ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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
Plegridy 125 micrograms solution for injection in pre-filled syringe
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

Plegridy 63 micrograms solution for injection in pre-filled syringe (for subcutaneous use)
Each pre-filled syringe contains 63 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Plegridy 94 micrograms solution for injection in pre-filled syringe (for subcutaneous use)
Each pre-filled syringe contains 94 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Plegridy 125 micrograms solution for injection in pre-filled syringe (for subcutaneous use)
Each pre-filled syringe contains 125 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Plegridy 125 micrograms solution for injection in pre-filled syringe (for intramuscular use)
Each pre-filled syringe contains 125 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Plegridy 63 micrograms solution for injection in pre-filled pen (for subcutaneous use)
Each pre-filled pen contains 63 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Plegridy 94 micrograms solution for injection in pre-filled pen (for subcutaneous use)
Each pre-filled pen contains 94 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

Plegridy 125 micrograms solution for injection in pre-filled pen (for subcutaneous use)
Each 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.

Plegridy may be administered subcutaneously (SC) using a single-use pre-filled pen or pre-filled syringe or intramuscularly (IM) using a single use pre-filled syringe.

Efficacy of peginterferon beta-1a administered subcutaneously has been demonstrated over placebo. Direct comparative data for peginterferon beta-1a versus non-pegylated interferon beta or data on efficacy of peginterferon beta-1a 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 SC or IM every 2 weeks (14 days).

Treatment initiation
It is generally recommended that patients start SC or IM 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 1a for SC use or Table 1b for IM use).

Subcutaneous route
An initiation pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Table 1a: Titration schedule at initiation via SC route

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)

Intramuscular route
An administration dose pack contains the full 125 microgram dose in 1 pre-filled syringe.

The Plegridy titration clips, designed for use with the pre-filled syringe are intended to limit the dose that is administered to 63 micrograms (dose 1 (1/2 dose), yellow titration clip) and 94 micrograms (dose 2 (3/4 dose), purple titration clip), for day 0 and day 14 respectively. Each Plegridy titration clip should be used once, and then discarded along with any remaining medicinal product. Patients should use the full dose of 125 micrograms (no clip required) from day 28 onwards (dosing every 14 days).

Table 1b Titration schedule at initiation via IM route

Dose	Time*	Amount (micrograms)	Titration clip
Dose 1	Day 0	63	Yellow
Dose 2	Day 14	94	Purple
Dose 3	Day 28	125 (full dose)	No clips needed

*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).

Switching between the SC and IM routes of administration and vice versa has not been studied. Based upon bioequivalence demonstrated between the two routes of administration it is not expected that dose titration will be required if switching between SC and IM, or vice versa (see sections 5.1 and 5.2).

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 peginterferon beta-1a within 7 days of each other.

Special populations

Elderly population
The safety and efficacy of peginterferon beta-1a 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
Peginterferon beta-1a has not been studied in patients with hepatic impairment (see section 4.4).

Paediatric population
The safety and efficacy of peginterferon beta-1a in children and adolescents aged 0 to 18 years have not been established in multiple sclerosis. No data are available.

Method of administration

It is recommended that a healthcare professional trains patients in the proper technique for self—administering SC injections using the SC pre-filled syringe/pre-filled pen or IM injections using the IM pre-filled syringes as appropriate. Patients should be advised to rotate sites for SC or IM injections every two weeks. The usual sites for subcutaneous injections include abdomen, arm, and thigh. The usual site for intramuscular injection is the thigh.

Each Plegridy pre-filled pen/syringe for SC is provided with the needle pre-attached. Plegridy prefilled syringe for IM use is supplied as a prefilled syringe with a separate needle for IM use.

Both IM and SC pre-filled syringes and SC 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 25 °C) for about 30 minutes prior to injection. External heat sources such as hot water must not be used to warm the medicinal product

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.

Plegridy pre-filled pen must not be used unless the 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 peginterferon beta-1a. Patients should be monitored for signs of hepatic injury (see section 4.8).

Depression

Peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a. Patients should be advised to discontinue treatment with peginterferon beta-1a and seek immediate medical care if they experience signs and symptoms of anaphylaxis or severe hypersensitivity. Treatment with peginterferon beta-1a 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 peginterferon beta-1a in clinical trials experienced an injection site necrosis with SC peginterferon beta-1a. 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 peginterferon beta-1a. 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 peginterferon beta-1a should be considered.

Severe renal impairment
Caution should be used when administering peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a 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

Peginterferon beta-1a 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 peginterferon beta-1a (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received peginterferon beta-1a 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 peginterferon beta-1a. Data from patients treated up to 2 years with peginterferon beta-1a administered SC 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, magnetic resonance imaging (MRI) lesions, and disability progression).

Hepatic impairment

Caution should be used and close monitoring considered when administering peginterferon beta-1a to patients with severe hepatic impairment. Patients should be monitored for signs of hepatic injury and caution exercised when interferons are used concomitantly with other 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 peginterferon beta-1a 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 peginterferon beta-1a 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 1,000 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 peginterferon beta-1ay may be considered during pregnancy.

Breast-feeding

Limited information available on the transfer of interferon beta-1a/peginterferon beta-1a into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1a/peginterferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Peginterferon beta-1a 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

Peginterferon beta-1a 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 Peginterferon beta-1a 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 peginterferon beta-1a 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Tabulated list of adverse reactions via subcutaneous route of administration
In clinical studies, a total of 1,468 patients received peginterferon beta-1a SC for up to 278 weeks with an overall exposure equivalent of 4,217 person -years. 1,285 patients received at least 1 year, 1,124 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 peginterferon beta-1a. 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.

Table 2 summarizes ADRs (incidence above placebo and with a reasonable possibility of causality) from 512 patients treated with peginterferon beta-1a 125 micrograms SC 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)

Table 2 Tabulated summary of adverse drug reactions

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	
	Gamma-glutamyltransferase increased	
	White blood cell count decreased	
	Haemoglobin decreased	

MedDRA system organ class	Adverse reaction	Frequency category
	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 via subcutaneous route of administration

Flu-like symptoms
Influenza -like illness was experienced by 47% of patients receiving peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a 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 (ISRs)
ISRs (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received peginterferon beta-1a 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 1,468 patients who received peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a in the clinical trials. Both cases resolved following discontinuation of the medicinal product.

Haematological disorders
Decreases in white blood cell (WBC) counts of $<3.0 \times 10^9$/L were observed in 7% of patients receiving peginterferon beta-1a and in 1% receiving placebo. Mean WBC counts remained within normal limits in patients treated with peginterferon beta-1a. Decreases in WBC 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 peginterferon beta-1a-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with peginterferon beta-1a: 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 peginterferon beta-1a. Slight decreases in mean red blood cell (RBC) counts were observed in peginterferon beta-1atreated patients. The incidence of potentially clinically significant decreases in RBC counts ($<3.3 \times 10^{12}$/L) was similar in peginterferon beta-1a treated patients compared to placebo- treated- patients.

Hypersensitivity reactions
Hypersensitivity events were reported in 16% of patients treated with peginterferon beta-1a 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of peginterferon beta-1a 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 peginterferon beta-1a 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.

Intramuscular route of administration

An open-label, crossover study enrolled 136 subjects to assess the bioequivalence of single doses of 125 micrograms of peginterferon beta-1a administered SC and IM injection in healthy volunteers. The most commonly reported AEs (with >10% incidence in either arm) across both treatment periods were chills (35.6% in IM vs 26.9% in SC), pain (22.0% in IM vs 14.2% in SC), injection site pain (11.4% in IM vs 14.9% in SC), injection site erythema (2.3% in IM vs 25.4% in SC), and headache (35.6% in IM vs 41.0% in SC). Injection site reactions were reported with a lower frequency in IM (14.4%) compared to SC (32.1%).

Abnormal urine protein was reported in 1/130 (0.8%) for the SC arm and 4/131 (3.1%) in the IM group without any associated adverse drug reactions.

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

Peginterferon beta-1a 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. peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a 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

Peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a, 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 peginterferon beta-1a, 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 via subcutaneous route

The efficacy and safety of peginterferon beta-1a 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 peginterferon beta-1a 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 .3

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 3: 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

RRMS: relapsing remitting multiple sclerosis
EDSS: expanded disability status scale
Gd+: gadolinium-enhancing

Peginterferon beta-1a every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo (p=0.0007) at one year (Table 4) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. peginterferon beta-1a 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 peginterferon beta-1a 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 peginterferon beta-1a 125 micrograms every two weeks showed a numerically greater treatment effect over the peginterferon beta-1a 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 peginterferon beta-1a every 2 weeks showed statistically significant reductions compared to patients exposed to peginterferon beta-1a 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 peginterferon beta-1a was maintained with continuous treatment up to 4 years as shown by clinical and MRI measures of MS disease activity. Of a total of 1,468 patients, 658 patients continued at least 4 years of treatment with peginterferon beta-1a.

Results for this study are shown in Table 4.

Table 4: Clinical and MRI results

	Placebo	Peginterferon beta-1a 125 micrograms every 2 weeks	Peginterferon beta-1a 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=1,401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for peginterferon beta-1a every 4 weeks and 0.25 for peginterferon beta-1a 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 peginterferon beta-1a every 4 weeks, and 0.33 for peginterferon beta-1a every 2 weeks.
  Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

IM and SC bioequivalence study
An -open-label, crossover study enrolled 136 subjects to assess the bioequivalence of single doses of 125 micrograms of Plegridy administered SC and IM injection in healthy volunteers.

The serum concentration of neopterin, a marker of interferon beta activity, following administration of 125 micrograms peginterferon beta-1a IM and SC was measured for pharmacodynamic (PD) analysis.

The serum neopterin concentration versus time profiles following single doses of 125 micrograms peginterferon beta-1a SC or 125 micrograms peginterferon beta-1a IM were similar, with maximal concentrations (E_{peak}) reached at a median E_{Tmax} of 40.1 hours and 44.0 hours, respectively. Geometric mean neopterin levels increased from baseline to maximum concentration similarly between the 2 injection routes, with the increase from 8.0 to 22.6 nmol/L for SC, and from 8.1 to 23.2 nmol/L for IM. The overall systemic exposure to neopterin ($EAUC_{0\ 336h}$ and $EAUC_{0\text{-}504h}$) were also similar between the 2 routes of administration.

Since bioequivalence was demonstrated between the IM and SC routes of administration, it is expected that IM and SC peginterferon beta-1a will have a similar efficacy profile.

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 peginterferon beta-1a. 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

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.

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.

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.

IM and SC bioequivalence study
The pharmacokinetic (PK) profiles following single doses of 125 micrograms peginterferon beta-1a IM and 125 micrograms peginterferon beta-1a SC in healthy volunteers were similar, with maximal concentrations reached at 40.0 hours post-dose (for both SC and IM), and $t_{1/2}$ values of 97.1 hours and 79.1 hours, respectively. Statistical analysis of C_{max} and AUC_{∞} further demonstrated bioequivalence between 125 micrograms peginterferon beta-1a IM and SC. The geometric mean ratio (90% confidence interval) of IM versus SC for C_{max} was 1.08 (0.98 to 1.20) and 1.09 (1.02 to 1.16) for AUC∞. These values fall within the designated 0.80 to 1.25 equivalence range.

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 peginterferon beta-1a 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 for SC or IM administration 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.

6.5 Nature and contents of container

Pre-filled syringe / pre-filled pen (subcutaneous)

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.

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.

Pack sizes
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.

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 or six 125 microgram pre-filled syringes (grey labelled syringes) in sealed plastic trays.

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.

Pre-filled syringe (intramuscular)

1 mL pre-filled Luer-Lok syringe made of glass (Type I) with a bromobutyl rubber stopper containing 0.5 mL of solution and supplied with a 23 gauge, 1.25 inch needle. A single pre-filled syringe contains 0.5 mL of solution of Plegridy containing 125 micrograms of peginterferon beta-1a.

Box of two or six 125 microgram pre-filled syringes in sealed plastic trays.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Plegridy prefilled syringes (for IM and SC administration) and pen (for SC administration) are for single-use only.

Before use check the dosage form to be used. It should not have any cracks or damage and the solution should be clear, colourless and not have any particles in it.

Once removed from the refrigerator, the Plegridy pre-filled syringe or pen to be used should be allowed to warm to room temperature (15°C to 30°C) for about 30 minutes.

Do not use external heat sources such as hot water to warm the Plegridy pre-filled syringe or pen Titration of Plegridy doses for patients initiating treatment is described in section 4.2.

Pre-filled syringe / pre-filled pen (subcutaneous)
Patients initiating treatment with Plegridy via SC administration should use initiation packs.

Pre-filled syringe (intramuscular)
Patients initiating treatment with Plegridy via IM administration should use Plegridy Titration clips which may be attached to the syringe to limit the dose.

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

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/001
EU/1/14/934/002
EU/1/14/934/003
EU/1/14/934/004
EU/1/14/934/005
EU/1/14/934/006
EU/1/14/934/007
EU/1/14/934/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2014
Date of latest renewal: 25 March 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

FUJIFILM Diosynth Biotechnologies Denmark ApS
Biotek Allé 1
DK-3400 Hillerød
Denmark

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 Marketing Authorisation Holder (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.

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, 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 Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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 Netherlands B.V.

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 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

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, 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 Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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 Netherlands B.V.

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 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

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, 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 Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

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, 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 Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK OUTER CARTON

Pre-filled pen 125 mcg Multipack (with bluebox)

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, arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

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 Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

MULTIPACK INNER CARTON

Pre-Filled Pen 125 mcg Multipack (without bluebox)

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, 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 Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Pre-Filled Syringe 125 mcg for intramuscular use

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, 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

Read the package leaflet before use.
Intramuscular use
For single use only.
If using Plegridy for the first time the dose may need to be increased gradually.

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

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Prins Mauritslaan 13
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The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/007
EU/1/14/934/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plegridy 125

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Pre-Filled Syringe Double Lid 125 mcg for intramuscular injection

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 Netherlands B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intramuscular 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 125 mcg for intramuscular injection

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

Plegridy 125 mcg injection
peginterferon beta-1a
IM

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

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

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
- **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.

Warnings and precautions
Talk to your doctor if you have ever had:
- **Depression** or problems affecting your mood
- **Thoughts about committing suicide**
    - 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.

Talk to your doctor, pharmacist or nurse before injecting Plegridy **if you have any of the conditions listed below.** They may get worse while using Plegridy**:**
- **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 pre-filled syringe*", at the end of this leaflet. This is to reduce the risk of injection site reactions.
- **Epilepsy** or other seizure disorders, not controlled by medicine
- **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

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.
- 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 breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Plegridy can be used during breast-feeding.

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

Plegridy contains sodium
This medicine contains less than 1 mmol sodium (23 mg), that is to say 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 pre-filled syringe*" 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 pre-filled syringe*" 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
    - **Contact a 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
    - **Contact a 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 a 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.
    - **Contact a 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
    - **Contact a 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, contact a doctor.**

Flu-like symptoms
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 and continue to take paracetamol or ibuprofen for the duration of your flu-like symptoms. 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)*
- Hair loss (*alopecia*)
- 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, contact a 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, contact a doctor.**

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.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

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.

- Store in the original package in order to protect from light. Only open the pack when you need a new syringe.

- **Store in a refrigerator** (fridge) 2º -8 ºC.
    - 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, arginine hydrochloride, polysorbate 20 and water for injections (see Section 2 “Plegridy contains sodium”).

What Plegridy looks like and contents of the pack
Plegridy is a clear and colourless solution for injection in a glass pre-filled syringe with an attached needle.

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.

Not all pack sizes may be marketed.

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The Netherlands

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Denmark

Biogen Netherlands B.V.
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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: https://www.ema.europa.eu.

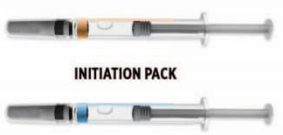
7. Instructions for injecting Plegridy pre-filled syringe

How to inject Plegridy

Read the instructions for use before you start using Plegridy and each time you get a refill of your prescription. There may be new information. This information does not take the place of talking to your doctor or nurse about your medical condition or your treatment.

Note:
- **Before you use the Plegridy pre-filled syringe for the first time**, your doctor or nurse should show you or your carer how to prepare and inject the Plegridy pre-filled syringe.
- Plegridy pre-filled syringe is for injecting the medicine under the skin only (subcutaneous)
- **Each Plegridy pre-filled syringe can be used once only.**
- ⚠ **Do not** share your Plegridy pre-filled syringe with anyone else to avoid giving an infection to them or getting an infection from them.
- ⚠ **Do not** use more than one pre-filled syringe every 14 days (every 2 weeks).
- ⚠ **Do not** use your syringe if it has been dropped or is visibly damaged.

Dosage schedule
The Initiation Pack contains your first two injections to gradually adjust your dose. Choose the correct syringe from a pack.

When	Which dose	Which pack
Day 0 (63 micrograms)	First injection: 63 micrograms, choose orange syringe	
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	

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

Supplies needed for your Plegridy injection

Plegridy pre-filled syringe (see Figure A)

Before Use – Parts of your Plegridy pre-filled syringe (Figure A)

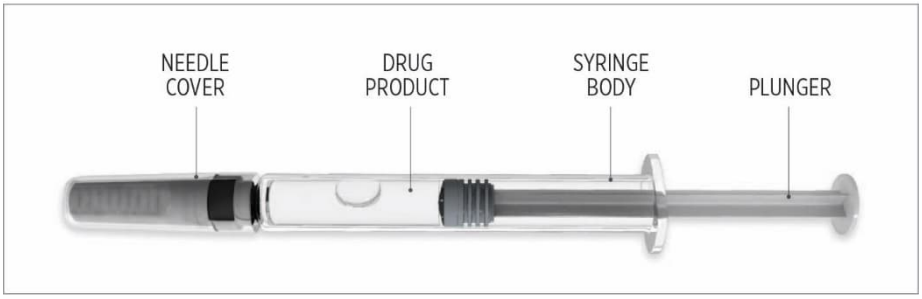


Figure A

Additional supplies which are not included in the pack (See Figure B):

- Alcohol wipe
- Gauze pad
- Adhesive bandage

Ask your doctor, pharmacist, or nurse for instructions on throwing away used syringes.

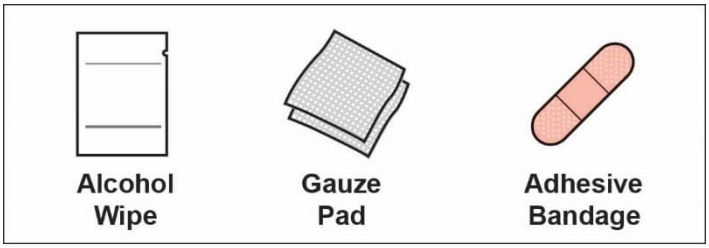


Figure B

Preparing for your injection

Step 1: Remove your pre-filled syringe from the fridge

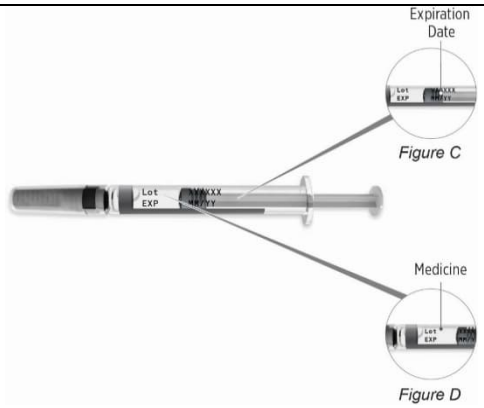
- Remove one Plegridy pack out of the fridge and select the appropriate pre-filled syringe from the pack**.**
- Close the pack and put pack back in the fridge after removing one pre-filled syringe.
- **Let the Plegridy pre-filled syringe warm to room temperature for at least 30 minutes**.
  - ⚠ **Do not** use external heat sources such as hot water to warm the Plegridy pre-filled syringe.

Step 2: Collect your supplies and wash your hands

- Find a well-lit, clean, flat surface to work on, like a table. Collect all the supplies you will need to give yourself or to receive an injection.
- Wash your hands with soap and water.

Step 3: Check the Plegridy pre-filled syringe

- Check the expiry date on the Plegridy pre-filled syringe (See Figure C).
  - ⚠ **Do not** use Plegridy pre-filled syringe past the expiry date.
- Check that your Plegridy medicine is clear and colourless (See Figure D).
  - ⚠ **Do not** use the Plegridy pre-filled syringe if the liquid is coloured, cloudy, or has floating particles in it.
  - o You might see air bubbles in the Plegridy medicine. This is normal and does not need to be expelled before your injection.



Giving your injection

Step 4: Choose and clean your injection site

- Plegridy pre-filled syringe is for subcutaneous injection (injection into skin).
- Plegridy pre-filled syringe should be injected into the abdomen, thigh, or the back of the upper arm. (See Figure E).
  - ⚠ **Do not** inject directly into your belly button.
  - ⚠ **Do not** inject into an area of the body where the skin is irritated, tender, red, bruised, tattooed, infected, or scarred.
- Choose an injection site and wipe the skin with an alcohol wipe.
- Let the injection site dry before injecting the dose.
  - ⚠ **Do not** touch or blow this area again before giving the injection.

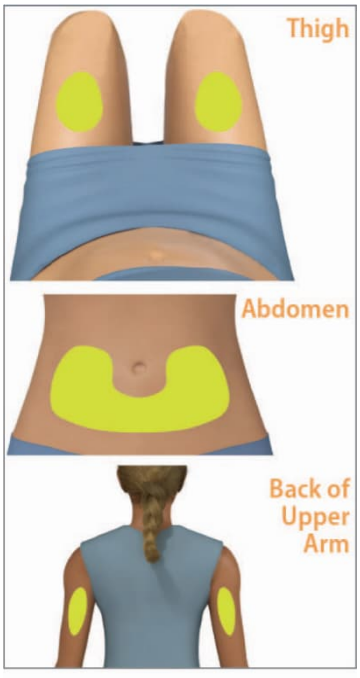


Figure E

Step 5: Firmly remove the needle cover

- Using one hand, hold the syringe by the glass barrel. With your other hand, firmly grasp needle cover and pull it straight off the needle (See Figure F).

  ⚠ **Use caution** when removing the needle cover to avoid getting a needle stick injury.

  ⚠ **Do not** touch the needle.

  ⚠ **Caution - Do not** recap the Plegridy pre-filled syringe. You could get a needle injury.

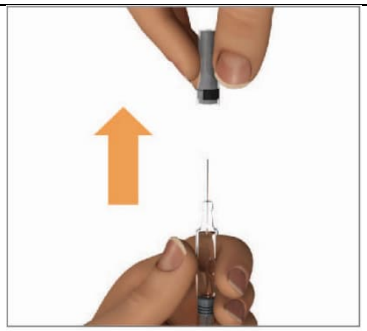


Figure F

Step 6: Gently pinch the injection site

- Gently pinch the skin around the cleaned injection site using thumb and forefinger to create a slight bulge (See Figure G).

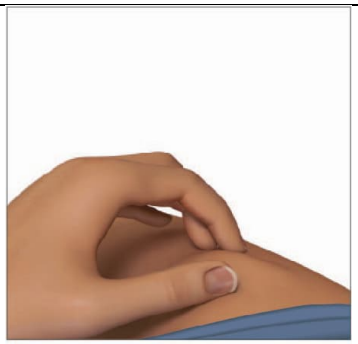


Figure G

Step 7: Inject medicine

- Hold the Plegridy pre-filled syringe at a 90° angle to the injection site. Quickly insert the needle straight into the skin fold until the needle is fully under the skin. (See Figure H).

- After the needle is in, let go of your skin.

  ⚠ **Do not** pull back on the plunger.

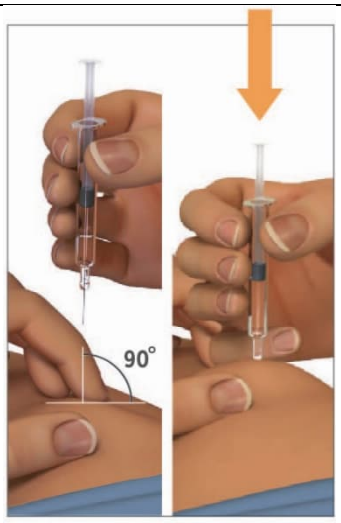
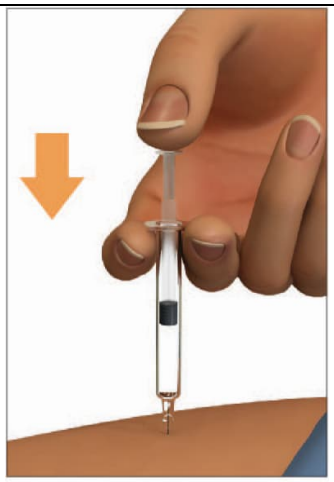
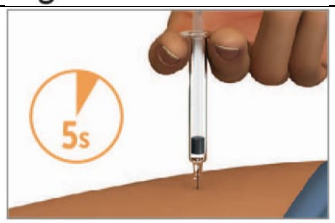
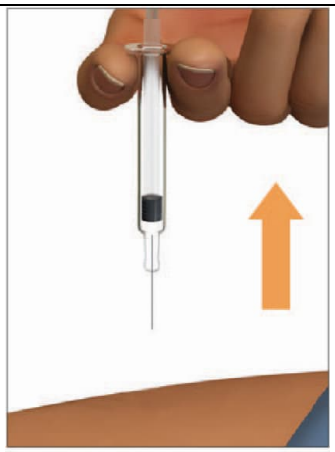


Figure H

• Slowly push the plunger all the way down until syringe is empty (See Figure I). ⚠ **Do not** take your Plegridy pre-filled syringe out of the injection site until you have pushed the plunger all the way down.	 *Figure I*
• Keep the needle inserted in for 5 seconds (see Figure J).	 *Figure J*

Step 8: Remove the pre-filled syringe from your injection site	
• Pull the needle straight out (See Figure K). ⚠ Caution - Do not recap the Plegridy pre-filled syringe. You could get a needle injury. ⚠ **Do not** reuse the Plegridy pre-filled syringe.	 *Figure K*

After your injection

Step 9: Disposing of the used Plegridy pre-filled syringe

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

Step 10: Care for your injection site

- If needed, apply a gauze pad or adhesive bandage to the injection site.

Step 11: Check your 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.

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.

General warnings

- **Do not** reuse your Plegridy pre-filled syringe.
- **Do not** share your Plegridy pre-filled syringe.
- **Keep Plegridy pre-filled syringe and all medicines out of reach of children.**

Storage

- Recommended storage is controlled refrigeration 2°C to 8°C in the closed original carton to protect from light.
- If needed, Plegridy may be stored in the closed original carton without refrigeration up to 25°C for up to 30 days.
- **Plegridy can be removed from and returned to, a refrigerator if necessary. The total combined time out of refrigeration at a temperature up to 25°C, should not exceed 30 days.**
- **Do not** freeze or expose to high temperatures.

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

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

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
- **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.

Warnings and precautions
Talk to your doctor if you have ever had:
- **Depression** or problems affecting your mood
- **Thoughts about committing suicide**
    - 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.

Talk to your doctor, pharmacist or nurse before injecting Plegridy **if you have any of the conditions listed below.** They may get worse while using Plegridy**:**
- **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 pre-filled pen*", at the end of this leaflet. This is to reduce the risk of injection site reactions.
- **Epilepsy** or other seizure disorders, not controlled by medicine
- **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

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 breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Plegridy can be used during breast-feeding.

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

Plegridy contains sodium
This medicine contains less than 1 mmol sodium (23 mg), that is to say 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 pre-filled pen*" 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 pre-filled pen*" 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
    - **Contact a 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
    - **Contact a 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 a 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.
    - **Contact a 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
    - **Contact a 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, contact a doctor.**

Flu-like symptoms
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 and continue to take paracetamol or ibuprofen for the duration of your flu-like symptoms. 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)*
- Hair loss (*alopecia*)
- 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.**

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.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

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.

- Store in the original package in order to protect from light. Only open the pack when you need a new pen.

- **Store in a refrigerator** (fridge), 2º-8ºC.
    - 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, arginine hydrochloride, polysorbate 20 and water for injections (see Section 2 “Plegridy contains Sodium”).

What Plegridy looks like and contents of the pack
Plegridy is a clear and colourless solution for injection in a glass pre-filled pen with an attached needle.

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.

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: https://www.ema.europa.eu.

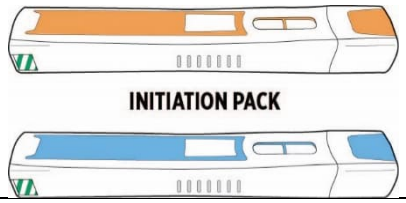
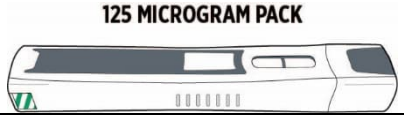
7. Instructions for injecting Plegridy pre-filled pen

⚠ **Caution! Do not** remove the cap until you are ready to inject.

How to Inject Plegridy
Read the instructions for use before you start using Plegridy and each time you get a refill of your prescription. There may be new information. This information does not take the place of talking to your doctor or nurse about your medical condition or your treatment.

Note:
- **Before you use the pen for the first time**, your doctor or nurse should show you or your carer how to prepare and inject the pen.
- The pen is for use under the skin only (subcutaneous).
- Each pen can be used once only.
- ⚠ **Do not share** the pen with anyone else to avoid giving an infection to them or getting an infection from them.
- ⚠ **Do not use more than 1** pen every 14 days (every 2 weeks).
- ⚠ **Do not** use the pen if it has been **dropped or is visibly damaged.**

Dosage schedule
The Initiation Pack contains your first two injections to gradually adjust your dose. Choose the correct pen from a pack.

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 pen per 14-day period (every 2 weeks).

Supplies needed for your Plegridy Pen injection:

- 1 Plegridy Pen (see Figure A)

Before use – Parts of Plegridy Pen (Figure A)

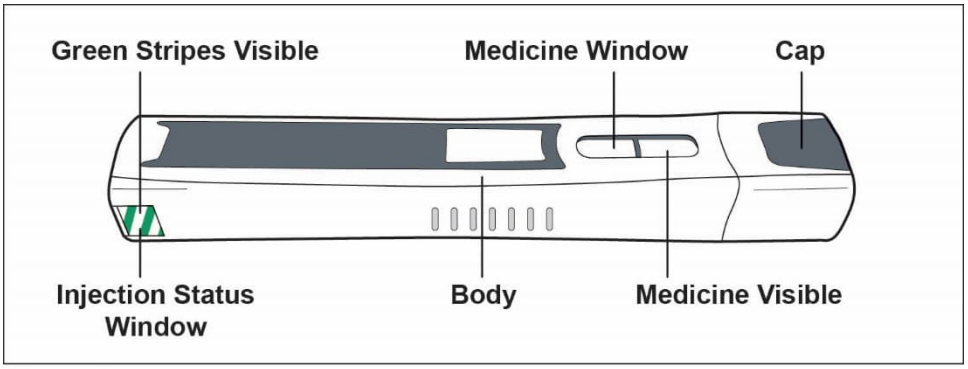


Figure A

⚠ **Caution! Do not remove the cap** until you are ready to inject. If you remove the cap, do not re-cap the pen. Re-capping could cause the pen to lock.

Additional supplies which are not included in the pack (see Figure B):

Figure B

Preparing for your injection

Step 1: Remove your pen from the fridge.

a. Remove your Plegridy pack from the fridge and select the appropriate pen (dosage) from the pack.
b. Close the pack and put back in the fridge after removing one pen.
c. **Let the pen warm to room temperature for at least 30 minutes.**
   ⚠ Do not use external heat sources, such as hot water, to warm your pen.

Step 2: Collect your supplies and wash your hands.

a. Find a well-lit, clean, flat surface to work on like a table. Collect all the supplies you will need to give yourself, or receive, an injection.
b. Wash your hands with soap and water.

Step 3: Check your Plegridy pen (see Figure C)

a. Check the injection status window. You should see green stripes.

b. Check the expiry date.

c. Check the medicine window and make sure the Plegridy medicine is clear and colourless.

⚠ **Do not** use the pen if:

- **You do not see the green stripes** in the injection status window.
- **It is expired.**
- **The liquid is coloured, cloudy or contains floating particles.**

Note: You might see air bubbles in the medicine window. This is normal and will not affect your dose.

⚠ **Do not use** the pen if it has been **dropped or is visibly damaged.**

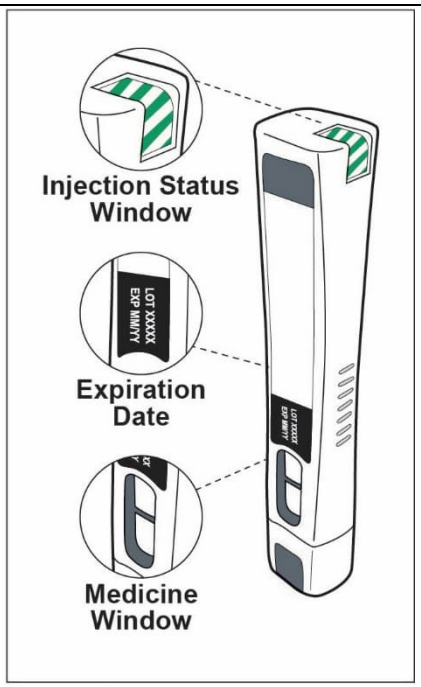


Figure C

Step 4: Choose and clean your injection site

a. Choose an injection site in your thigh, abdomen, or the back of your upper arm (see highlighted areas in Figure D).

- If some areas are too difficult for you to reach, ask a carer who has been trained to help you.

⚠ **Do not** inject into an area of your body where **the skin is irritated, red, bruised, tattooed, infected, or scarred.**

⚠ **Do not** inject directly **into your belly button.**

b. Wipe your skin with an alcohol wipe.

⚠ **Note: Do not touch or blow** on this area again before giving your injection.

c. Let your injection site dry on its own before injecting your dose.

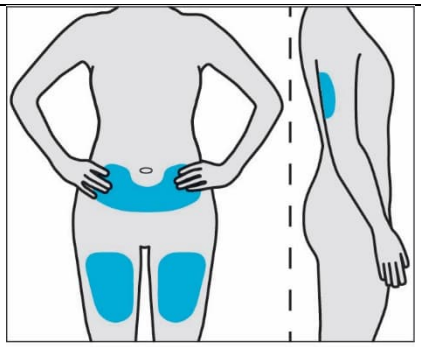


Figure D

Giving your injection

Step 5: Remove the Plegridy pen cap

a. Pull the pen cap straight off and set it aside (see Figure E). Your pen is now ready to inject.

⚠ **Warning! Do not** touch, clean, or manipulate the needle cover. You could get a needle injury or the pen may lock.

⚠ **Caution! Do not** re-cap your pen. This could lock the pen

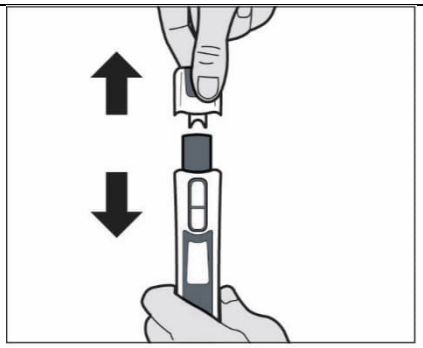


Figure E

Step 6: Give the injection

a. Hold the pen over your injection site. Make sure you can see the green stripes in the injection status window (see Figure F).

- You should hold the pen over your injection site at 90° angle.

⚠ **Warning!** Do not rest the pen on the injection site until you are ready to inject. This may cause the pen to accidently lock.

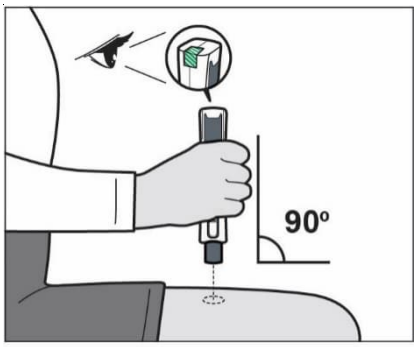


Figure F

b. Firmly press and hold down the pen on your injection site. You will hear the clicking sounds start. This tells you that the injection is happening (see Figure G).

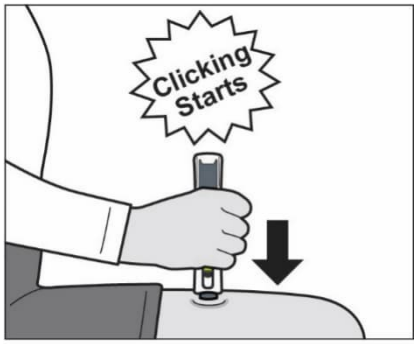


Figure G

c. Continue to hold the pen firmly down on your injection site until the clicking sounds have stopped (see Figure H).

⚠ **Do not** lift your pen off your injection site until the clicking sounds stop and you see green ticks in the injection status window.

⚠ **Warning! If you do not hear clicking sounds or you do not see green ticks** in the injection status window after attempting to inject, the pen may have locked and you may not have received your injection. You should then **contact your doctor, nurse or pharmacist.**

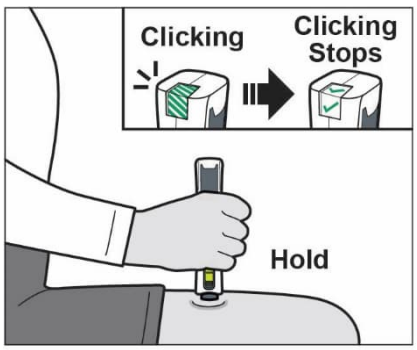


Figure H

Step 7: Remove the Plegridy pen from your injection site

a. After the clicking sound has stopped, lift the pen from your injection site. The needle cover will extend to cover the needle and will lock (see Figure I).
   - If you see blood at your injection site, wipe it off with the gauze pad and apply an adhesive bandage or plaster

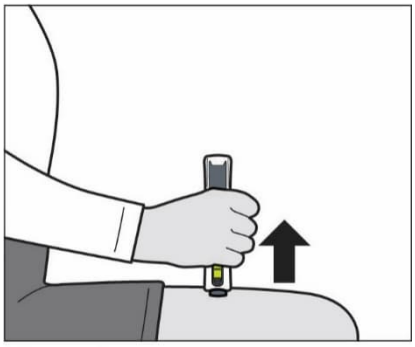


Figure I

Step 8: Check to make sure you received your full dose of Plegridy (see Figure J)

a. Check the injection status window. You should see green ticks.
b. Check the medicine window. You should see a yellow plunger.

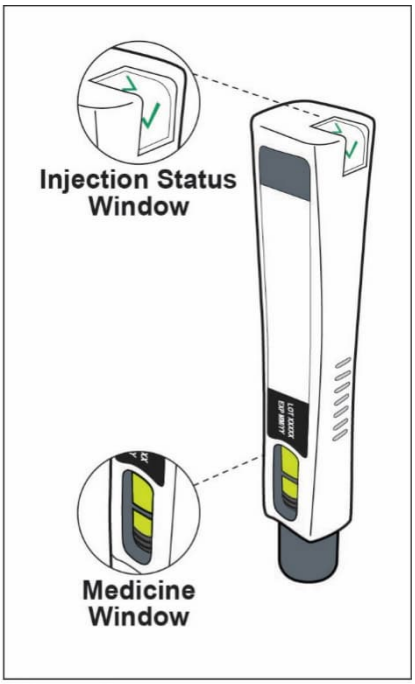


Figure J

After the injection

After Use – Parts of your Plegridy pen (see Figure K):

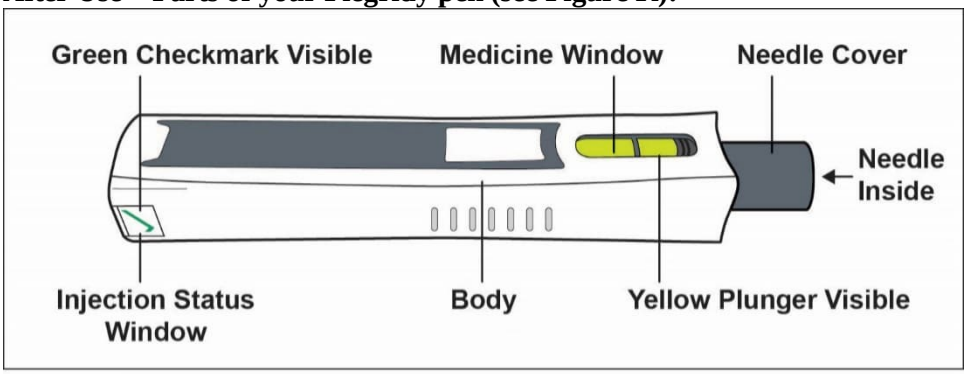


Figure K

Note: After the pen has been removed from the injection site, the needle cover will lock to protect against needle injury. **Do not re-cap the pen.**

Step 9: Dispose of used Plegridy pen

- Check with your doctor, pharmacist or nurse about the right way to throw away the used pen.
- ⚠ **Do not re-cap the pen.**

Step 10: Care for your injection site

- If needed, apply a gauze pad or adhesive bandage or plaster to the injection site.

Step 11: 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.

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.

General warnings

- ⚠ Do not reuse your Plegridy pen.
- ⚠ Do not share your Plegridy pen.
- **Keep Plegridy pen and all medicines out of reach of children.**

Storage

- Recommended storage is controlled refrigeration 2°C to 8°C in the closed original carton to protect from light.
- If needed, Plegridy may be stored in the closed original carton without refrigeration up to 25°C for up to 30 days.
- **Plegridy can be removed from and returned to the refrigerator if necessary. The total combined time out of refrigeration at a temperature up to 25°C, should not exceed 30 days.**
- ⚠ **Do not** freeze or expose to high temperatures.

Package leaflet: Information for the user

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

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

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 years 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
- **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.

Warnings and precautions
Talk to your doctor if you have ever had:
- **Depression** or problems affecting your mood
- **Thoughts about committing suicide**
    - 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.

Talk to your doctor, pharmacist or nurse before injecting Plegridy **if you have any of the conditions listed below.** They may get worse while using Plegridy**:**
- **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 pre-filled syringe*", at the end of this leaflet. This is to reduce the risk of injection site reactions.
- **Epilepsy** or other seizure disorders, not controlled by medicine
- **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

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.
- 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 breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Plegridy can be used during breast-feeding.

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

Plegridy contains sodium
This medicine contains less than 1 mmol sodium (23 mg), that is to say 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 for intramuscular use
If you are new to Plegridy, your doctor **may advise you to gradually increase your dose** during the first month of treatment. This means that your body can adjust to the effects of Plegridy before getting the full dose.

The full dose from the Plegridy intramuscular pre-filled syringe is 125 micrograms. Plegridy Titration Clips can be attached to the syringe so that you can gradually increase your dose:

Dose 1 on day 0:
1/2 dose (63 micrograms) with YELLOW titration clip

Dose 2 on day 14:
3/4 dose (94 micrograms) with PURPLE titration clip

Dose 3 on day 28 and then every 2 weeks:
full dose (125 micrograms) – NO titration clip needed

Plegridy supplied in this pack is meant for injection into your thigh muscle.

Read the instructions in section 7 "*Instructions for injecting Plegridy pre-filled syringe*" at the end of this leaflet before you start using Plegridy.

Check with your doctor nurse or pharmacist if you are unsure how you should inject your medicine.

Intramuscular is abbreviated as IM on the syringe label.

Injecting yourself
Plegridy is to be injected into the thigh muscle (*intramuscular 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 pre-filled syringe*" 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
    - **Contact a 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
    - **Contact a 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 a 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.
    - **Contact a 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
    - **Contact a 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, contact a doctor.**

Flu-like symptoms
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 and continue to take paracetamol or ibuprofen for the duration of your flu-like symptoms. 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)*
- Hair loss (*alopecia*)
- 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, contact a 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, contact a doctor.**

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.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

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.

- Store in the original package in order to protect from light. Only open the pack when you need a new syringe.

- **Store in a refrigerator** (fridge) 2 º-8 ºC.
    - 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 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, arginine hydrochloride, polysorbate 20 and water for injections (see Section 2 “Plegridy contains sodium”).

What Plegridy looks like and contents of the pack
Plegridy is a clear and colourless solution for injection in a glass pre-filled syringe supplied with a needle.

Pack sizes:
- The syringes are provided in a pack containing either two or six pre-filled syringes with 23 gauge, 1.25 inch long sterile needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
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The Netherlands

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Biogen Netherlands B.V.
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Other sources of information

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

7. Instructions for injecting Plegridy pre-filled syringe

How to inject Plegridy

Read the instructions for use before you start using Plegridy pre-filled syringe. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Supplies you will need for the Plegridy injection:

- 1 Plegridy Administration Dose Pack that contains:
    - 1 Plegridy pre-filled syringe
    - 23 gauge, 1.25 inch long sterile needle
- a puncture resistant container for disposal of used syringes and needles
- **Additional supplies which are not included in the pack:**
    - Alcohol wipe
    - Gauze pad
    - Adhesive bandage

If you are new to Plegridy your dose may be titrated over 2 injections by using the syringe with the Plegridy titration kit.

o Dose 1:
½ dose (yellow titration clip) **(not supplied as part of the pack)**

o Dose 2:
¾ dose (purple titration clip) **(not supplied as part of the pack)**

o Dose 3:
a full dose (no clip required)

• The Plegridy titration clips are for single use only with the Plegridy pre-filled syringe. Do not re-use the syringe or titration clips.

• You must prepare the Plegridy pre-filled syringe and needle before you put it into the Plegridy titration clip

Preparing the dose of Plegridy:

- Find a well-lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or receive an injection.
- Take 1 Plegridy pre-filled syringe out of the refrigerator about 30 minutes before you plan on injecting the Plegridy dose to allow it to reach room temperature. **Do not** use external heat sources such as hot water to warm the Plegridy pre-filled syringe.
- Check the expiration date printed on syringe label, lid and outer carton. **Do not** use Plegridy pre-filled syringe past the expiration date.
- Wash your hands with soap and water.

Preparing the Plegridy injection:

Step 1: Check the syringe (See Figure A):

- The syringe should not have any cracks or damage.
- Check that the cap is intact and has not been removed.
- Plegridy should look clear, colorless, and should not have any particles in it.

- **Do not** use the Plegridy pre-filled syringe if:
  - the syringe is cracked or damaged
  - the solution is cloudy, colored, or has lumps or particles in it
  - the cap has been removed or is not tightly attached

Do not use that syringe if you see any of the above. Get a new syringe.

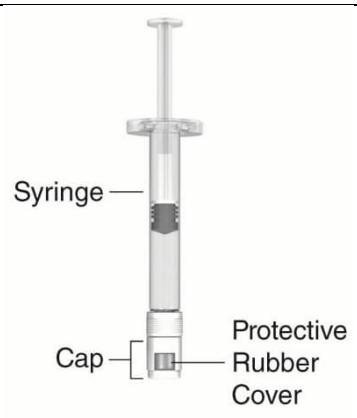
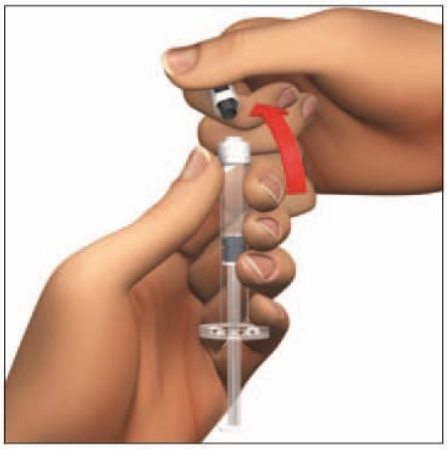
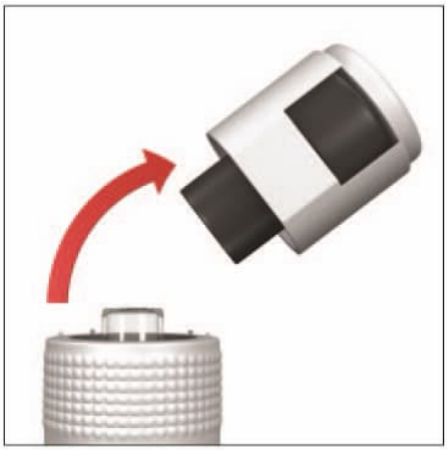
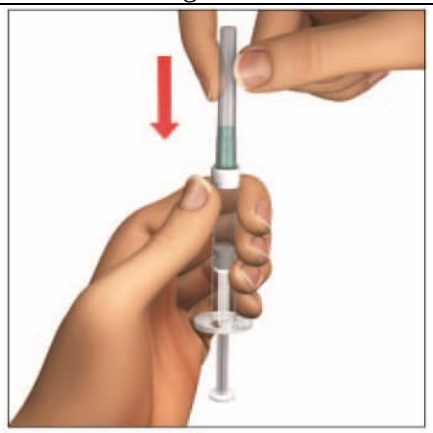


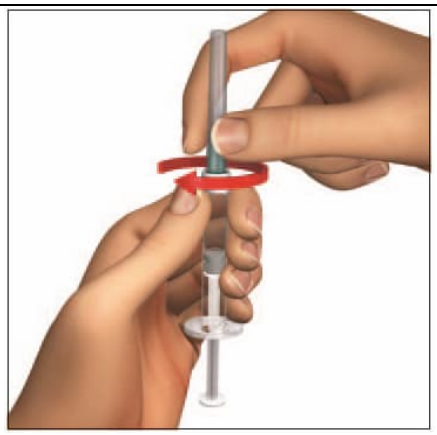
Figure A

Step 2: With 1 hand, hold the syringe right under the cap and with the cap pointing up (See Figure B).

- Make sure you are holding the syringe by the ridged part, directly under the cap.

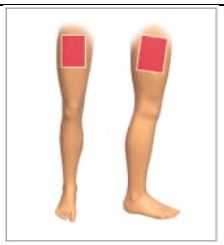
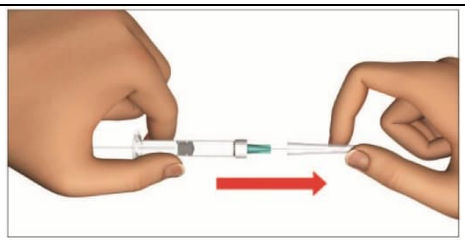
Figure B

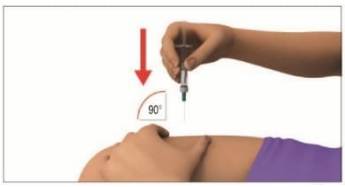
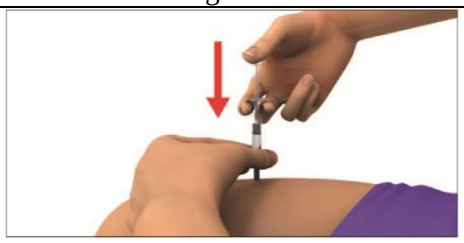
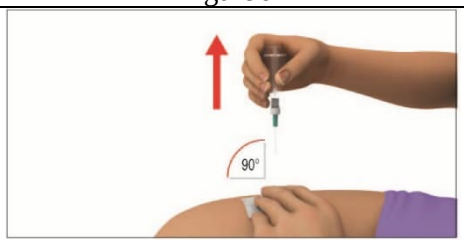
Step 3: With the other hand, grasp the cap and bend it at a 90º angle until the cap snaps off (See Figure C).	 Figure C
This will expose the syringe glass tip (See Figure D).	 Figure D
Step 4: Open the single use sterile needle package and take out the covered needle. Hold the syringe with the glass syringe tip pointing up. Press the needle on the syringe glass tip (See Figure E).	 Figure E

Step 5: Gently turn the needle forward (clockwise) until it is tight and firmly attached (See Figure F). • If the needle is not firmly attached, the syringe may leak and you may not get your full dose of Plegridy. • **Do not** remove the plastic cover from the needle.	 Figure F

Giving the Plegridy injection:

- Your healthcare provider should show you or a caregiver how to prepare and inject the dose of Plegridy before a syringe is used for the first time. Your healthcare provider or nurse should watch you inject the dose of Plegridy the first time the syringe is used.
- Inject your Plegridy exactly as your healthcare provider has shown you.
- Plegridy is injected into the muscle (intramuscularly).
- Plegridy should be injected into the thigh (See Figure G).
- Change (rotate) your injection sites for each dose. **Do not** use the same injection site for each injection.
- **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.

Step 6: Choose either your left or right thigh and wipe the skin with an alcohol wipe (See Figure G). Let the injection site dry before injecting the dose. • **Do not** touch, blow or wipe this area again before giving the injection.	 Figure G
Step 7: Pull the protective cover straight off the needle (See Figure H). **Do not** twist the cover off.	 Figure H

Step 8: With 1 hand, stretch the skin out around the injection site. With the other hand, hold the syringe like a pencil. Use a quick dart-like motion and insert the needle at a 90 ° degree angle, through the skin and into the muscle (See Figure I). Once the needle is in, let go of the skin.	 Figure I
Step 9: Slowly push the plunger down until the syringe is empty (See Figure J).	 Figure J
Step 10: Pull the needle out of the skin (See Figure K). Press down on the injection site with the gauze pad for a few seconds or rub gently in a circular motion. • If you see blood after you press the injection site for a few seconds, wipe it off with gauze pad • and apply an adhesive bandage.	 Figure K

After the Plegridy injection:

- **Do not** recap the needle. Recapping the needle can lead to a needle stick injury.
- Throw away the used syringes and needles in a sharps container or some type of hard plastic or metal container with a screw cap such as a detergent bottle or coffee can. Check with your healthcare provider about the right way to throw away the container. There may be local or state laws about how to throw away used syringes and needles. **Do not** throw away used syringes and needles in household trash or recycling bins.
- Plegridy may commonly cause redness, pain, or swelling of your skin at the injection site.
- Call your healthcare provider right away if your injection site becomes swollen and painful or the area looks infected and does not heal within a few days.

General information about the safe and effective use of Plegridy

- Always use a new syringe and needle for each injection. **Do not** re-use your Plegridy syringe or needles.
- **Do not** share your syringe or needles.