ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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.
Plegridy 125 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.
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.

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 (see section 5.1).

Posology

The recommended dose 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.

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 (up to 30°C) for 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 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 medicinal product 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.
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 including cases of anaphylaxis have been reported as a rare complication of treatment with interferon beta, including Plegridy. Patients should be advised to discontinue Plegridy and seek immediate medical care if they experience signs and symptoms of anaphylaxis or severe hypersensitivity. Treatment with Plegridy should not be restarted (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 (class effects)

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) (class effects)

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.

Three percent of patients (18/681) developed persistent antibodies to the PEG moiety of peginterferon beta-1a. In the clinical study conducted, the development of antibodies against the PEG moiety of peginterferon beta-1a had no discernible impact on safety, or clinical efficacy (including annualised relapse rate, 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

This medicinal product contains less than 1 mmol (23 mg) sodium that is to say it is 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

Pregnancy

A large amount of data (more than 1000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Plegridy may be considered during pregnancy.

Breast-feeding

It is not known whether peginterferon beta-1a is secreted in human milk. Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Plegridy can be used during breast-feeding.

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

Plegridy has no or negligible influence on the ability to drive and use machines.

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 and post-marketing data.

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 (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1, 000 to <1/100)
- Rare (≥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	Angioedema	Uncommon
	Hypersensitivity	
	Anaphylaxis[1]	Not known
Psychiatric disorders	Depression	Common
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	Alopecia[§]	Common
	Pruritus	
	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	Influenza like illness	Very common
	Pyrexia	
	Chills	
	Injection site erythema	
	Injection site pain	
	Injection site pruritus	
	Asthenia	
	Hyperthermia	Common
	Injection site inflammation	
	Pain	
	Injection site haematoma	
	Injection site swelling	
	Injection site oedema	
	Injection site rash	
	Injection site warmth	
	Injection site discolouration	
	Injection site necrosis	Rare
Investigations	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	

MedDRA System Organ Class	Adverse reaction	Frequency category
	Gamma-glutamyltransferase increased	
	White blood cell count decreased	
	Haemoglobin decreased	
	Body temperature increased	
	Platelet count decreased	Uncommon

*Class label for interferon beta products (see section 4.4).
+ Class label for interferon products, see below *Pulmonary arterial hypertension*.
$ Class label for interferon products
[1] Adverse reactions derived only during post marketing experience

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) (≤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 x 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. In post marketing experience, serious hypersensitivity events including cases of anaphylaxis (frequency not known) have been reported following Plegridy administration.

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.

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 95% CI P-value		0.64 0.50 – 0.83 p=0.0007	0.72 0.56 – 0.93 p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR 95% CI P-value		0.61 0.47 – 0.80 p=0.0003	0.74 0.57 – 0.95 p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR 95% CI P-value		0.62 0.40 – 0.97 p=0.0383	0.62 0.40 – 0.97 p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR 95% CI P-value		0.46 (0.26 – 0.81) p=0.0069	0.67 (0.41 – 1.10) 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) P-value		0.33 (0.27, 0.40) p≤0.0001	0.72 (0.60, 0.87) 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 P-value		86 p<0.0001	36 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 P-value		53 p<0.0001	18 0.0815

HR: Hazard ratio
CI: Confidence interval
* Sustained disability progression was defined as at least a 1 point increase from baseline EDSS ≥ 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±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±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±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/1.73m^2), moderate (estimated glomerular filtration rate 30 to <50 mL/min/1.73m^2), and severe (estimated glomerular filtration rate <30 mL/min/1.73m^2) renal impairment, compared to subjects with normal renal function (estimated glomerular filtration rate >80 mL/min/1.73m^2). 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
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 30°C) for up to 7 days as long as it is stored away from light. If Plegridy is at room temperature for a total of 7 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 7 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.

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. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe.

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.

Box of two 125 microgram pre filled pens (grey labelled pens) 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 Ltd.
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70 Norden Road
Maidenhead
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SL6 4AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

63/94 micrograms: 1/52316
125 micrograms: 1/52416

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 May 2017

10. DATE OF REVISION OF THE TEXT

October 2019