0.0001$ for all). In the ATTAIN extension study, long-term efficacy with Plegridy was maintained with continuous treatment up to 4 years as shown by clinical and MRI measures of MS disease activity. Of a total of 1468 patients, 658 patients continued at least 4 years of treatment with Plegridy.

Results for this study are shown in Table 3.

Table 3: Clinical and MRI results

	Placebo	Plegridy 125 micrograms every 2 weeks	Plegridy 125 micrograms every 4 weeks
Clinical endpoints			
N	500	512	500
Annualised relapse rate	0.397	0.256	0.288
Rate ratio		0.64	0.72
95% CI		0.50 – 0.83	0.56 – 0.93
P-value		p=0.0007	p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR		0.61	0.74
95% CI		0.47 – 0.80	0.57 – 0.95
P-value		p=0.0003	p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR		0.62	0.62
95% CI		0.40 – 0.97	0.40 – 0.97
P-value		p=0.0383	p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR		0.46	0.67
95% CI		(0.26 – 0.81)	(0.41 – 1.10)
P-value		p=0.0069	p=0.1116
MRI endpoints			
N	476	457	462
Mean [Median] no. of new or newly enlarging T2 hyperintense lesions (range)	13.3 [6.0] (0 – 148)	4.1 [1.0] (0 – 69)	9.2 [3.0] (0 – 113)
Lesion mean ratio (95% CI)		0.33 (0.27, 0.40)	0.72 (0.60, 0.87)
P-value		p≤0.0001	p=0.0008
Mean [Median] no. of Gd-enhancing lesions (range)	1.4 [^] [0.0] (0 – 39)	0.2 [0.0] (0 – 13)	0.9 [0.0] (0 – 41)
% reduction vs placebo		86	36
P-value		p<0.0001	p=0.0738
Mean [Median] no. of new T1 hypointense lesions (range)	3.8 [1.0] (0 – 56)	1.8 [0.0] (0 – 39)	3.1 [1.0] (0 – 61)
% reduction vs placebo		53	18
P-value		p<0.0001	0.0815

HR: Hazard ratio

CI: Confidence interval

* Sustained disability progression was defined as at least a 1 point increase from baseline EDSS \geq 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 / 24 weeks.

[^]n=477

Patients who failed previous MS treatment were not included in the study.

Subgroups of patients with higher disease activity were defined by relapse and MRI criteria as reported below, with the following efficacy results:

- For patients with ≥ 1 relapse in the previous year and ≥ 9 T2 lesions or ≥ 1 Gd+ lesion (n=1401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for Plegridy every 4 weeks and 0.25 for Plegridy every 2 weeks.

Results in this subgroup were consistent with those in the overall population.

- For patients with ≥ 2 relapses in the previous year and at least 1 Gd+ lesion (n=273), the annual relapse rate at 1 year was 0.47 for placebo, 0.35 for Plegridy every 4 weeks, and 0.33 for Plegridy every 2 weeks.

Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Plegridy in one or more subsets of the paediatric population in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum half-life of peginterferon beta-1a is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 to 188 micrograms as observed in a single dose and a multiple dose study in healthy subjects. Pharmacokinetics observed in multiple sclerosis patients were consistent with those seen in healthy subjects.

Absorption

Following subcutaneous administration of peginterferon beta-1a in multiple sclerosis patients, the peak concentration was reached between 1 to 1.5 days post-dose. The observed C_{max} (mean \pm SE) was 280 ± 79 pg/mL following repeat dosing of 125 micrograms every two weeks. Subcutaneous peginterferon beta-1a resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2-, 3.5- and 5-fold higher C_{max} , following single doses of 63 (6 MIU), 125 (12 MIU), and 188 (18 MIU) micrograms respectively, compared to intramuscular administration of 30 (6 MIU) micrograms non-pegylated beta-1a.

Distribution

Following repeat dosing of 125 micrograms doses every two weeks by subcutaneous administration, the volume of distribution uncorrected for bioavailability (mean \pm SE) was 481 ± 105 L.

Biotransformation and elimination

Urinary (renal) clearance is postulated to be a major excretory pathway for Plegridy. The process of covalently conjugating a PEG moiety to a protein can alter the in vivo properties of the unmodified protein, including decreased renal clearance and decreased proteolysis thus extending the circulating half-life. Accordingly, the half-life ($t_{1/2}$) of peginterferon beta-1a is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean \pm SE) of peginterferon beta-1a was 78 ± 15 hours at steady state. The mean steady state clearance of peginterferon beta-1a was 4.1 ± 0.4 L/hr.

Special populations

Renal impairment

A single-dose study in healthy subjects and subjects with various degrees of renal impairment (mild, moderate, and severe renal impairment as well as subjects with end state renal disease) showed a fractional increase in AUC (13-62%) and C_{\max} (42-71%) in subjects with mild (estimated glomerular filtration rate 50 to ≤ 80 mL/min/1.73m²), moderate (estimated glomerular filtration rate 30 to < 50 mL/min/1.73m²), and severe (estimated glomerular filtration rate < 30 mL/min/1.73m²) renal impairment, compared to subjects with normal renal function (estimated glomerular filtration rate > 80 mL/min/1.73m²). Subjects with end stage renal disease requiring 2-3 times haemodialysis weekly showed similar AUC and C_{\max} as compared to subjects with normal renal function. Each haemodialysis reduced peginterferon beta-1a concentration by approximately 24%, suggesting that haemodialysis partially removes peginterferon beta-1a from systemic circulation.

Hepatic function

The pharmacokinetics of peginterferon beta-1a has not been evaluated in patients with hepatic insufficiency.

Elderly patients

Clinical experience in patients aged above 65 years is limited. However, results from a population pharmacokinetic analysis (in patients up to 65 years) suggest that age does not impact peginterferon beta-1a clearance.

Gender

No gender effect on the pharmacokinetics of peginterferon beta-1a was found in a population pharmacokinetic analysis.

Race

Race had no effect on the pharmacokinetics of peginterferon beta-1a in a population pharmacokinetic analysis.

5.3 Preclinical safety data

Toxicity

Following repeated subcutaneous administration of peginterferon beta-1a in rhesus monkeys at doses up to 400-fold (based on exposure, AUC) the recommended therapeutic dose; no effects other than the known mild pharmacological responses by rhesus monkeys to interferon beta-1a were observed after the first and second weekly dose. Repeated dose toxicology studies were limited to 5 weeks as exposure was greatly diminished from 3 weeks onwards, due to the formation of anti-drug antibodies by rhesus monkeys to human interferon beta-1a. Therefore, the long-term safety of chronic administration of Plegridy to patients cannot be assessed on the basis of these studies.

Mutagenesis

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.

Carcinogenesis

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.

Reproductive Toxicity

Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Fertility and developmental studies in rhesus monkeys have been carried out with non-pegylated interferon beta-1a. At very high doses, anovulatory and abortifacient effects were observed in animals. No information is available on the potential effects of peginterferon beta-1a on male fertility. Upon repeated dosing with peginterferon beta-1a of sexually mature female monkeys, effects on menstrual cycle length and progesterone levels were observed. Reversibility of the effects on menstrual cycle length was demonstrated. The validity of extrapolating these non-clinical data to humans is unknown.

Data from studies with other interferon beta compounds did not show teratogenic potential. The available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
L-Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Plegridy can be stored at room temperature (up to 25°C) for up to 30 days as long as it is stored away from light. If Plegridy is at room temperature for a total of 30 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 30 days or more, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

See section 6.3 for additional information on storage at room temperature (up to 25°C).

6.5 Nature and contents of container

A pre-filled syringe of Plegridy is contained within a single-use, disposable, spring-powered pen injector called Plegridy Pen. The syringe inside the pen is a 1 mL pre-filled syringe made of glass (Type I) with a bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield, containing 0.5 mL of solution.

Pack sizes: Box of two 125 microgram pre-filled pens (grey labelled pens) in a protective plastic tray. Multipacks containing 6 (3 packs of 2) 125 microgram pre-filled pens (grey labelled pens). The pack contains 3 inner cartons. Each inner carton contains 2 pens in a protective plastic tray.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOGEN IDEC LIMITED

Innovation House

70 Norden Road

Maidenhead

Berkshire

SL6 4AY

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/005

EU/1/14/934/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Biogen Inc.
250 Binney Street
Cambridge, MA 02142
USA

Biogen Inc.
5000 Davis Drive
Research Triangle Park, NC 27709-4627
USA

Name and address of the manufacturer(s) responsible for batch release

Biogen (Denmark) Manufacturing ApS
Biogen Allé 1
DK-3400 Hillerød
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Pre-Filled Syringe Initiation Pack

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 63 micrograms solution for injection in pre-filled syringe

Plegridy 94 micrograms solution for injection in pre-filled syringe

peginterferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe contains 63 micrograms of peginterferon beta-1a in 0.5 mL.

1 pre-filled syringe contains 94 micrograms of peginterferon beta-1a in 0.5 mL.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Initiation Pack

1 pre-filled syringe of 63 micrograms

1 pre-filled syringe of 94 micrograms

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

For single use only.

Table on the inner lid

Injection Record

Day 0 (63 micrograms)

Day 14 (94 micrograms)

Date

Injection Site

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

If a refrigerator is not available, syringes can be left at room temperature (up to 25°C) for up to 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plegridy 63

Plegridy 94

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Pre-Filled Pen Initiation Pack

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 63 micrograms solution for injection in pre-filled pen

Plegridy 94 micrograms solution for injection in pre-filled pen

peginterferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled pen contains 63 micrograms of peginterferon beta-1a in 0.5 mL.

1 pre-filled pen contains 94 micrograms of peginterferon beta-1a in 0.5 mL.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Initiation Pack

1 pre-filled pen of 63 micrograms

1 pre-filled pen of 94 micrograms

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

For single use only.

Table on the inner lid

Injection Record

Day 0 (63 micrograms)

Day 14 (94 micrograms)

Date

Injection Site

open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

If a refrigerator is not available, pens can be left at room temperature (up to 25°C) for up to 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plegridy 63

Plegridy 94

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Pre-Filled Syringe 125 mcg

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled syringe
peginterferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 125 micrograms of peginterferon beta-1a in 0.5 mL.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

2 pre-filled syringes
6 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

If a refrigerator is not available, syringes can be left at room temperature (up to 25°C) for up to 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/003
EU/1/14/934/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Plegridy 125

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Pre-Filled Pen 125 mcg

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled pen
peginterferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 125 micrograms of peginterferon beta-1a in 0.5 mL.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

2 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

For single use only.

open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

If a refrigerator is not available, pens can be left at room temperature (up to 25°C) for up to 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plegridy 125

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK OUTER CARTON

Pre-filled pen 125 mcg Multipack

(Contains blue box)

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled pen
peginterferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 125 micrograms of peginterferon beta-1a in 0.5 mL.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

6 pre-filled pens
Multipack: 6 (3 packs of 2) pre-filled pens of 125 micrograms.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

If a refrigerator is not available, pens can be left at room temperature (up to 25°C) for up to 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plegridy 125

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

MULTIPACK INNER CARTON

Pre-Filled Pen 125 mcg Multipack

(Does not contain blue box)

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled pen
peginterferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 125 micrograms of peginterferon beta-1a in 0.5mL.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

2 pre-filled pens. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

For single use only.

open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

If a refrigerator is not available, pens can be left at room temperature (up to 25°C) for up to 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plegridy 125

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Pre-Filled Syringe Double Lid Initiation Pack

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 63 micrograms solution for injection in pre-filled syringe
Plegridy 94 micrograms solution for injection in pre-filled syringe

peginterferon beta-1a

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Initiation Pack

Subcutaneous use

Read the package leaflet before use.

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Pre-Filled Syringe Double Lid 125 mcg

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 125 micrograms solution for injection in pre-filled syringe
peginterferon beta-1a

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Subcutaneous use

Read the package leaflet before use.

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-Filled Syringe Label Initiation Pack

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Plegridy 63 mcg injection

Plegridy 94 mcg injection

peginterferon beta-1a

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-Filled Syringe Label 125 mcg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Plegridy 125 mcg injection

peginterferon beta-1a

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-Filled Pen Label Initiation pack

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Plegridy 63 mcg injection
Plegridy 94 mcg injection

peginterferon beta-1a
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-Filled Pen Label 125 mcg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Plegridy 125 mcg injection

peginterferon beta-1a

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Plegridy 63 micrograms solution for injection in pre-filled syringe
Plegridy 94 micrograms solution for injection in pre-filled syringe
Plegridy 125 micrograms solution for injection in pre-filled syringe
Peginterferon beta-1a

▼ **This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.**

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- - This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Plegridy is and what it is used for**
2. **What you need to know before you use Plegridy**
3. **How to use Plegridy**
4. **Possible side effects**
5. **How to store Plegridy**
6. **Contents of the pack and other information**
7. **Instructions for injecting Plegridy**

1. **What Plegridy is and what it is used for**

What Plegridy is

The active substance in Plegridy is peginterferon beta-1a. Peginterferon beta-1a is a modified long-acting form of interferon. Interferons are natural substances made in the body to help protect from infections and diseases.

What Plegridy is used for

This medicine is used to treat relapsing-remitting multiple sclerosis (MS) in adults aged 18 or over.

MS is a long term illness that affects the central nervous system (CNS), including the brain and spinal cord, in which the body's immune system (its natural defences) damages the protective layer (myelin) that surrounds the nerves in the brain and spinal cord. This disrupts the messages between the brain and other parts of the body, causing the symptoms of MS. Patients with relapsing-remitting MS have periods when the disease is not active (remission) in between flare-ups of symptoms (relapses).

Everyone has their own set of MS symptoms. These can include:

- Feeling off-balance or light headed, walking problems, stiffness and muscle spasms, tiredness, numbness in the face, arms or legs
- Acute or chronic pain, bladder and bowel problems, sexual problems and problems with vision
- Difficulty thinking and concentrating, depression.

How Plegridy works

Plegridy seems to work by stopping the body's immune system from damaging your brain and spinal cord. This can help to reduce the number of relapses that you have and slow down the disabling effects of MS. Treatment with Plegridy can help to prevent you from getting worse, although it will not cure MS.

2. What you need to know before you use Plegridy

Do not use Plegridy

- **Do not use Plegridy:**
 - **If you are allergic** to peginterferon beta-1a, interferon beta-1a or any of the ingredients of this medicine (listed in section 6). See section 4 for the symptoms of an allergic reaction.
 - **If you have severe depression** or think about committing suicide.
- **Do not start** using Plegridy if you are **already pregnant**.

Warnings and precautions

- **If you have ever had:**
 - **Depression** or problems affecting your mood
 - **Thoughts about committing suicide**
 - **Talk to your doctor.** Your doctor may still prescribe Plegridy for you, but it's important to let your doctor know if you have had depression or any similar problems affecting your mood in the past.
- **If you have any of the conditions listed below:**
 - **Serious liver or kidney problems**
 - **Irritation at an injection site**, which can lead to skin and tissue damage (*injection site necrosis*). When you are ready to inject, carefully follow the instructions in section 7 "*Instructions for injecting Plegridy*", at the end of this leaflet. This is to reduce the risk of injection site reactions.
 - **Epilepsy** or other seizure disorders, not controlled by medication
 - **Heart problems**, which can cause symptoms such as chest pain (*angina*), particularly after any activity; swollen ankles, shortness of breath (*congestive heart failure*); or an irregular heartbeat (*arrhythmia*).
 - **Thyroid problems**
 - **A low number of white blood cells or platelets**, which can cause an increased risk of infection, or bleeding
 - **Talk to your doctor, pharmacist or nurse** before injecting Plegridy if any of these apply to you. They may get worse while using Plegridy.

Other things to consider when using Plegridy

- You will need blood tests to determine your numbers of blood cells, blood chemistry and your levels of liver enzymes. These will be performed before you start using Plegridy, regularly after treatment with Plegridy has been initiated and then periodically during treatment, even if you have no particular symptoms. These blood tests will be in addition to the tests which are normally done to monitor your MS.
- The functioning of your thyroid gland will be checked regularly or whenever thought necessary by your doctor for other reasons.
- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Plegridy. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidneys.

If you accidentally prick yourself or someone else with the needle in Plegridy, the area affected should be washed **immediately** with soap and water and a **doctor or nurse should be contacted as soon as possible**.

Children and adolescents

Plegridy is **not to be used** in children and adolescents below 18 years old. The safety and effectiveness of Plegridy in this age group are not known.

Other medicines and Plegridy

Plegridy should be used carefully with medicines that are broken down in the body by a group of proteins called “cytochrome P450” (e.g. some medicines used for epilepsy or depression).

- Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, especially those used to treat epilepsy or depression. This includes any medicines obtained without a prescription.

Sometimes you will need to remind other healthcare professionals that you are being treated with Plegridy. For example, if you are prescribed other medicines, or if you have a blood test. Plegridy may affect the other medicines or the test result.

Pregnancy and breastfeeding

- **Do not start using Plegridy if you are already pregnant.**
- **If you could get pregnant**, you need to use contraception while you use Plegridy.
- **If you are planning to have a baby or if you do become pregnant** while you are using Plegridy, tell your doctor. You and your doctor can discuss if you should carry on with treatment.
- **If you want to breastfeed** while using Plegridy, talk to your doctor first.

Driving and using machines

Plegridy may make you feel sick (see section 4 “*Possible side effects*”). Do not drive or use machines if you notice this or anything that could affect your ability to drive.

Plegridy contains sodium

Each syringe contains less than 1 mmol sodium (23 mg). i.e. it is essentially “sodium-free”.

3. How to use Plegridy

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose:

One injection of Plegridy 125 micrograms every 14 days (every two weeks). Try to use Plegridy at the same time on the same day, every time you inject.

Starting Plegridy

If you are new to Plegridy, your doctor may advise you to gradually increase your dose so that you can adjust to the effects of Plegridy before taking the full dose. You will be provided with an Initiation Pack containing your first 2 injections: one orange syringe with Plegridy 63 micrograms (for day 0) and one blue syringe with Plegridy 94 micrograms (for day 14).

After that you will be provided with a maintenance pack containing grey syringes with Plegridy 125 micrograms (for day 28 and then every two weeks).

Read the instructions in section 7 “*Instructions for injecting Plegridy*” at the end of this leaflet before you start using Plegridy.

Use the record table printed on the inside of the lid of the Initiation Pack to keep a track of your injection dates.

Injecting yourself

Plegridy is to be injected under the skin (*subcutaneous injection*). Alternate the sites you use for injections. Do not use the same injection site for consecutive injections.

You can inject Plegridy yourself without the help of your doctor, if you have been trained how to do this.

- Read and follow the advice given in the instructions in section 7 “*Instructions for injecting Plegridy*” before you start.
- **If you have trouble** handling the syringe, ask your doctor or nurse who may be able to help.

How long to use Plegridy

Your doctor will tell you how long you need to keep using Plegridy. It is important to continue using Plegridy regularly. Do not make changes unless your doctor tells you.

If you use more Plegridy than you should

You must only inject Plegridy once every 2 weeks.

- If you have used more than one injection of Plegridy in a 7-day period, **contact your doctor or nurse straight away.**

If you forget to use Plegridy

You need to inject Plegridy once every 2 weeks. This regular schedule helps to deliver the treatment as evenly as possible.

If you do miss your usual day, inject as soon as you can and carry on as usual. However, do not inject more than once in a 7-day period. Do not use two injections to make up for a missed injection.

- If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

- Liver problems

(common - may affect up to 1 in 10 people)

If you get any of these symptoms:

- Yellowing of your skin or the whites of your eyes
- Itching all over
- Feeling sick, being sick (*nausea and vomiting*)
- Easy bruising of the skin
- **Call your doctor immediately.** They may be signs of a possible liver problem.

- Depression

(common - may affect up to 1 in 10 people)

If you:

- Feel unusually sad, anxious or worthless or
- Have thoughts about suicide
- **Call your doctor immediately.**

- Serious allergic reaction

(uncommon - may affect up to 1 in 100 people)

If you get any of these:

- Difficulty breathing
- Swelling around the face (lips, tongue or throat)
- Skin rashes or redness
- **Contact a doctor immediately.**

- Seizures

(uncommon - may affect up to 1 in 100 people)

If you have a seizure or a fit

- **Contact a doctor immediately.**

- Injection site damage

(rare - may affect up to 1 in 1,000 people)

If you get any of these symptoms:

- Any break in the skin together with swelling, inflammation or fluid leaking around the injection site
- **Contact your doctor for advice.**

- **Kidney problems including scarring that may reduce your kidney function**

(rare - may affect up to 1 in 1,000 people)

If you get some or all of these symptoms:

- Foamy urine
- Fatigue
- Swelling, particularly in the ankles and eyelids, and weight gain.
- **Tell your doctor as they may be signs of a possible kidney problem.**

- **Blood problems**

(rare - may affect up to 1 in 1,000 people)

The following may occur: Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

If you get some or all of these symptoms:

- Increased bruising or bleeding
- Extreme weakness
- Headache, dizziness or light-headedness
- **Tell your doctor immediately.**

Other side effects

Very common side effects

(may affect more than 1 in 10 people)

- Flu-like symptoms. These symptoms are not really flu, see below. You can't pass it on to anyone else.
- Headache
- Muscle pain (*myalgia*)
- Pain in your joints, arms, legs or neck (*arthralgia*)
- Chills
- Fever
- Feeling weak and tired (*asthenia*)
- Redness, itching or pain around the place you have injected
- **If any of these effects trouble you, talk to your doctor.**

Flu-like symptoms: not really flu

Flu-like symptoms are more common when you first start using Plegridy. They gradually get less as you keep using your injections. See below for simple ways to manage these flu-like symptoms if you get them.

Three simple ways to help reduce the impact of flu-like symptoms:

1. Consider the timing of your Plegridy injection. The start and end of flu-like symptoms are different for every patient. On average, flu-like symptoms begin approximately 10 hours after injection and last between 12 and 24 hours.
2. Take paracetamol or ibuprofen half an hour before your Plegridy injection. Speak to your doctor or pharmacist about how much to take and how long to take it.
3. If you have a fever, drink plenty of water to keep you hydrated.

Common side effects

(may affect up to 1 in 10 people)

- Feeling or being sick (*nausea or vomiting*)
- Itchy skin (*pruritus*)
- Increase in body temperature
- Changes around the place you have injected such as swelling, inflammation, bruising, warmth, rash or colour change
- Changes in your blood which might cause tiredness or reduced ability to fight infection
- Increases in liver enzymes in the blood (will show up in blood tests)
- **If any of these effects trouble you, talk to your doctor.**

Uncommon side effects

(may affect up to 1 in 100 people)

- Hives
- Changes in your blood which might cause unexplained bruising or bleeding.
- **If any of these effects trouble you, talk to your doctor.**

Other side effects

(frequency not known - frequency cannot be estimated from the available data)

- Pulmonary arterial hypertension: A disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with interferon beta-products.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Plegridy

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after “EXP”. The expiry date refers to the last day of that month.

- Keep Plegridy in the original package in order to protect it from light. Only open the pack when you need a new syringe.
- **Store in a refrigerator** (fridge), between 2° and 8°C.
 - Do not freeze. Throw away any Plegridy that is accidentally frozen.
- Plegridy can be kept outside a fridge at room temperature (up to 25°C) for up to 30 days but it must be kept **away from light**.
 - Packs can be taken out of the fridge and then put back in a fridge more than once if you need to.
 - Make sure the time the syringes spend out of a fridge is **no more than 30 days in total**.
 - Throw away any syringe that is kept out of the fridge for more than 30 days.
 - If you are unsure of the number of days you have kept a syringe out of the fridge, throw the syringe away.
- Do not use this medicine if you notice any of the following:
 - If the syringe is broken.
 - If the solution is coloured, cloudy or you can see particles floating in it.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Plegridy contains

The active ingredient is: peginterferon beta-1a.

Each 63 microgram pre-filled syringe contains 63 micrograms of peginterferon beta-1a in 0.5 mL solution

for injection.

Each 94 microgram pre-filled syringe contains 94 micrograms of peginterferon beta-1a in 0.5 mL solution for injection.

Each 125 microgram pre-filled syringe contains 125 micrograms of peginterferon beta-1a in 0.5 mL solution for injection.

The other ingredients are: Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20 and water for injections.

What Plegridy looks like and contents of the pack

Plegridy is a clear and colourless solution for injection in a pre-filled syringe.

Pack sizes:

- The Plegridy Initiation Pack contains one orange pre-filled syringe of 63 micrograms and one blue pre-filled syringe of 94 micrograms.

- The 125 micrograms grey syringes are provided in a pack containing either two or six pre-filled syringes.

In all packs the needles are attached to the syringes ready to inject.

Not all pack sizes may be marketed.

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Manufacturer

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This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

7. Instructions for injecting Plegridy




BEFORE YOU START

Read these instructions for use before you start using Plegridy and each time you get a new pack. This information does not replace talking to your doctor or nurse about your medical condition or your treatment.

Before you first use the Plegridy pre-filled syringe, your doctor or nurse must show you (or your carer) how to prepare and inject your Plegridy pre-filled syringe the right way.

Dosage schedule

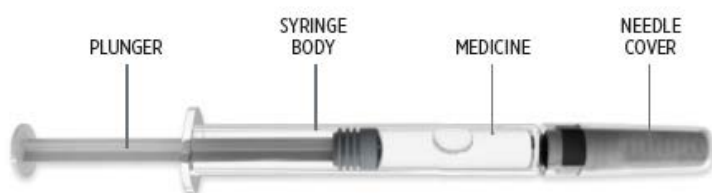
Each pre-filled syringe is for single-use and cannot be re-used. Choose the correct Plegridy pre-filled syringe from a pack. Plegridy pre-filled syringe Initiation Pack contains your first two injections to gradually adjust your dose.

When	Which dose	Which pack
Day 0 (63 micrograms)	First injection: 63 micrograms, choose orange syringe	 INITIATION PACK
Day 14 (94 micrograms)	Second injection: 94 micrograms, choose blue syringe	
Day 28 and then every two weeks after that (125 micrograms)	Full dose injection: 125 micrograms, choose grey syringe	 125 MICROGRAM PACK

Do not use more than one pre-filled syringe per 14-day period (every 2 weeks).

PREPARING FOR INJECTION

Know the pre-filled syringe features



Prepare work surface

Find a well-lit, clean, flat surface like a table and collect all the supplies you will need to give yourself or to receive an injection.

Collect supplies. You will need the following supplies to perform the injection:

- Alcohol wipe
- Gauze pad
- Adhesive bandage/plaster
- A puncture resistant container for disposal of used syringes

Remove from fridge

Remove 1 Plegridy pack out of the fridge and select the appropriate pre-filled syringe from the pack.


Put the pack back in the fridge after removing the first pre-filled syringe. If there's no fridge available, see section 5 "How to store Plegridy".

Check the pack and the pre-filled syringe

Check the expiry date printed on the pre-filled syringe and the carton.

Do not use the Plegridy pre-filled syringe past the expiry date.

Leave Plegridy to warm to room temperature before injecting. This takes about 30 minutes.
Do not use external heat sources such as hot water to warm the Plegridy pre-filled syringe.

Check that the liquid is clear and colourless	
Do not use the Plegridy pre-filled syringe if the liquid is coloured, cloudy, or contains floating particles. You may see a bubble. This is normal.	

GIVING THE INJECTION

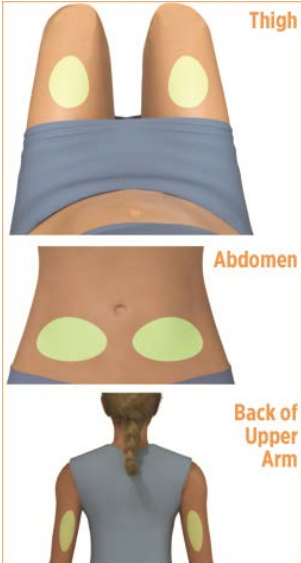
Plegridy pre-filled syringe is for injection under the skin (*subcutaneous injection*).






Inject the Plegridy pre-filled syringe exactly as your doctor or nurse has shown you.

Do not inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way. Alternate the sites you use for injections. Do not use the same injection site for consecutive injections.

Do not remove the needle cover until ready to inject.

Wash your hands with soap and water.

<p>1. Choose the injection site</p> <p>Plegridy pre-filled syringe should be injected into the thigh, abdomen or back of the upper arm. Choose an injection site and wipe the skin with an alcohol wipe. Let the injection site dry before injecting the dose. Do not touch this area again before giving the injection.</p>	
<p>2. Firmly remove needle cover</p>	

<p>Pull the needle cover straight off the needle and dispose of the needle cover. Do not touch the needle. Do not recap the Plegridy pre-filled syringe.</p>	
<p>3. Prepare injection site and position pre-filled syringe</p>	
<p>Pinch the skin around the cleaned injection site using thumb and forefinger. Hold the Plegridy syringe at a 90° angle to the injection site.</p>	
<p>4. Inject medicine</p>	
<p>Insert the needle with a quick dart-like motion, straight into the skin fold. The needle must go all the way in. The skin fold can be released after needle insertion.</p>	
<p>Slowly push the plunger in one smooth motion until syringe is empty. This should take about 5 seconds. Do not lift the pre-filled syringe off the injection site.</p>	
<p>5. Wait 5 seconds</p>	
<p>Keep the needle inserted for 5 seconds.</p>	
<p>6. Remove syringe from site</p>	

Pull the needle straight out.
Do not recap the Plegridy pre-filled syringe.
Do not reuse the Plegridy pre-filled syringe.



AFTER THE INJECTION

Care for the injection site

Apply pressure to the injection site for a few seconds using a sterile gauze pad.
If there is blood, wipe it off.
Apply an adhesive plaster if needed.

Dispose of pre-filled syringe

Throw away the used Plegridy pre-filled syringe into a special secure container, such as a sharps bin.
Check with your doctor, pharmacist or nurse about the right way to throw away the container.

Record date and location

Record the date and location of each injection.
For the first injections, you can use the record table printed on the inside of the lid of the Initiation Pack.

Check injection site

After 2 hours, check the injection site for redness, swelling, or tenderness.
If you have a skin reaction and it does not clear up in a few days, contact your doctor or nurse.

General warnings

Do not reuse your Plegridy pre-filled syringe.
Do not share your Plegridy pre-filled syringe.

Package leaflet: Information for the user

Plegridy 63 micrograms solution for injection in pre-filled pen
Plegridy 94 micrograms solution for injection in pre-filled pen
Plegridy 125 micrograms solution for injection in pre-filled pen
Peginterferon beta-1a

▼ **This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.**

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- - This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Plegridy is and what it is used for**
2. **What you need to know before you use Plegridy**
3. **How to use Plegridy**
4. **Possible side effects**
5. **How to store Plegridy**
6. **Contents of the pack and other information**
7. **Instructions for injecting Plegridy**

1. What Plegridy is and what it is used for

What Plegridy is

The active substance in Plegridy is peginterferon beta-1a. Peginterferon beta-1a is a modified long-acting form of interferon. Interferons are natural substances made in the body to help protect from infections and diseases.

What Plegridy is used for

This medicine is used to treat relapsing-remitting multiple sclerosis (MS) in adults aged 18 or over.

MS is a long term illness that affects the central nervous system (CNS), including the brain and spinal cord, in which the body's immune system (its natural defences) damages the protective layer (myelin) that surrounds the nerves in the brain and spinal cord. This disrupts the messages between the brain and other parts of the body, causing the symptoms of MS. Patients with relapsing-remitting MS have periods when the disease is not active (remission) in between flare-ups of symptoms (relapses).

Everyone has their own set of MS symptoms. These can include:

- Feeling off-balance or light headed, walking problems, stiffness and muscle spasms, tiredness, numbness in the face, arms or legs
- Acute or chronic pain, bladder and bowel problems, sexual problems and problems with vision
- Difficulty thinking and concentrating, depression.

How Plegridy works

Plegridy seems to work by stopping the body's immune system from damaging your brain and spinal cord. This can help to reduce the number of relapses that you have and slow down the disabling effects of MS. Treatment with Plegridy can help to prevent you from getting worse, although it will not cure MS.

2. What you need to know before you use Plegridy

Do not use Plegridy

- **Do not use Plegridy:**
 - **If you are allergic** to peginterferon beta-1a, interferon beta-1a or any of the ingredients of this medicine (listed in section 6). See section 4 for the symptoms of an allergic reaction.
 - **If you have severe depression** or think about committing suicide.
- **Do not start** using Plegridy if you are **already pregnant**.

Warnings and precautions

- **If you have ever had:**
 - **Depression** or problems affecting your mood
 - **Thoughts about committing suicide**
 - **Talk to your doctor.** Your doctor may still prescribe Plegridy for you, but it's important to let your doctor know if you have had depression or any similar problems affecting your mood in the past.
- **If you have any of the conditions listed below:**
 - **Serious liver or kidney problems**
 - **Irritation at an injection site**, which can lead to skin and tissue damage (*injection site necrosis*). When you are ready to inject, carefully follow the instructions in section 7 "*Instructions for injecting Plegridy*", at the end of this leaflet. This is to reduce the risk of injection site reactions.
 - **Epilepsy** or other seizure disorders, not controlled by medication
 - **Heart problems**, which can cause symptoms such as chest pain (*angina*), particularly after any activity; swollen ankles, shortness of breath (*congestive heart failure*); or an irregular heartbeat (*arrhythmia*).
 - **Thyroid problems**
 - **A low number of white blood cells or platelets**, which can cause an increased risk of infection, or bleeding
 - **Talk to your doctor, pharmacist or nurse** before injecting Plegridy if any of these apply to you. They may get worse while using Plegridy.

Other things to consider when using Plegridy

- You will need blood tests to determine your numbers of blood cells, blood chemistry and your levels of liver enzymes. These will be performed before you start using Plegridy, regularly after treatment with Plegridy has been initiated and then periodically during treatment, even if you have no particular symptoms. These blood tests will be in addition to the tests which are normally done to monitor your MS.
- The functioning of your thyroid gland will be checked regularly or whenever thought necessary by your doctor for other reasons.
- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Plegridy. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidneys.

If you accidentally prick yourself or someone else with the needle in Plegridy, the area affected should be washed **immediately** with soap and water and a **doctor or nurse should be contacted as soon as possible**.

Children and adolescents

Plegridy is **not to be used** in children and adolescents below 18 years old. The safety and effectiveness of Plegridy in this age group are not known.

Other medicines and Plegridy

Plegridy should be used carefully with medicines that are broken down in the body by a group of proteins called “cytochrome P450” (e.g. some medicines used for epilepsy or depression).

- Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, especially those used to treat epilepsy or depression. This includes any medicines obtained without a prescription.

Sometimes you will need to remind other healthcare professionals that you are being treated with Plegridy. For example, if you are prescribed other medicines, or if you have a blood test. Plegridy may affect the other medicines or the test result.

Pregnancy and breastfeeding

- **Do not start using Plegridy if you are already pregnant.**
- **If you could get pregnant**, you need to use contraception while you use Plegridy.
- **If you are planning to have a baby or if you do become pregnant** while you are using Plegridy, tell your doctor. You and your doctor can discuss if you should carry on with treatment.
- **If you want to breastfeed** while using Plegridy, talk to your doctor first.

Driving and using machines

Plegridy may make you feel sick (see section 4 “*Possible side effects*”). Do not drive or use machines if you notice this or anything that could affect your ability to drive.

Plegridy contains sodium

Each pen contains less than 1 mmol sodium (23 mg). i.e. it is essentially “sodium-free”.

3. How to use Plegridy

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose:

One injection of Plegridy 125 micrograms every 14 days (every two weeks). Try to use Plegridy at the same time on the same day, every time you inject.

Starting Plegridy

If you are new to Plegridy, your doctor may advise you to gradually increase your dose so that you can adjust to the effects of Plegridy before taking the full dose. You will be provided with an Initiation Pack containing your first 2 injections: one orange pen with Plegridy 63 micrograms (for day 0) and one blue pen with Plegridy 94 micrograms (for day 14).

After that you will be provided with a maintenance pack containing grey pens with Plegridy 125 micrograms (for day 28 and then every two weeks).

Read the instructions in section 7 “*Instructions for injecting Plegridy*” at the end of this leaflet before you start using Plegridy.

Use the record table printed on the inside of the lid of the Initiation Pack to keep a track of your injection dates.

Injecting yourself

Plegridy is to be injected under the skin (*subcutaneous injection*). Alternate the sites you use for injections. Do not use the same injection site for consecutive injections.

You can inject Plegridy yourself without the help of your doctor, if you have been trained how to do this.

- Read and follow the advice given in the instructions in section 7 “*Instructions for injecting Plegridy*” before you start.
- **If you have trouble** handling the pen, ask your doctor or nurse who may be able to help.

How long to use Plegridy

Your doctor will tell you how long you need to keep using Plegridy. It is important to continue using Plegridy regularly. Do not make changes unless your doctor tells you.

If you use more Plegridy than you should

You must only inject Plegridy once every 2 weeks.

- If you have used more than one injection of Plegridy in a 7-day period, **contact your doctor or nurse straight away.**

If you forget to use Plegridy

You need to inject Plegridy once every 2 weeks. This regular schedule helps to deliver the treatment as evenly as possible.

If you do miss your usual day, inject as soon as you can and carry on as usual. However, do not inject more than once in a 7-day period. Do not use two injections to make up for a missed injection.

- If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

- Liver problems

(common - may affect up to 1 in 10 people)

If you get any of these symptoms:

- Yellowing of your skin or the whites of your eyes
- Itching all over
- Feeling sick, being sick (*nausea and vomiting*)
- Easy bruising of the skin
- **Call your doctor immediately.** They may be signs of a possible liver problem.

- Depression

(common - may affect up to 1 in 10 people)

If you:

- Feel unusually sad, anxious or worthless or
- Have thoughts about suicide
- **Call your doctor immediately.**

- Serious allergic reaction

(uncommon - may affect up to 1 in 100 people)

If you get any of these:

- Difficulty breathing
- Swelling around the face (lips, tongue or throat)
- Skin rashes or redness
- **Contact a doctor immediately.**

- Seizures

(uncommon - may affect up to 1 in 100 people)

If you have a seizure or a fit

- **Contact a doctor immediately.**

- Injection site damage

(rare - may affect up to 1 in 1,000 people)

If you get any of these symptoms:

- Any break in the skin together with swelling, inflammation or fluid leaking around the injection site
- **Contact your doctor for advice.**

- **Kidney problems including scarring that may reduce your kidney function**

(rare - may affect up to 1 in 1,000 people)

If you get some or all of these symptoms:

- Foamy urine
- Fatigue
- Swelling, particularly in the ankles and eyelids, and weight gain.
- **Tell your doctor as they may be signs of a possible kidney problem.**

- **Blood problems**

(rare - may affect up to 1 in 1,000 people)

The following may occur: Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

If you get some or all of these symptoms:

- Increased bruising or bleeding
- Extreme weakness
- Headache, dizziness or light-headedness
- **Tell your doctor immediately.**

Other side effects

Very common side effects

(may affect more than 1 in 10 people)

- Flu-like symptoms. These symptoms are not really flu, see below. You can't pass it on to anyone else.
- Headache
- Muscle pain (*myalgia*)
- Pain in your joints, arms, legs or neck (*arthralgia*)
- Chills
- Fever
- Feeling weak and tired (*asthenia*)
- Redness, itching or pain around the place you have injected
- **If any of these effects trouble you, talk to your doctor.**

Flu-like symptoms: not really flu

Flu-like symptoms are more common when you first start using Plegridy. They gradually get less as you keep using your injections. See below for simple ways to manage these flu-like symptoms if you get them.

Three simple ways to help reduce the impact of flu-like symptoms:

1. Consider the timing of your Plegridy injection. The start and end of flu-like symptoms are different for every patient. On average, flu-like symptoms begin approximately 10 hours after injection and last between 12 and 24 hours.
2. Take paracetamol or ibuprofen half an hour before your Plegridy injection. Speak to your doctor or pharmacist about how much to take and how long to take it.
3. If you have a fever, drink plenty of water to keep you hydrated.

Common side effects

(may affect up to 1 in 10 people)

- Feeling or being sick (*nausea or vomiting*)
- Itchy skin (*pruritus*)
- Increase in body temperature
- Changes around the place you have injected such as swelling, inflammation, bruising, warmth, rash or colour change
- Changes in your blood which might cause tiredness or reduced ability to fight infection
- Increases in liver enzymes in the blood (will show up in blood tests)
- **If any of these effects trouble you, talk to your doctor.**

Uncommon side effects

(may affect up to 1 in 100 people)

- Hives
- Changes in your blood which might cause unexplained bruising or bleeding.
- **If any of these effects trouble you, talk to your doctor.**

Other side effects

(frequency not known - frequency cannot be estimated from the available data)

- Pulmonary arterial hypertension: A disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with interferon beta-products.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Plegridy

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.

- Keep Plegridy in the original package in order to protect it from light. Only open the pack when you need a new pen.
- **Store in a refrigerator** (fridge), between 2° and 8°C.
 - Do not freeze. Throw away any Plegridy that is accidentally frozen.
- Plegridy can be kept outside a fridge at room temperature (up to 25°C) for up to 30 days but it must be kept **away from light**.
 - Packs can be taken out of the fridge and then put back in a fridge more than once if you need to.
 - Make sure the time the pens spend out of a fridge is **no more than 30 days in total**.
 - Throw away any pen that is kept out of the fridge for more than 30 days.
 - If you are unsure of the number of days you have kept a pen out of the fridge, throw the pen away.
- Do not use this medicine if you notice any of the following:
 - If the pen is broken.
 - If the solution is coloured, cloudy or you can see particles floating in it.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Plegridy contains

The active ingredient is: peginterferon beta-1a.

Each 63 microgram pre-filled pen contains 63 micrograms of peginterferon beta-1a in 0.5 mL solution for injection.

Each 94 microgram pre-filled pen contains 94 micrograms of peginterferon beta-1a in 0.5 mL solution for injection.

Each 125 microgram pre-filled pen contains 125 micrograms of peginterferon beta-1a in 0.5 mL solution for injection.

The other ingredients are: Sodium acetate trihydrate, acetic acid glacial, L-arginine hydrochloride, polysorbate 20 and water for injections.

What Plegridy looks like and contents of the pack

Plegridy is a clear and colourless solution for injection in a pre-filled pen.

Pack sizes:

- The Plegridy Initiation Pack contains one orange pre-filled pen of 63 micrograms and one blue pre-filled pen of 94 micrograms.

- The 125 micrograms grey pens are provided in a pack containing either two or six pre-filled pens.

In all packs the needles are attached to the pens ready to inject.

Not all pack sizes may be marketed.

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This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

7. Instructions for injecting Plegridy



BEFORE YOU START

Read these instructions for use before you start using Plegridy and each time you get a new pack. This information does not replace talking to your doctor or nurse about your medical condition or your treatment.

Before you first use the Plegridy pen, your doctor or nurse must show you (or your carer) how to prepare and inject your Plegridy pen the right way.

Dosage schedule

Plegridy is a single-use pen. It cannot be re-used. Choose the correct Plegridy pen from a pack. Plegridy pen Initiation Pack contains your first two injections to gradually adjust your dose.

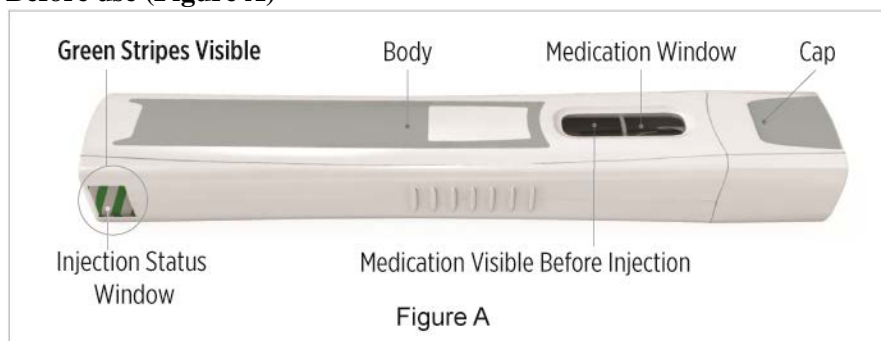
When	Which dose	Which pack
Day 0 (63 micrograms)	First injection: 63 micrograms, choose orange pen	 INITIATION PACK
Day 14 (94 micrograms)	Second injection: 94 micrograms, choose blue pen	
Day 28 and then every two weeks after that (125 micrograms)	Full dose injection: 125 micrograms, choose grey pen	 125 MICROGRAM PACK

Do not use more than one pre-filled pen per 14-day period (every 2 weeks).

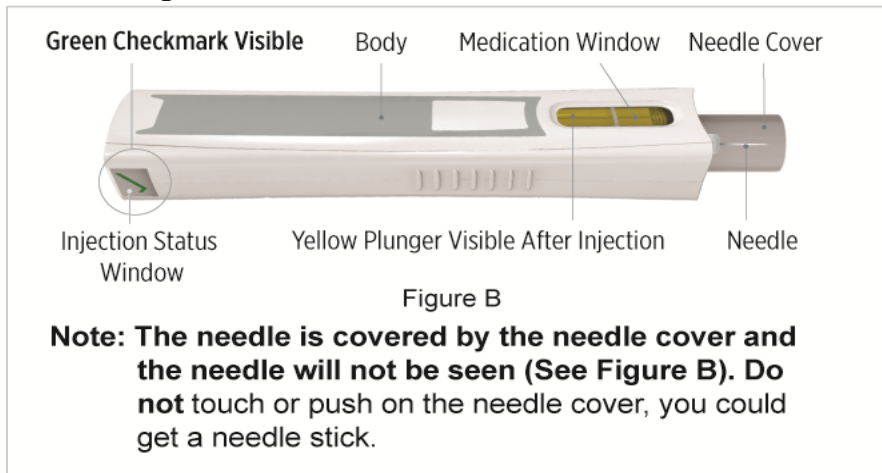
PREPARING FOR INJECTION

Know the Pen features

Before use (Figure A)



After use (Figure B)



Prepare work surface

Find a well-lit, clean, flat surface like a table and collect all the supplies you will need to give yourself or to receive an injection.

Collect supplies. You will need the following supplies to perform the injection:

- Alcohol wipe
- Gauze pad
- Adhesive bandage/plaster
- A puncture resistant container for disposal of used pens

Remove from fridge

Remove 1 Plegridy pack out of the fridge and select the appropriate pre-filled pen from the pack. Put the pack back in the fridge after removing the first pen. If there's no fridge available, see section 5 "*How to store Plegridy*".

Check pack and pen

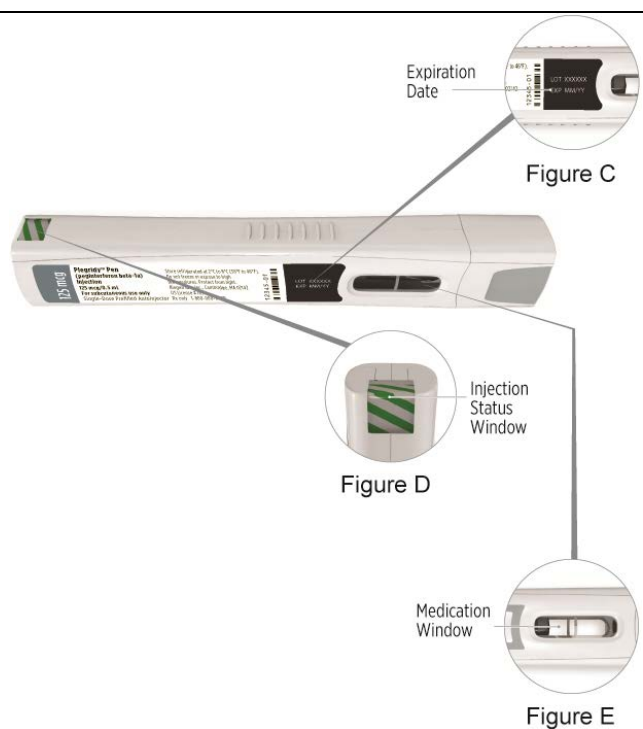
Check the expiry date printed on the pen (Figure C) and the carton. Do not use the pen past the expiry date.

Leave Plegridy to warm to room temperature before injecting. This takes about 30 minutes. Do not use external heat sources such as hot water to warm the Plegridy pen.

Check the Plegridy pen

Check the injection status. Make sure that green stripes are visible (Figure D).
Do not use the pen unless the injection status window shows green stripes.

Check that the liquid is clear and colourless in the medication window (Figure E).
Do not use the Plegridy pen if the liquid is coloured, cloudy, or contains floating particles.
You may see a bubble. This is normal.



GIVING THE INJECTION

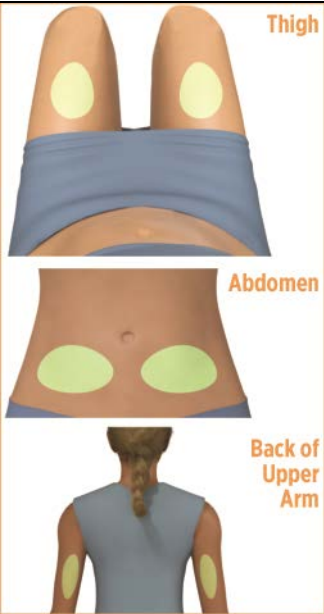
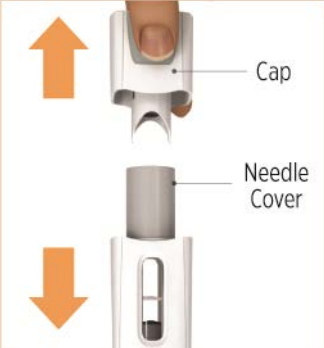
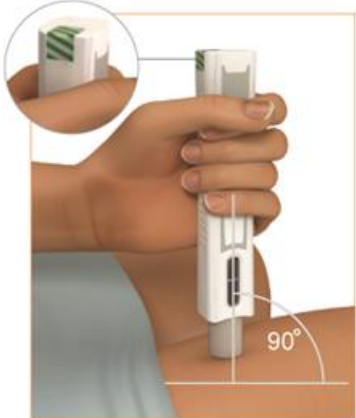
Plegridy pen is for injection under the skin (*subcutaneous injection*).

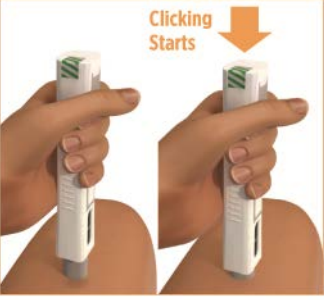


Inject the Plegridy pen exactly as your doctor or nurse has shown you.

Do not inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way. Alternate the sites you use for injections. Do not use the same injection site for consecutive injections.

Do not remove the cap until ready to inject.

Wash your hands with soap and water.

<p>1. Choose the injection site (Figure F)</p> <p>Plegridy pen should be injected into the thigh, abdomen or back of the upper arm.</p> <p>Choose an injection site and wipe the skin with an alcohol wipe.</p> <p>Let the injection site dry before injecting the dose.</p> <p>Do not touch this area again before giving the injection.</p>	 <p style="text-align: center;">Figure F</p>
<p>2. Remove cap (Figure G)</p> <p>Pull the cap off and dispose of it.</p> <p>Do not recap the Plegridy Pen.</p> <p>The needle is covered by the needle cover and will not be visible.</p> <p>Do not touch or push down on the needle cover, you could get a needle stick injury.</p> <p>The Plegridy pen is ready to inject after the cap is removed.</p>	 <p style="text-align: center;">Figure G</p>
<p>3. Position pen and check (Figure H)</p> <p>Place the Plegridy pen on your chosen injection site.</p> <p>You should hold the Plegridy Pen at a 90° angle to your injection site so that you can see the green stripes in the injection status window.</p> <p>Do not use the Plegridy pen unless you see green stripes in the injection status window.</p>	 <p style="text-align: center;">Figure H</p>

<p>4. Inject medicine (Figure I)</p> <p>Press the pen into injection site and hold. Pressing the pen down will insert the needle and automatically start the injection.</p> <p>Do not lift the pen. Do not make any movements until injection is completed. Continue to firmly press, keeping still during the injection process.</p> <p>Wait until the clicking stops and the green tick marks appear.</p>	 <p>Figure I</p>
<p>During the injection process (Figure J):</p> <ul style="list-style-type: none"> - Plegridy pen will “click” several times. - The green stripes will be moving in the injection status window. <p>The pen’s clicking sounds will stop when the injection is complete. This should take about 5 seconds.</p> <p>Make sure the green tick marks have appeared in the injection status window.</p>	 <p>Figure J</p>
<p>5. Remove pen from site (Figure K)</p> <p>Lift the Plegridy pen from the injection site. The needle cover will extend covering the needle completely.</p>	 <p>Figure K</p>

AFTER THE INJECTION

Care for injection site

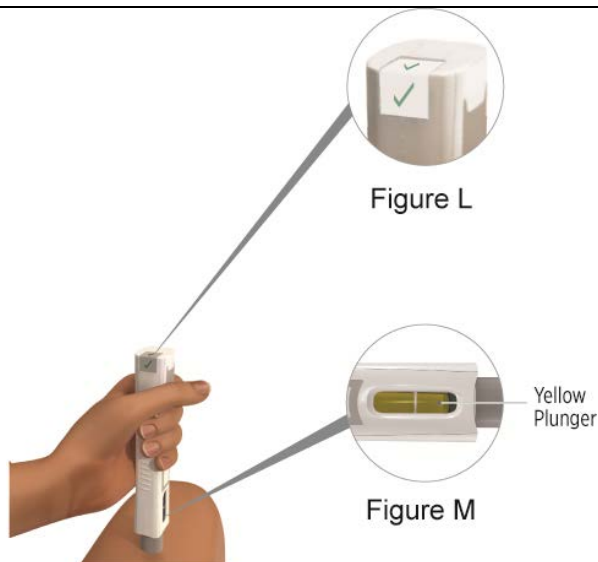
Apply pressure to the injection site for a few seconds using a sterile gauze pad.
If there is blood, wipe it off.
Apply an adhesive plaster if needed.

Confirm dose delivery

Check the injection status window. You should see green tick marks in the injection status window (Figure L).

Check the medication window. You should see a yellow plunger in the medication window (Figure M)

An extended yellow plunger indicates that the entire dose has been successfully administered. Do not reuse the pen.



Dispose of pen

Throw away the used Plegridy pen into a special secure container, such as a sharps bin.

Check with your doctor, pharmacist or nurse about the right way to throw away the container.

Record date and location

Record the date and location of each injection.

For the Initiation Pack injections, you can use the record table printed on the inside of the lid of the Initiation Pack.

Check injection site

After 2 hours, check the injection site for redness, swelling, or tenderness.

If you have a skin reaction and it does not clear up in a few days, contact your doctor or nurse.

General warnings

Do not reuse your Plegridy pen.

Do not share your Plegridy pen.