

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrPLEGRIDY™

peginterferon beta-1a

Liquid for injection

Immunomodulator

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RECENT MAJOR LABEL CHANGES

7.1.1 Pregnant Women	05/2020
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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PLEGRIDY™ (peginterferon beta-1a) is indicated for:

- treatment of relapsing remitting multiple sclerosis (RRMS) for adult patients
 - to reduce the frequency of clinical exacerbations
 - to slow the progression of disability.

The safety and efficacy of PLEGRIDY™ have not been established in patients with primary and secondary progressive multiple sclerosis.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of PLEGRIDY™ in patients below 18 years of age has not been studied (see [7 WARNINGS AND PRECAUTIONS, Special Populations](#)).

1.2 Geriatrics

Geriatrics (> 65 years of age): The safety and efficacy of PLEGRIDY™ in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials. Refer to [7 WARNINGS and PRECAUTIONS, Special population](#).

2 CONTRAINDICATIONS

PLEGRIDY™ (peginterferon beta-1a) is contraindicated in:

- patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon
- patients with a history of hypersensitivity to, any other component of the formulation or the container.
- Patients with current severe depression and/or suicidal ideation (see [7 WARNINGS and PRECAUTIONS](#)).

For a complete listing, see the [6 DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING](#) section of the product monograph.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Intended for use under the guidance and supervision of a physician.
- Patients may self-inject only:
 - If their physician determines that it is appropriate.
 - Appropriate medical follow-up is provided.

- After proper training in SC injection technique for either PLEGRIDY™ PS/PLEGRIDY™ PEN.
- Injection sites should be rotated. The usual sites for subcutaneous injections include thigh, abdomen, and upper arm. Avoid injection into an area of skin that is sore, red, infected or otherwise damaged.
- Before initiating a patient on PLEGRIDY™ PS/PLEGRIDY™ PEN therapy, note the Contraindications.
- Review the [7 WARNINGS AND PRECAUTIONS](#) section and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential.
- Patients should be advised of the side-effects of PLEGRIDY™ PS/PLEGRIDY™ PEN and instructed on the use of aseptic technique when administering PLEGRIDY PS/PLEGRIDY PEN. The [Patient Medication Information](#) should be carefully reviewed with all patients, and patients should be educated on self-care and advised to continue to refer to Part III during treatment with PLEGRIDY™ PS/PLEGRIDY™ PEN.

4.2 Recommended Dose and Dosage Adjustment

PLEGRIDY™ (peginterferon beta-1a) is administered subcutaneously using a single-use, pre-filled syringe/pen.

The recommended dosage of PLEGRIDY™ is 125 micrograms injected subcutaneously every 2 weeks.

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (on day 0) increasing to 94 micrograms at dose 2 (on day 14) reaching the full dose of 125 micrograms by dose 3 (on day 28) and continuing with the full dose (125 micrograms) every 14 days (2 weeks) thereafter ([Table 1](#)).

Table 1 – Titration Schedule at Initiation

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

* Dosed once 14 days (2 weeks)

A Starter Pack is available containing the first 2 doses, 63 micrograms (dose 1, orange labeled syringe/pen) and 94 micrograms (dose 2, blue labeled syringe/pen) for day 0 and day 14 respectively. Patients should use the Administration Dose Pack containing the full dose of 125 micrograms (full dose, grey labeled syringe/pen) from day 28 onwards (dosing every 14, days).

Pediatrics

Health Canada has not authorized an indication for pediatric use.

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.

4.4 Administration

- It is recommended that a health care professional trains patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe/pen. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections include thigh, abdomen, and upper arm.
- Each PLEGRIDY™ pre-filled syringe/pen is provided with the needle pre-attached. Pre-filled syringes/pens are for single use only and should be discarded after use. 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 analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment.

4.5 Missed Dose

If a dose of PLEGRIDY™ is missed, it should be administered as soon as possible:

- If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.
- If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose.

A patient should not administer two doses of PLEGRIDY™ within 7 days of each other.

5 OVERDOSAGE

No case of overdose has been reported. In case of over dosage, appropriate supportive treatment should be given.

In case of overdose with PLEGRIDY™, the patient should be advised to seek medical attention.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

PLEGRIDY™ (peginterferon beta-1a) is available in the following presentations:

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Pre-filled Syringe, 63 µg or 94 µg or 125 µg peginterferon beta-1a per 1 mL, Sterile Clear Liquid for Injection	Sodium Acetate Trihydrate USP, Ph.Eur, Glacial Acetic Acid USP, Ph.Eur, L-Arginine Hydrochloride USP, Ph.Eur, and Polysorbate 20 USP, Ph.Eur in Water for Injection, USP, Ph.Eur
Subcutaneous	Autoinjector Pen, 63 µg or	Sodium Acetate Trihydrate USP, Ph.Eur, Glacial

	94 µg or 125 µg peginterferon beta-1a per 0.5 mL, Sterile Clear Liquid for Injection	Acetic Acid USP, Ph.Eur, L-Arginine Hydrochloride USP, Ph.Eur, and Polysorbate 20 USP, Ph.Eur in Water for Injection, USP, Ph.Eur
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Packaging and Pack Size(s)

Pre-filled syringe

PLEGRIDY™ (peginterferon beta-1a) is formulated as a sterile clear liquid for subcutaneous injection. Each unit of PLEGRIDY is stored in a 1mL Type I glass syringe with a latex free bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single pre-filled syringe contains 0.5mL of solution of PLEGRIDY™ containing 63 micrograms, 94, micrograms or 125 micrograms of peginterferon beta-1a.

Pre-filled pen

The single pre-filled syringe contains 0.5mL of solution of PLEGRIDY™ containing 63 micrograms, 94 micrograms, or 125 micrograms of peginterferon beta-1a. The glass syringe is contained within a single-use, disposable, injection device (pre-filled pen).

Description

The interferon beta-1a portion of PLEGRIDY™ is produced as a glycosylated protein using genetically-engineered Chinese hamster ovary cells into which the human beta interferon gene has been introduced. The amino acid sequence of the recombinant interferon beta-1a is identical to that of natural human beta interferon. The molecular mass of PLEGRIDY™ is approximately 44,000 Da, consistent with the mass of the protein (approximately 20,000 Da), the carbohydrate moiety (approximately 2,500 Da), and the attached poly(ethylene glycol). However, due to the extended and flexible nature of the attached poly(ethylene glycol) chain, the apparent mass of PLEGRIDY™ in solution is greater than 300,000 Da. The more than 10-fold increase in apparent mass of PLEGRIDY™ compared to interferon beta-1a has been shown to contribute to the reduced clearance in vivo.

PLEGRIDY™ 125 micrograms contains 125 micrograms of interferon beta-1a plus 125 micrograms of poly(ethylene glycol). Using the World Health Organization International Standard for beta interferon, PLEGRIDY™ has a specific antiviral activity of approximately 100 million International Units (MIU) per mg of protein as determined using an in vitro cytopathic effect assay. PLEGRIDY™ 125 micrograms contains approximately 12 MIU of antiviral activity.

7 WARNINGS AND PRECAUTIONS

General

PLEGRIDY™ (peginterferon beta-1a) should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional (see [4 DOSAGE AND ADMINISTRATION](#)).

Patients should be informed of the following information:

- The most common adverse events associated with interferon beta administration, including symptoms of the flu-like syndrome (see [8 ADVERSE REACTIONS](#)). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment. Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Concurrent use of analgesics and/or antipyretics may help reduce flu-like symptoms on treatment days.
- Immediately report any symptoms of depression and/or suicidal ideation.
- The risk of decreased blood counts including white blood cells and platelet counts and of the requirement for periodic laboratory testing. Patients should be advised to report immediately any clinical symptoms associated with blood cell count abnormalities and laboratory testing should be performed according to standard medical practice. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.
- The potential risk of liver injury with interferon beta therapy, and of the requirement for frequent laboratory testing. Patients should be informed of the symptoms of suggestive liver dysfunction, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, and jaundice, and advised to consult with their physician immediately should such symptoms arise.
- To report any symptoms of thyroid dysfunction (hypo or hyperthyroidism) and thyroid function tests should be performed according to standard medical practice.
- Female patients should be advised about the abortifacient potential of PLEGRIDY™ and instructed to take adequate contraceptive measures. Patients should be advised to discuss with their health care provider the potential risks and benefits of continued treatment while attempting to conceive. It is not known if interferons alter the efficacy of hormonal contraceptives.
- When a physician determines that PLEGRIDY PS/PLEGRIDY PEN can be used outside the physician's office, persons who will be administering PLEGRIDY PS/PLEGRIDY PEN should receive instruction in reconstitution and/or injection, including the review of the injection procedures (see [PATIENT MEDICATION INFORMATION](#)). If a patient is to self-administer, the physical ability of the patient to self-inject subcutaneously should be assessed. If home use is chosen, the first injection should be performed under the supervision of a qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of injection site reactions. A puncture-resistant container for disposal of needles, syringes and autoinjectors should be used. Patients should be instructed in the technique and importance of proper syringe, needle and autoinjector disposal and be cautioned against reuse of these items.
- Thrombotic microangiopathy (TMA): Cases of thrombotic microangiopathy, 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 after 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. If clinical features of TMA are observed, testing of blood platelet levels, serum lactate dehydrogenase (LDH), schistocytes (erythrocyte fragmentation) on a blood film with negative Coombs test and renal function is recommended. Prompt treatment of TTP/HUS is required and immediate discontinuation of treatment with PLEGRIDY™ is recommended.

Carcinogenesis and Mutagenesis

No carcinogenicity data for interferon beta-1a are available in animals or humans.

Interferon beta-1a was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation.

Cardiovascular

Worsening of cardiac disease has been reported in patients receiving interferon beta. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia should be monitored for worsening of their cardiac condition, particularly during initiation of treatment (see [8 ADVERSE REACTIONS](#)).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed.

Endocrine and Metabolism

Endocrine Disorders: hyperthyroidism

Metabolism and Nutrition Disorders: hypercholesterolaemia, vitamin B12 deficiency, vitamin D deficiency, hypernatraemia, hypoglycaemia, hypokalaemia, increased appetite, malnutrition

Hematologic

Decreased Peripheral Blood Counts:

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with PLEGRIDY™. Patients should be monitored for symptoms or signs of decreased peripheral blood counts (see [8 ADVERSE REACTIONS](#)).

Hepatic/Biliary/Pancreatic

Severe hepatic injury, including elevated serum hepatic transaminase levels, hepatitis, and autoimmune hepatitis, and rare cases of severe hepatic failure, has been reported with interferon beta. Elevations in hepatic enzymes, noninfectious hepatitis and hepatic injury have been observed with the use of PLEGRIDY™. Patients should be monitored for signs and symptoms of hepatic injury. (see [8 ADVERSE REACTIONS](#)). Treatment with PLEGRIDY™ should be stopped if icterus or other clinical symptoms of hepatic dysfunction appear.

Patients with Hepatic Impairment: Caution should be used and close monitoring considered when administering PLEGRIDY™ to patients with severe hepatic impairment. Patients should be monitored

for signs of hepatic injury and caution exercised when interferons are used concomitantly with other drugs associated with hepatic injury. (see [8 ADVERSE REACTIONS](#) and [10.3 Pharmacokinetics](#))

Immune

Patients may develop antibodies to PLEGRIDY™. Data from patients treated up to 2 years with PLEGRIDY™ suggests that less than 1% (5/715) developed persistent-neutralising antibodies to the interferon beta-1a portion of peginterferon beta-1a. Neutralising antibodies have the potential to reduce clinical efficacy. There were 3% of patients (18/681) that developed persistent antibodies to the PEG moiety of peginterferon beta-1a.

Injection Site Reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. One patient treated with PLEGRIDY™ in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see [8 ADVERSE REACTIONS](#)).

Monitoring and Laboratory Tests

Laboratory abnormalities are associated with the use of interferons. Complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests, are recommended during PLEGRIDY™ therapy. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Neurologic

Seizures:

Seizures have been associated with the use of interferon beta. Caution should be exercised when administering PLEGRIDY™ to patients with pre-existing seizure disorder (see [8 ADVERSE REACTIONS](#)).

Psychiatric

Depression and Suicide: Depression and suicidal ideation have been reported to occur with increased frequency in patients receiving interferon beta. If a patient develops depression or other severe psychiatric symptoms, cessation of PLEGRIDY™ therapy should be considered (see [8 ADVERSE REACTIONS](#)).

Sensitivity/Resistance

Anaphylactic and Hypersensitivity reactions

Serious hypersensitivity reactions, including cases of anaphylaxis, have been reported as a rare complication of treatment with interferon beta, including PLEGRIDY™. Discontinue PLEGRIDY™. Patients should be advised to discontinue PLEGRIDY™ and seek immediate medical care if they experience signs and symptoms of anaphylaxis or severe hypersensitivity. Treatment should not be restarted (see [8 ADVERSE REACTIONS](#)).

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women:

There are no adequate and well-controlled studies of peginterferon beta1-a in pregnant women. The

administration of PLEGRIDY™ during confirmed pregnancy should be avoided, unless clearly needed.

A European registry study collected data on 948 prospective pregnancies in women with MS who were treated with one of five interferon beta medications. There were few patients (n=51) that were exposed to PLEGRIDY™, the only pegylated form of interferon beta, in this registry. The rates of aggregated adverse pregnancy outcomes were in line with reference ranges published in the literature. It is unknown if the safety profile in pregnancy of pegylated interferon beta is different from non-pegylated formulations.

Data from a retrospective register-based study in Sweden and Finland have not indicated an increased risk of major congenital anomalies after early pregnancy exposure to drugs in the interferon beta class.

In the studies discussed above, the duration of exposure during the first trimester was uncertain since data were collected when interferon beta use was contraindicated during pregnancy, and treatment was interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health.

PLEGRIDY™ has not been tested for developmental toxicity in pregnant animals; it is not known if PLEGRIDY™ is teratogenic. Administration of PLEGRIDY to mature female rhesus monkeys resulted in menstrual irregularities accompanied by decreases in serum progesterone and 17-beta estradiol. These effects are consistent with the abortifacient effects of non-pegylated type I interferons.

The risk of spontaneous abortions in pregnant women exposed to peginterferon beta cannot be evaluated based on the currently available data.

7.1.2 Breast-feeding

Limited information available from published literature on the transfer of interferon beta-1a/peginterferon beta-1a into breast milk suggests that levels of interferon beta-1a excreted in human milk are low. A risk to the nursing infant cannot be excluded.

The benefit and potential risk of breastfeeding should be considered along with the patient's medical need for interferon beta-1a therapy.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): There were 6 (<1%) patients age 60-65, with no patients ages 65 and over in the clinical trial 105MS301 at baseline.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse drug reactions for PLEGRIDY™ 125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia. Multiple sclerosis relapse was the most

frequent serious adverse event (7% PLEGRIDY™ every 2 weeks vs. 11% placebo). The most commonly reported adverse events leading to discontinuation in patients treated with PLEGRIDY™ 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of PLEGRIDY™ (peginterferon beta-1a) is based on the assessment of data from one pivotal phase III, randomized, double-blind, parallel-group clinical trial (study 105MS301). This study was composed of a 1-year placebo-controlled treatment period, followed by a second year of treatment during which all patients received PLEGRIDY™. The first year of the study explored a single dose of PLEGRIDY™ 125 micrograms SC administered with 2 dosing frequencies (dosing every 2 or every 4 weeks) as compared to placebo. The second year of the study explored a single dose of PLEGRIDY™ 125 micrograms SC administered either every 2 weeks or every 4 weeks.

Table 3 summarizes adverse drug reactions reported from 512 patients treated with PLEGRIDY™ 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 1 year.

A total of 512 and 500 patients received PLEGRIDY™ 125 micrograms every 2 weeks or every 4 weeks, respectively, during the placebo-controlled phase of the 105MS301 study, in Year 1. In Year 2 of the 105MS301 study, the 500 patients who had received placebo during Year 1 were re-randomized to receive PLEGRIDY™ 125 micrograms every 2 weeks or every 4 weeks; patients who had received PLEGRIDY™ every 2 weeks or every 4 weeks in Year 1 continued on their randomized treatment through Year 2. Patients who enrolled in the 105MS302 extension study remained on their 105MS301 Year 2 treatment (PLEGRIDY™ every 2 weeks or every 4 weeks). In an analysis integrating interim data from the 105MS301 study and the extension study, 105MS302, a total of 1468 patients with relapsing multiple sclerosis received PLEGRIDY for up to 278 weeks (65 months), with an overall exposure equivalent to 4217 person-years. A total of 1285 patients received at least 1 year, 1124 patients received at least 2 years, 947 patients received at least 3 years, and 658 patients received at least 4 years of treatment with PLEGRIDY™. The mean exposure to treatment in the extension study alone was 106 weeks with a range of 2-182 weeks.

The experience in Year 2 of the 105MS301 study and in the extension study 105MS302 was consistent with the experience in the 1-year placebo-controlled phase of the 105MS301 study.

The adverse reactions are presented as MedDRA preferred terms under the MedDRA system organ class (SOC) (MedDRA Version 15.0).

Table 3 – Adverse Reactions reported for PLEGRIDY™ 125 micrograms subcutaneously every 2 weeks at > 1% higher incidence than placebo

	Placebo n = 500 (%)	PLEGRIDY™ n = 512 (%)	PLEGRIDY™ Frequency category*	
			Very Common (≥1/10)	Common (≥1/100 - <1/10)
Infections and Infestations				
Upper respiratory tract infection	27 (5%)	29 (6%)		Common
Urinary tract infection	21 (4%)	28 (5%)		Common
Oral Herpes	7 (1%)	12 (2%)		Common
Cystitis	2 (<1%)	9 (2%)		Common
Psychiatric Disorders				
Insomnia	19 (4%)	28 (5%)		Common
Anxiety	12 (2%)	13 (3%)		Common
Nervous System Disorders				
Headache	165 (33%)	244 (44%)	Very Common	
Dizziness	31 (6%)	35 (7%)		Common
Somnolence	5 (1%)	10 (2%)		Common
Balance disorder	7 (1%)	9 (2%)		Common
Tremor	6 (1%)	9 (2%)		Common
Dysgeusia	0	6 (1%)		Common
Gastrointestinal disorders				
Nausea	31 (6%)	44 (9%)		Common
Vomiting	11 (2%)	26 (5%)		Common
Abdominal Pain	10 (2%)	16 (3%)		Common
Toothache	11 (2%)	16 (3%)		Common
Eye Disorders				
Visual Impairment	5 (1%)	9 (2%)		Common
Vascular Disorder				
Hypertension	10 (2%)	14 (3%)		Common
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal disorders	31 (6%)	34 (7%)		Common
Musculoskeletal and Connective Tissue Disorders				
Myalgia	30 (6%)	97 (19%)	Very Common	
Back Pain	57 (11%)	61 (12%)	Very Common	
Arthralgia	35 (7%)	57 (11%)	Very Common	
Musculoskeletal stiffness	9 (2%)	15 (3%)		Common
Bone Pain	1 (<1%)	11 (2%)		Common

	Placebo n = 500 (%)	PLEGRIDY™ n = 512 (%)	PLEGRIDY™ Frequency category*	
			Very Common (≥1/10)	Common (≥1/100 - <1/10)
General Disorders and Administration Site Conditions				
Injection site erythema	33 (7%)	315 (62%)	Very Common	
Influenza like illness	63 (13%)	239 (47%)	Very Common	
Pyrexia	76 (15%)	228 (45%)	Very Common	
Chills	23 (5%)	88 (17%)	Very Common	
Injection site pain	15 (3%)	77 (15%)	Very Common	
Asthenia	38 (8%)	68 (13%)	Very Common	
Injection site pruritis	6 (1%)	68 (13%)	Very Common	
Hyperthermia	6 (1%)	21 (4%)		Common
Pain	16 (3%)	25 (5%)		Common
Injection site oedema	0	15 (3%)		Common
Injection site warmth	0	16 (3%)		Common
Injection site hematoma	7 (1%)	15 (3%)		Common
Feeling cold	2 (<1%)	9 (2%)		Common
Injection site swelling	1 (<1%)	9 (2%)		Common
Injection site inflammation	0	7 (1%)		Common
Injection site rash	0	8 (2%)		Common
Injection site reaction	0	6 (1%)		Common
Investigations				
Body temperature increased	14 (3%)	31 (6%)		Common
Alanine aminotransferase increased	13 (3%)	29 (6%)		Common
Aspartate aminotransferase increased	8 (2%)	18 (4%)		Common
Gamma-glutamyl-transferase increased	7 (1%)	15 (3%)		Common
Blood glucose increased	4 (<4%)	10 (2%)		Common
Haemoglobin decreased	3 (<1%)	10 (2%)		Common
Skin and Subcutaneous Tissue Disorder				
Pruritus	6 (1%)	19 (4%)		Common
Alopecia	6 (1%)	8 (2%)		Common
Erythema	1 (<1%)	8 (2%)		Common

* ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10); Uncommon (≥1/1,000 - <1/100); Rare (≥1/10,000 - <1/1,000); Very Rare (<1/10,000)

Flu Like Symptoms

Influenza-like illness was experienced by 47% of patients receiving PLEGRIDY™ 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest during the initiation of treatment and generally decreased over the first 6 months.

Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received PLEGRIDY™ during the placebo controlled phase of 105MS301 discontinued treatment due to flu-like symptoms.

Injection Site Reactions

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

Hepatic Transaminase Abnormalities

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

Hematological Disorders

Decreases in white blood cell counts of $<3.0 \times 10^9/L$ were observed in 7% of patients receiving PLEGRIDY™ and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with PLEGRIDY™. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts ($<0.5 \times 10^9/L$) (<1%), neutrophil ($\leq 1.0 \times 10^9/L$) (<1%) counts, platelet counts ($\leq 100 \times 10^9/L$) ($\leq 1\%$) was similar in PLEGRIDY™-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with PLEGRIDY™: one patient (<1%) experienced severe thrombocytopenia (platelet count $<10 \times 10^9/L$), another patient (<1%) experienced severe neutropenia (neutrophil count $<0.5 \times 10^9/L$). In both patients, cell counts recovered after discontinuation of PLEGRIDY™. Compared to placebo, there were no significant differences observed in red blood cell counts in PLEGRIDY™ treated patients.

Hypersensitivity reactions

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

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both PLEGRIDY™ 125 micrograms every 2 weeks and placebo groups. The incidence of serious events

related to depression and suicidal ideation were similar and low (<1%) in both PLEGRIDY™ 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

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

Cardiovascular disorders

The incidence of cardiovascular events was similar between PLEGRIDY™ (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received PLEGRIDY™ in the 105MS301 study.

8.3 Less Common Clinical Trial Adverse Reactions

Infections and Infestations: laryngitis, conjunctivitis infective, tonsillitis, ear infection, furuncle, otitis externa, vulvovaginal candidiasis, dengue fever, fungal infection, gastric infection, pulpitis dental, salpingo-oophoritis, tooth infection, tracheitis, viral pharyngitis, abscess oral, conjunctivitis viral, cytomegalovirus infection, erysipelas, Escherichia urinary tract infection, eye infection viral, eyelid infection, folliculitis, fungal skin infection, gastrointestinal viral infection, genital candidiasis, gingival abscess, helicobacter gastritis, helicobacter infection, herpes simplex, herpes virus infection, hordeolum, incision site infection, infected bites, infection, infection parasitic, infectious mononucleosis, injection site cellulitis, mastoiditis, mumps, orchitis, otitis media acute, rash pustular, sepsis, septic shock, sinusitis bacterial, tinea cruris, tinea pedis, tonsillitis bacterial, ureaplasma infection, urosepsis, vaginitis bacterial, vulvitis, wound infection.

Neoplasms Benign Malignant and Unspecified (including cysts and polyps): benign vulval neoplasm, breast cancer, cervix carcinoma, lipoma, uterine leiomyoma, vulvovaginal human papilloma virus infection

Blood and Lymphatic System Disorders: lymphadenopathy, lymphadenitis, thrombocytopenia, thrombocytosis, febrile neutropenia, hypercoagulation, leukopenia, lymph node pain, lymphadenopathy mediastinal, lymphoid tissue hyperplasia, normochromatic normocytic anaemia, polychromasia.

Immune System Disorders: drug hypersensitivity, anaphylactic reaction, house dust allergy, hypersensitivity

Endocrine Disorders: hyperthyroidism

Metabolism and Nutrition Disorders: hypercholesterolaemia, vitamin B12 deficiency, vitamin D deficiency, hypernatraemia, hypoglycaemia, hypokalaemia, increased appetite, malnutrition

Psychiatric Disorders: nervousness, affect lability, mood altered, suicidal ideation, anxiety disorder, confusional state, panic attack, bradyphrenia, dysphoria, dyssomnia, emotional disorder, initial insomnia, mood disorder due to a general medical condition, personality disorder, TIC.

Nervous System Disorders: syncope, memory impairment, dysgeusia, hyperaesthesia, trigeminal neuralgia, ataxia, multiple sclerosis, sinus headache, monoparesis, speech disorder, carpal tunnel syndrome, convulsion, dysgraphia, loss of consciousness, allodynia, automatic nervous system imbalance, cerebellar ataxia, hypertonia, paraparesis, post-traumatic headache, radicular pain, sensory

loss, cerebellar syndrome, cerebral ischaemia, cerebrovascular insufficiency, cervicogenic headache, cognitive disorder, dysstasia, formication, hemiparesis, hypogeusia, intercostal neuralgia, migraine with aura, movement disorder, neuritis, neuritis cranial, oromandibular dystonia, paresis, partial seizures, pyramidal tract syndrome, quadriplegia, vascular headache.

Eye Disorder: visual acuity reduced, diplopia, conjunctivitis, blindness unilateral, eyelid oedema, blindness transient, chalazion, conjunctival hyperaemia, eye swelling, eyelid ptosis, glaucoma, ocular hyperaemia, photophobia, scotoma, ulcerative keratitis, vitreous floaters.

Ear and Labyrinth Disorders: tinnitus

Cardiac Disorders: palpitations, angina pectoris, bundle branch block right, conduction disorder, atrioventricular block first degree, cardiovascular disorder, mitral valve prolapse, supraventricular extrasystoles, ventricular extrasystoles.

Vascular Disorders: hyperaemia, peripheral coldness, deep vein thrombosis, phlebitis, raynaud's phenomenon, thrombophlebitis, venous thrombosis.

Respiratory, Thoracic and Mediastinal Disorders: nasal congestion, dysphonia, throat irritation, bronchospasm, diaphragmalgia, epiglottic cyst, hiccups, lung cyst, nasal septum disorder, pharyngeal hypoaesthesia, pharyngeal oedema, rales, respiratory tract congestion, rhonchi, sinus congestion, upper respiratory tract congestion, wheezing.

Gastrointestinal Disorders: flatulence, abdominal discomfort, gingivitis, dry mouth, gastrooesophageal reflux disease, haemorrhoids, hypoaesthesia oral, dysphagia, gastrointestinal disorder, aphthous stomatitis, dental caries, gastric disorder, periodontitis, reflux gastritis, tongue ulceration, aerophagia, breath odour, dental necrosis, erosive duodenitis, gingival bleeding, inguinal hernia, intestinal obstruction, lumbar hernia, malabsorption, obstruction gastric, odynophagia, salivary hypersecretion, tongue disorder.

Heptobiliary disorder: hyperbilirubnaemia, acute hepatic failure, bile duct stone, biliary colic, cholelithiasis, gallbladder disorder.

Skin and Subcutaneous Tissue Disorder: erythema, urticaria, dermatitis, night sweats, skin burning sensation, pruritus generalised, skin lesion, dry skin, livedo reticularis, pityriasis rosea, psoriasis, rash generalised, rosacea, skin discolouration, alopecia areata, dermatitis atopic, hyperkeratosis, hyperkeratosis palmaris and plantaris, macule, nail discolouration, prurigo, rash macular, rash pruritic, skin chapped, skin fissures, skin ulcer.

Musculoskeletal and Connective Tissue Disorders: groin pain, mobility decreased, flank pain, intervertebral disc disorder, joint swelling, tendonitis, back disorder, chondromalacia, coccydynia, fracture pain, intervertebral disc protrusion, joint effusion, limb discomfort, myosclerosis, osteitis, pain in jaw, patellofemoral pain syndrome, periostitis, spinal deformity, tenosynovitis, trigger finger.

Renal and Urinary Disorders: dysuria, micturition urgency, bladder pain, nephrolithiasis, renal pain, renal colic, cystitis-like symptom, hydronephrosis, incontinence, micturition disorder, nocturia, renal cyst.

Pregnancy, Puerperium and Perinatal Conditions: abortion incomplete, abortion spontaneous

Reproductive System and Breast Disorders: metrorrhagia, amenorrhoea, menstrual disorder, benign prostatic hyperplasia, endometrial hyperplasia, vaginal haemorrhage, adenomyosis, Bartholinitis, breast cyst, cervical dysplasia, cervical polyp, cervix erythema, dyspareunia, erectile dysfunction, genital tract inflammation, menopausal symptoms, menstruation delayed, pelvic pain, postmenopausal

haemorrhage, prostatitis, testicular swelling, uterine cervical erosion, vaginal inflammation, vulvovaginal pain.

General Disorders and Administration Site Conditions: injection site rash, injection site induration, feeling of body temperature change, chest pain, discomfort, facial pain, injection site exfoliation, non-cardiac chest pain, puncture site pain, face oedema, injection site dermatitis, injection site dryness, tenderness, chest discomfort, injection site macule, injection site urticaria, injection site vesicles, axillary pain, exercise tolerance decreased, general physical health deterioration, injection site anaesthesia, injection site discomfort, injection site extravasation, injection site hypersensitivity, injection site irritation, injection site lymphadenopathy, injection site nodule, injection site papule, injection site paraesthesia, oedema, sensation of pressure.

Investigations: haemoglobin decreased, weight decreased, haematocrit decreased, nitrite urine present, platelet count decreased, bacterial test positive, blood pressure increased, blood bilirubin increased, electrocardiogram T wave abnormal, hepatic enzyme increased, red blood cell count decreased, white blood cells urine positive, blood lactate dehydrogenase increased, blood potassium decreased, blood urine present, protein urine present, transaminases increased, blood creatinine increased, electrocardiogram abnormal, liver function test abnormal, anti-thyroid antibody positive, biopsy endometrium abnormal, blood iron decreased, blood PH increased, blood potassium increased, blood pressure decreased, blood sodium increased, crystal urine, ECG signs of ventricular hypertrophy, electrocardiogram QRS complex prolonged, electrocardiogram QT shortened, electrocardiogram ST segment abnormal, gastric PH decreased, laboratory test abnormal, red blood cell count increased, urinary sediment present, urine ketone body present, white blood cell count increased.

Injury, Poisoning and Procedural Complications: procedural pain, laceration, post-traumatic pain, animal bite, animal scratch, burns first degree, burns second degree, face injury, facial bones fracture, foreign body, foreign body in eye, hip fracture, joint dislocation, overdose, radiation skin injury, subcutaneous haematoma.

Surgical and Medical Procedures: carpal tunnel decompression, dental implantation, dental operation, osteoporosis prophylaxis, peripheral nerve decompression, ureteral catheterisation, varicose vein operation, wart excision.

Social Circumstances: menopause

8.5 Post-Market Adverse Reactions

Anaphylactic reactions: In post marketing experience, serious hypersensitivity events including cases of anaphylaxis have been reported following PLEGRIDY™ administration (see [7 WARNINGS AND PRECAUTIONS](#)).

Hepatic injury: In post marketing experience, noninfectious hepatitis (including serious hepatitis) cases have been reported following PLEGRIDY™ administration (see [7 Warnings and Precautions](#)).

Respiratory, Thoracic, and Mediastinal Disorders: cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with PLEGRIDY™ (peginterferon beta-1a).

Patients who experienced a relapse in the study could receive standard therapy with corticosteroids.

9.4 Drug-Drug Interactions

As with all interferon products, proper monitoring of patients is required if PLEGRIDY™ is given in combination with myelosuppressive agents.

Interactions with other drugs have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

A definitive mechanism of action of PLEGRIDY™ (peginterferon beta-1a) in multiple sclerosis is not known. PLEGRIDY™ binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression, including 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.

10.2 Pharmacodynamics

There are no known biochemical or physiological responses that are related directly to the clinical effect of PLEGRIDY™. In healthy subjects, pharmacodynamic parameters, measured by neopterin and 2',5'-OAS responses, increased with an increase in the PLEGRIDY™ dose but was less than dose-proportional. The duration of the pharmacodynamics response was sustained and prolonged for PLEGRIDY™, with elevations detected up to 15 days, compared to 4 days for the non-pegylated interferon beta-1a. In multiple sclerosis patients, following PLEGRIDY™ treatment at Q2W, neopterin concentrations peaked at approximately 3 days post-dosing and was sustained and prolonged for and lasted 10 to 14 days compared to 5 days observed for non-pegylated interferon beta-1a. The neopterin response was still observed when PLEGRIDY™ level was undetectable.

10.3 Pharmacokinetics

Following a single SC dose from 63 to 188 micrograms in healthy subjects, serum PLEGRIDY™ peak concentration (C_{max}) and total exposure over time (AUC) increased in approximately dose-proportional. PLEGRIDY™ did not accumulate following multiple SC dose at every 2 weeks (Q2W) in healthy subjects. Pharmacokinetic parameters for PLEGRIDY™, including C_{max} and AUC, did not differ significantly between healthy volunteers and multiple sclerosis patients or between single-dose and multiple-dose administrations. However, the coefficient of variation (% CV) between individual patients for AUC, C_{max}, and half-life was high. At Week 24 following 125 μ g at Q2W, %CV of 50%, 89%, and 57% for AUC_{tau}, C_{max}, t_{1/2}, respectively, was observed.

Absorption

In healthy subjects, C_{max} was reached from 1 to 1.5 days (T_{max}) post dose and then declined. Following subcutaneous administration of 125 microgram PLEGRIDY™ every two weeks in multiple sclerosis patients, the peak concentration C_{max} of 280 \pm 79 pg/mL was reached between 1 – 1.5 days post-dose, and the AUC over the 14 day dosing interval was 34.8 ng.hr/mL.

Distribution:

Following repeat dosing of 125 microgram doses every two weeks by subcutaneous administration in

multiple sclerosis patients, PLEGRIDY™ was widely distributed with a volume of distribution of 481 ± 105 L (mean \pm SE).

Metabolism:

PLEGRIDY™ is not extensively metabolized in the liver.

Elimination

Renal excretion is the major excretory elimination pathway for PLEGRIDY™. In healthy subjects, the half-life ($t_{1/2}$) was approximately 2 to 3 days ($t_{1/2}$ median ranged 36 – 134 hours). The half-life ($t_{1/2}$) of PLEGRIDY™ is approximately 2-fold longer than intramuscular non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean \pm SE) of PLEGRIDY™ was 78 ± 15 hours at steady state. The mean steady state clearance of PLEGRIDY™ was 4.1 ± 0.4 L/hr.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of PLEGRIDY™ in patients below 18 years of age has not been studied.
- **Geriatrics:** The safety and efficacy of PLEGRIDY™ in patients over the age of 65 have not been adequately studied due to the limited number of such patients included in clinical trials. However, results from a population pharmacokinetic analysis suggest that age does not impact peginterferon beta-1a clearance.
- **Patients with Renal Impairment:** Following single subcutaneous dose of PLEGRIDY™ at 125 μ g in subjects with various degrees of renal impairment, there was an increase in AUC (30-53%) and C_{max} (26-42%) in subjects with mild (creatinine clearance 50 to \leq 80 mL/minute), moderate (creatinine clearance 30 to $<$ 50 mL/minute), and severe (creatinine clearance $<$ 30 mL/minute) renal impairment, compared to subjects with normal renal function (creatinine clearance $>$ 80 mL/minute). Geometric mean apparent clearance (CL/F) decreased by 20%, 24%, 39% and the half-life was 51, 48, and 78 hours for mild, moderate, and severe renal impairment, respectively. Subjects with end stage renal disease requiring 2-3 times hemodialysis weekly showed similar AUC and C_{max} as compared to subjects with normal renal function. Each hemodialysis reduced PLEGRIDY concentration by approximately 24%, suggesting that hemodialysis partially removes peginterferon beta-1a from systemic circulation.

11 STORAGE, STABILITY AND DISPOSAL

Pre-filled syringe /pre-filled pen

Store in the closed original carton to protect from light until ready for injection. Store in a refrigerator between 2°C to 8 °C. Do not freeze. Discard if frozen. The formulation is preservative-free.

When no refrigerator is available, PLEGRIDY™ (peginterferon beta-1a) may be stored protected from light between 2°C to 25°C for a maximum of 30 days in total. Once removed from the refrigerator, PLEGRIDY™ should be allowed to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm PLEGRIDY™.

PLEGRIDY™ can be removed from and returned to the refrigerator if necessary. The total combined time out of refrigeration should not exceed 30 days, at a temperature that does not exceed 2°C to 25°C, protected from light.

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

12 SPECIAL HANDLING INSTRUCTIONS

Instructions for Disposal

Dispose via a sharps-bin container or other hard plastic or metal sealable container. Always follow local regulations for disposal.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: peginterferon beta-1a

Chemical name: peginterferon beta-1a

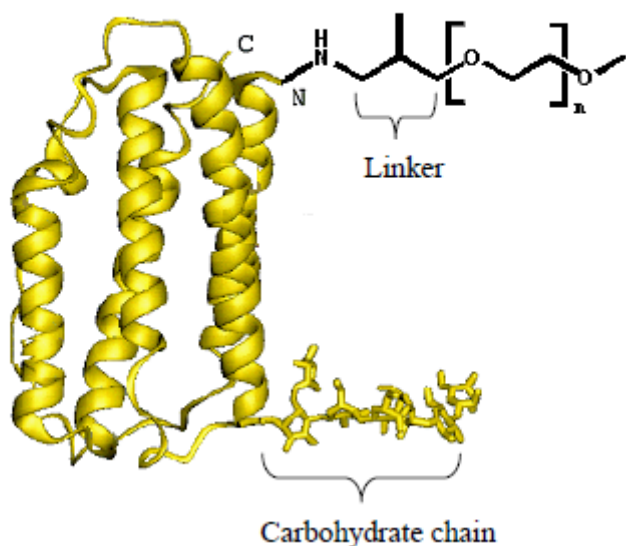
Glycosylated recombinant interferon beta-1a that is pegylated with a single, linear 20 kDa methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde moiety at the N-terminus.

Molecular formula and molecular mass: The molecular weight of peginterferon beta-1a DS batches manufactured with the intended commercial process range between 43.9 and 44.7 kDa.

CAS Index Number: 1211327-92-2

Structural formula:

Schematic of the Peginterferon beta-1a Structure



Physicochemical properties: peginterferon beta-1a drug substance is clear to slightly opalescent, colourless to slightly yellow solution containing 1.1 mg/mL peginterferon beta-1a in 20 mM sodium acetate, 150 mM arginine HCl.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
105MS301 (Efficacy, Safety, PK/PD)	Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled (year 1) Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects with Relapsing Remitting Multiple Sclerosis	125 micrograms PLEGRIDY injected subcutaneously every 2 or 4 weeks OR placebo; Two-year study (see additional information on study design)	Subjects with Multiple Sclerosis; n=1512	37 years (18-61 years)	Female: 71%
105MS302 (Long term Safety and Efficacy)	Phase 3, multicenter, parallel group, dose frequency blinded extension	BIIB017 125 mcg SC every 2 weeks or BIIB017 125 mcg SC every 4 weeks	As of 13 March 2015: 1077 enrolled/1076 dosed; 833 completed	38.4 years (20 to 63 years)	Female: 72%

The efficacy and safety of PLEGRIDY™ (peginterferon beta-1a) were assessed from the randomized, double-blind, placebo-controlled phase (year 1) of a 2 year clinical study in patients with relapsing remitting multiple sclerosis (105MS301). At study entry 1512 patients were randomized and dosed to 125 micrograms PLEGRIDY™ injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500). The trial compare clinical and MRI outcomes at 48 weeks. At the end of the first year, patients who received placebo were randomized to PLEGRIDY™ every 2 or every 4 weeks while the patients randomized to PLEGRIDY™ in the first year remained on their original dose assignment. Efficacy results were derived from the placebo-controlled first year of the study.

The study enrolled patients with active disease, who had experienced at least 2 relapses within the prior three years including at least 1 in the year prior to randomization and had an Expanded Disability Status Scale (EDSS) score ranging from 0 to 5. Neurological evaluations were performed at baseline, every 12 weeks and at time of suspected relapse. Brain MRI evaluations were performed at baseline, weeks 24 and 48. The primary endpoint was the annualized relapse rate (ARR) over 1 year. Secondary endpoints included the proportion of subjects relapsing, new or newly enlarging T2 hyperintense lesions and time to confirmed disability progression, defined as at least a 1 point increase from baseline EDSS \geq 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 weeks. The trial excluded patients with progressive forms of multiple sclerosis.

The mean age of the study population was 37 (18-61) years, the mean disease duration was 3.6 (0-40) years and the mean EDSS at baseline was 2.46 (0.0-5.5). The majority of the patients were female (71%). There were 171 (11%) patients ages 50 and over studied in the clinical trial 105MS301.

14.2 Study Results

105MS301, Year 1

PLEGRIDY™ every 2 weeks reduced the ARR by 36% compared to placebo (p=0.0007) at one year (Table 5). Complete results for this study are shown in Table 5 and Figure 1.

At 1 year, the estimated proportion of subjects with disability progression confirmed at 24 weeks was 4% in the PLEGRIDY™ group and 8.4% in the placebo group. The mean number of Gd enhancing lesions was 0.2 in the PLEGRIDY™ group and 1.4 in the placebo group. A treatment effect was observed as early as 6 months.

105MS301, Year 2

The adjusted annualized relapse rate over 2 years based on the ITT population (N=512) for subjects in the PLEGRIDY™ group was 0.221, and the estimated proportion of subjects with disability progression confirmed at 12 weeks was 11.2%.

Table 5 Clinical and MRI Results of 105MS301

Endpoint		Placebo	PLEGRIDY™ 125 micrograms every 2 weeks
Clinical endpoints		n=500	n=512
Annualized relapse rate (primary endpoint)	Adjusted rate [95% CI]	0.397 [0.328, 0.481]	0.256 [0.206, 0.318]
	% reduction vs placebo ^{a+} [95%CI]	—	36 [17, 50] (p=0.0007)
Proportion of subjects relapsed	Estimated proportion	0.291	0.187
	% risk reduction vs placebo [95%CI] ^{b+}	—	39 [20, 53] (p=0.0003)
Disability progression (12 weeks)	Estimated proportion of subjects progressed	0.105	0.068
	% risk reduction vs placebo [95%CI] ^{c+}	—	38 [3, 60] (p=0.0383)
MRI endpoints^d		n=476	n=457
New or newly enlarging T2 hyperintense lesions	Adjusted mean	10.9	3.6
	% reduction vs placebo [95%CI] ^{e+}	—	67 [60, 73] (p<0.0001)

a Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. >=4), baseline relapse rate, age (<40 vs. >=40).

b Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. >=4), age (<40 vs. >=40), baseline relapse rate, and baseline Gd enhancing lesions (presence vs. absence).

c Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. >=4), age (<40 vs. >=40).

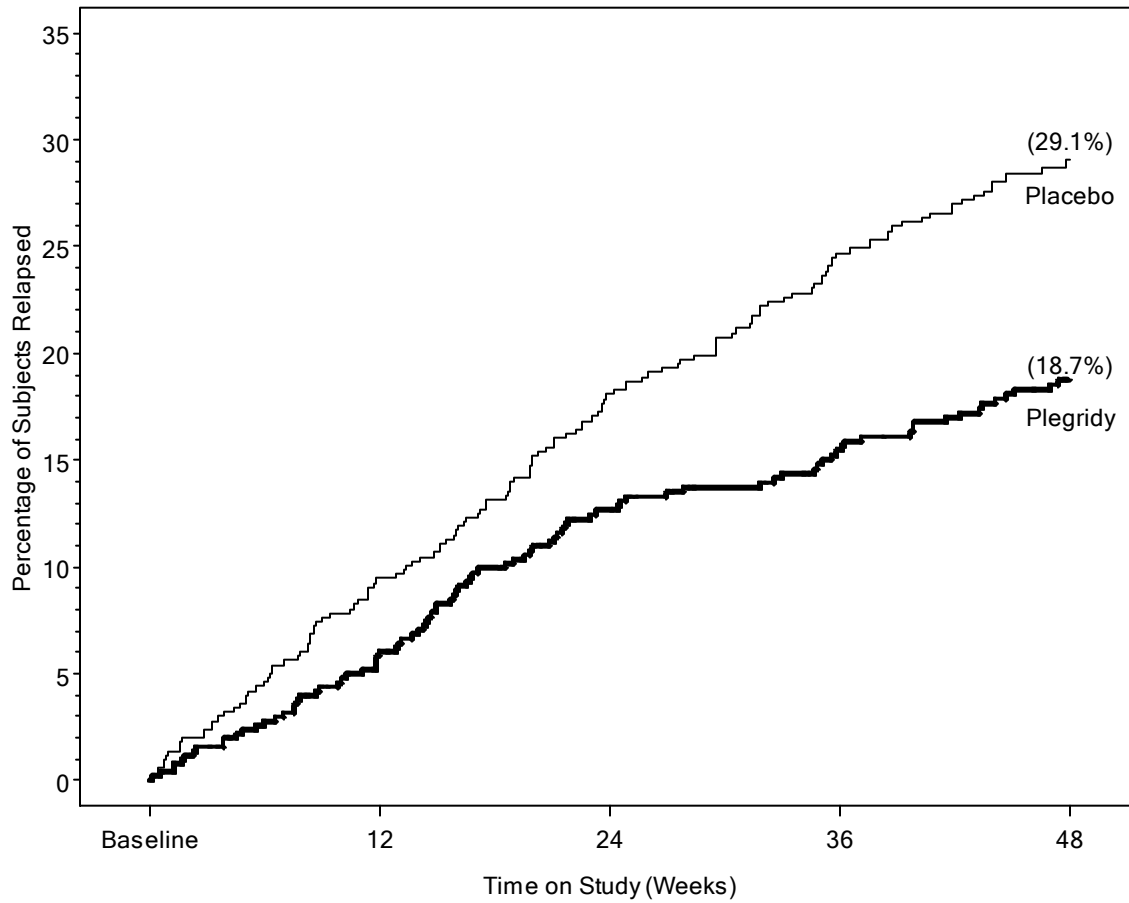
d ITT population in which subject who had at least one post baseline MRI scan were included in the analysis of MRI endpoints.

e Based on negative binomial regression, adjusted for baseline number of T2 lesion.

+ A sequential (closed) testing procedure was used to control the overall type I error rate due to multiple comparison. in the following order:

Annualized relapse rate, New or newly enlarge T2 hyperintense lesions, Proportion of subjects relapsed and Disability progression (12 weeks).

Figure 1 Time to First Relapse



PLEGRIDY™ (PLEGRIDY™) 125 mcg every 2 weeks (n= 512) versus placebo (n=500) Hazard Ratio (95% CI) = 0.61 (0.47, 0.80), p=0.0003

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In the 5 weeks study in rhesus monkeys, dose-dependent changes included a transient increase in body temperature and a reduction in lymphocyte counts, consistent with the known mechanism of action of interferon beta-1a. In addition, dose-dependent increases of alanine aminotransferase and aspartate aminotransferase were observed. The weights of adrenals of females and thymus of male animals were not increased in the main study animals but were increased in animals following a 4-week recovery period.

Carcinogenicity: Peginterferon beta-1a has not been tested for carcinogenicity in animals.

Mutagenicity: 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.

Reproductive and Developmental Toxicology:

Impairment of Fertility

The weekly subcutaneous administration of PLEGRIDY™ (peginterferon beta-1a) at 125 µg/kg/week to sexually mature female rhesus monkeys over the course of one menstrual cycle (up to 5 weeks), resulted in menstrual irregularities, anovulation, and decreased hormones (serum progesterone and 17-beta estradiol). The effects at 125 µg/kg were reversible after discontinuation of drug administration and are consistent with those observed with non-pegylated interferon beta. These effects were not seen at the lower dose of 2.5 µg/kg, which is similar to the nominal clinical dose (approximately 2 µg/kg). The validity of extrapolating nonclinical data from studies with PLEGRIDY to humans is unknown.

PLEGRIDY™ has not been tested for reproductive toxicity in pregnant animals. In monkeys administered non-pegylated interferon beta by subcutaneous injection over the course of one menstrual cycle, menstrual irregularities, anovulation, abortifacient effects and decreased serum progesterone levels were observed.

No information is available on the potential effects of peginterferon beta-1a on male fertility.

Toxicology studies in juvenile animals were not performed for peginterferon beta-1.

Teratogenicity

Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PLEGRIDY® (pronounced PLEGG-rih-dee) (peginterferon beta-1a)

Solution for injection, for subcutaneous use, pre-filled syringe

Read this carefully before you start taking **PLEGRIDY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PLEGRIDY**.

What is PLEGRIDY used for?

The active substance in PLEGRIDY is peginterferon beta-1a. Peginterferon beta-1a is a long-acting form of interferon. Interferons are natural substances made in your body to help protect you from infections and diseases. PLEGRIDY is intended for use under the guidance and supervision of a physician familiar with the treatment of MS.

Multiple Sclerosis (MS) is a long term illness that affects the central nervous system (CNS), including the brain and spinal cord. In multiple sclerosis, your body's immune system damages the protective covering (myelin) that surrounds the nerves in your brain and spinal cord. This disrupts the messages between the brain and other parts of the body causing the symptoms of MS.

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 in thinking and concentrating, depression.

MS symptoms also tend to flare up from time to time: this is called a relapse.

How does PLEGRIDY work?

PLEGRIDY seems to work by stopping the body's immune system from damaging the protective covering (myelin) that surrounds the nerves in 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.

Your doctor will advise you for how long you can use PLEGRIDY or when to stop.

What are the ingredients in PLEGRIDY?

Medicinal ingredients: peginterferon beta 1a.

Non-medicinal ingredients: L-Arginine Hydrochloride, Glacial Acetic Acid, Polysorbate 20 in Water for Injection, and Sodium Acetate Trihydrate.

PLEGRIDY comes in the following dosage forms:

PLEGRIDY is a liquid for subcutaneous injection provided in a pre-filled syringe or pre-filled pen. Three strengths are available, 63 µg, 94 µg and 125 µg.

**not all dosage forms may be available*

Do not use PLEGRIDY if:

- you are allergic (hypersensitive) to interferon beta, peginterferon beta-1a or any of the ingredients in PLEGRIDY
- you currently experience severe depression and thoughts about committing suicide

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AVONEX PS/AVONEX PEN. Talk about any health conditions or problems you may have, including if:

- you have ever experienced:
 - depression or problems affecting your mood
 - thoughts about committing suicide
- you are pregnant or are planning to become pregnant. Tell your healthcare provider if you become pregnant during your treatment with PLEGRIDY.
- you are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will use PLEGRIDY or breastfeed

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 moods in the past.

- If you have:
 - serious liver problems
 - irritation at your injection site, which can lead to skin and tissue damage, (injection site necrosis). Read carefully and follow the instructions given under “How to inject PLEGRIDY” to reduce the risk of injection site necrosis
 - a low number of white blood cells or platelets, which can cause an increased risk of infection, bleeding or anaemia
 - seizure disorders, not controlled by medication
 - heart problems, which can cause symptoms such as chest pain (angina), particularly after any activity; swollen ankles, shortness of breath (congestive heart failure); or an irregular heartbeat (arrhythmias)

PLEGRIDY may affect your white blood cell counts and your liver function. Your doctor may periodically do a blood test to count the number of your white blood cells or platelets and to check that your liver is working properly.

While you are using PLEGRIDY talk to your doctor or pharmacist if:

- There are changes to your mood, for example you have thoughts about suicide; feel unusually sad, anxious or worthless.

Other warnings you should know about:

If you notice signs of allergy

- Because PLEGRIDY is based on a protein, there is a small chance of an allergic reaction. Signs of an allergic reaction may include:
 - becoming very wheezy or having difficulty breathing
 - swelling around the face (lips, tongue or throat)

- skin rashes or redness

Usually these symptoms will be signs of less serious side effects. But they may be more serious.

If you know you are allergic or notice any of these symptoms contact a doctor as soon as possible.

Women of childbearing potential:

If you are a woman of childbearing potential and are taking PLEGRIDY, you should use effective methods of contraception unless you are planning to become pregnant and have talked to your doctor about the potential risks and benefits of staying on PLEGRIDY. It is not known if interferons interfere with hormonal contraceptives.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Sometimes you will need to remind other medical staff 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.

There are no known interactions with PLEGRIDY.

How to take PLEGRIDY:

Usual dose:

PLEGRIDY is only to be injected once every two weeks. PLEGRIDY is injected under the skin (subcutaneously). 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 side effects of PLEGRIDY before taking the full dose. You will be provided with a Starter Pack containing your first 2 injections: one orange labelled syringe/pen with PLEGRIDY 63 micrograms (for day 0) and one blue labelled syringe/pen with PLEGRIDY 94 micrograms (for day 14). After that you will be provided with a maintenance pack containing grey pens/syringes with PLEGRIDY 125 micrograms (for day 28 and then every 2 weeks). Read the instructions on how to inject before you start using PLEGRIDY.

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

Injecting yourself

Only inject PLEGRIDY by yourself once you have been trained by a healthcare professional. Read and follow the advice given in the instructions on how to inject yourself before you start.

If you have trouble handling the pen or syringe, ask your doctor or nurse who will be able to assist you.

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.

Children and adolescents

PLEGRIDY has not been tested in children and adolescents below 18 years old.

Elderly

PLEGRIDY has not been tested in people older than 65 years old. If you are over 65 your doctor may still prescribe PLEGRIDY.

Overdose:

You must only inject PLEGRIDY once every 14 days (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 think you, or a person you are caring for, have taken too much PLEGRIDY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

You need to inject PLEGRIDY once every 14 days (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, never inject more than once in a 7-day period. Do not use two injections to make up for a missed dose.

If you have problems with your dosing schedule, talk to your doctor or nurse.

What are possible side effects from using PLEGRIDY?

These are the side effects that people reported when PLEGRIDY was being tested. The figures are based on how many people reported these events It gives you an idea how likely you are to get similar side effects

Very common side effects:_(at least 1 in 10 people are affected)

Flu-like symptoms

These symptoms are not really the flu.

You can't pass it on to anyone else. They are more common symptoms when you first start using PLEGRIDY. Using the Starter Pack to gradually increase the amount of PLEGRIDY you inject when you start treatment can help reduce symptoms. As you keep using your injections, the flu-like symptoms gradually lessen.

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. Use your PLEGRIDY injection just before bed time. This may allow you to sleep through the effects.
2. Take acetaminophen or ibuprofen half an hour before your PLEGRIDY injection. Speak to your doctor or pharmacist about how much to take and how long to take it.
3. If you have a fever, drink plenty of water to keep you hydrated.

Injection site reactions

You may get reactions around the place you inject. These usually lessen over time. To reduce injection site reactions:

- Alternate the sites you use for injections
- Do not use the same injection site for consecutive injections
- After injecting, check the 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. Read and follow the advice given in the instructions on How to inject PLEGRIDY.

Liver Problems

Your liver function may be affected, symptoms may include:

- Yellowing of your skin or the whites of your eyes (jaundice)
- Itching all over
- Feeling sick, being sick (nausea and vomiting)
- Easy bruising of the skin.

Call a doctor immediately if you do get any of these symptoms. They may be signs of a possible liver problem.

Less common side effects reported in association with interferon beta include:

Respiratory System: shortness of breath, tiredness, chest tightness or pain (pulmonary arterial hypertension).

If any of the effects trouble you, talk to your doctor.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
COMMON				
Flu-like symptoms	Headache, muscle aches, chills or a fever	✓		
Injection site reactions	Redness, itching or pain	✓		
	Swelling, bruising, warmth or rash at injection site	✓		
Changes to levels of liver enzymes	Yellowing of your skin or the whites of your eyes (jaundice)		✓	
	Itching all over		✓	
	Feeling sick, being sick (nausea and vomiting)		✓	
	Easy bruising of the skin		✓	
Other	Headache	✓		

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	Muscle pain (myalgia)	✓		
	Pain in your joints, arms, legs or neck (arthralgia)	✓		
	Chills, feeling cold	✓		
	Feeling weak and tired (asthenia)	✓		
	Feeling sick or being sick (nausea or vomiting)	✓		
	Itchy skin (pruritus)	✓		
	Increase in body temperature	✓		

This is not a complete list of side effects. For any unexpected effects while taking PLEGRIDY, contact your doctor or pharmacist.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Do not use after the expiry date stated on the carton. The expiry refers to the last day of the month.

Keep PLEGRIDY syringes and pens in the outer carton in the refrigerator (between 2°C and 8°C). If a refrigerator is not available, PLEGRIDY can be left at room temperature 2°C to 25°C for up to 30 days.

Keep the outer carton closed to protect PLEGRIDY from light. Do not freeze.

PLEGRIDY does not contain preservatives.

Do NOT use PLEGRIDY if you notice any of the following:

- If the pre-filled pen or syringe is broken.
- If the solution is coloured or you can see particles floating in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Disposal:

Ask your pharmacist how to dispose of used pens/syringes and any unused medicines. Dispose of any unused medicine according to community guidelines. Pens/syringes should not be disposed of in a recycling bin.

INSTRUCTIONS FOR USE

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PLEGRIDY™ (pronounced PLEGG-rih-dee) (peginterferon beta-1a)

Solution for injection, for subcutaneous use, pre-filled syringe



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 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 how to prepare and inject your PLEGRIDY pre-filled syringe the right way.
- If you experience difficulty or have questions about how to inject, call the Biogen ONE® Support Program at 1-855-676-6300.
- PLEGRIDY pre-filled syringe is for use under the skin only (subcutaneous).
- Each PLEGRIDY pre-filled syringe can be used 1 time 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 1 pre-filled syringe every 14 days (every 2 weeks).
- **Do not** use your PLEGRIDY pre-filled syringe if it has been dropped or visibly damaged.

DOSE SCHEDULE

Choose the correct PLEGRIDY pre-filled syringe from a pack. PLEGRIDY pre-filled syringe Starter Pack contains your first two injections to gradually adjust your dose.

WHEN	WHICH DOSE	WHICH PACK
Day 0* (63 micrograms)	First injection: 63 micrograms, choose orange labelled syringe	 STARTER PACK
Day 14* (94 micrograms)	Second injection 94 micrograms, choose blue labelled syringe	
Day 28* and then every 2 weeks after (125 micrograms)	Full dose injection: 125 micrograms, choose grey labelled syringe	 ADMINISTRATION DOSE PACK

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

Supplies needed for your PLEGRIDY injection:

- 1 PLEGRIDY pre-filled syringe (see Figure A)

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

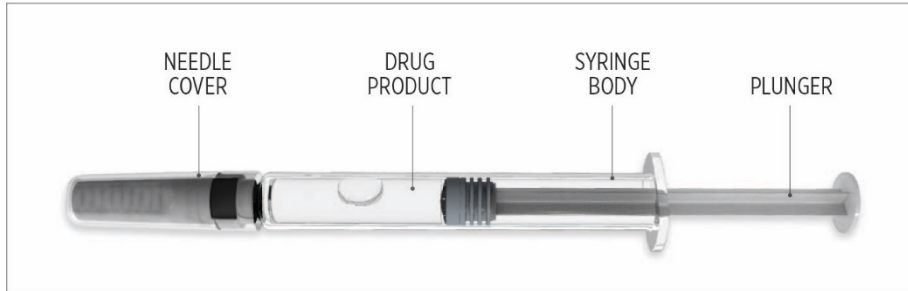


Figure A

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

- Alcohol wipe
- Gauze pad
- Adhesive bandage
- 1 sharps container for throwing away used needles and PLEGRIDY pre-filled syringes. See “Disposing of Your Used PLEGRIDY pre-filled Syringes” at the end of these instructions.
- A well-lit area and clean flat surface to work on, like a table.



Figure B

Preparing for Your Injection

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

- a) Remove your PLEGRIDY pack from the refrigerator and select the appropriate pre-filled syringe (dosage) from the pack.
- b) Close the pack and put back in the refrigerator after removing one pre-filled syringe.
- c) **Let the PLEGRIDY pre-filled syringe come 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

- 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 to receive an injection
- b) Wash your hands with soap and water and dry thoroughly.

Step 3: Check your PLEGRIDY pre-filled syringe

- a) Check the expiration date printed on your PLEGRIDY pre-filled syringe (See Figure C)
 - Check that your PLEGRIDY medicine is clear and colourless (see Figure D).
- ⚠ Do not** use external heat sources, such as hot water, to warm your pre-filled syringe.
- It is past the expiration date.
 - The liquid is cloudy, or has floating particles in it.



Note you might see air bubbles in your PLEGRIDY medicine. This is normal and does not need to be expelled prior to your injection.

Giving the Injection

Step 4: Choose and clean the injection site

- a) PLEGRIDY pre-filled syringe is for subcutaneous injection (injection into the skin).
- b) 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.

- c) Choose an injection site and wipe the skin with an alcohol wipe.
- d) Let the injection site dry before injecting the dose.

⚠ Do not touch this area again before giving the injection.



Figure E

Giving Your injection

Step 5: Firmly Remove Needle Cover

- a) Pull the needle cover straight off the needle and dispose of the needle cover (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 stick injury.



Figure F

Step 6: Gently Pinch the Injection Site

- a) Gently pinch the skin around the cleaned injection site using thumb and forefinger to create a slight bulge or fold. (see figure G).

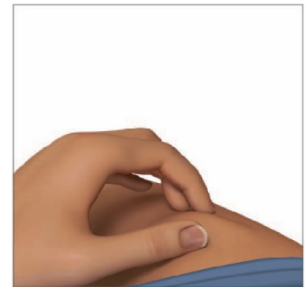


Figure G

Step 7: Give Your Injection

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

! Do not pull back on the plunger.

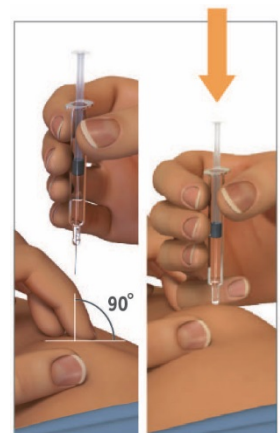


Figure H

- c) Slowly push the plunger all the way down until the 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

- d) Keep the needle in for 5 seconds (See Figure J).



Figure J

Step 8: Remove your PLEGRIDY pre-filled syringe from your injection site

- a) Pull the needle straight out. (See Figure K)

⚠ Caution – do not recap the PLEGRIDY pre-filled syringe. You could get a needle stick injury.

⚠ Do not reuse the PLEGRIDY pre-filled syringe.

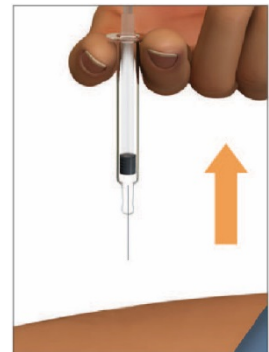


Figure K

After your Injection

Step 9: Dispose of your used PLEGRIDY pre-filled syringe

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

⚠ Do not dispose of your used pre-filled syringe or disposal container in your household trash unless your community guidelines permit this.

Step 10: Care of your injection site

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

Step 11: Check your injection site

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

General Warnings

 **Do not** reuse your PLEGRIDY pre-filled syringe.

 **Do not** share your PLEGRIDY pre-filled syringe.

- a) Keep PLEGRIDY pre-filled syringe and all medications out of reach of children.

Record Date and Location

- a) Record the date and location of each injection and alternate sites between your injections.
- b) Do not use the same injection site for consecutive injections.

Storage

- a) Recommended storage is controlled refrigeration 2° to 8°C (36°F to 46°F) in the closed original carton to protect from light.
- b) If needed, PLEGRIDY may be stored in the closed original carton without refrigeration up to 25°C (77°F) for up to 30 days.
- c) **PLEGRIDY can be removed from and returned to the refrigerator if necessary. The total combined time out of the refrigeration should not exceed 30 days, at a temperature up to 25°C (up to 77°F).**

Do not freeze or expose to high temperatures.

INSTRUCTIONS FOR USE

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PLEGRIDY™ (pronounced PLEGG-rih-dee) (peginterferon beta-1a)

Solution for injection, for subcutaneous injection in a single use, pre-filled pen

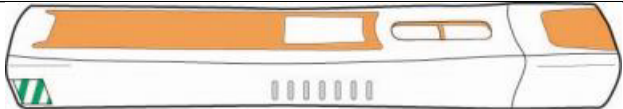
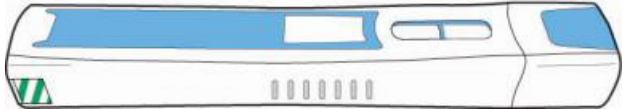

Read the Instructions for Use before you start using PLEGRIDY and each time you get a refill of your prescription. There may be new information. This information does not take the place of talking to your doctor or nurse about your medical condition or your treatment.

Note:

- **Before you use the PLEGRIDY pre-filled pen for the first time**, your doctor or nurse should show you or your caregiver how to prepare and inject your PLEGRIDY pen the right way.
- If you experience difficulty or have questions about how to inject, call the Biogen ONE® Support Program at 1-855-676-6300.
- PLEGRIDY pen is for use under the skin only (subcutaneous).
- Each PLEGRIDY pen can be used 1 time only.
- **Do not** share your PLEGRIDY 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 your PLEGRIDY Pen if it has been dropped or visibly damaged.

DOSE SCHEDULE

Choose the correct PLEGRIDY Pen from the pack. PLEGRIDY pre-filled pen Starter Pack contains your first two injections to gradually adjust your dose.

WHEN	WHICH DOSE	WHICH PACK
Day 0* (63 micrograms)	First injection: 63 micrograms, choose orange pen	 STARTER PACK
Day 14* (94 micrograms)	Second injection 94 micrograms, choose blue pen	
Day 28* and then every 2 weeks after (125 micrograms)	Full dose injection: 125 micrograms, choose gray pen	 ADMINISTRATION DOSE PACK

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

REMOVE FROM REFRIGERATOR

Remove 1 PLEGRIDY pack out of the refrigerator and select the appropriate pen (dosage) from the pack. Close the pack and put back in the refrigerator after removal of the first injection pre-filled pen.

CHECK PACK AND PEN

Check the expiration date printed on the PLEGRIDY Pen, PLEGRIDY Pen carton, and the outer carton. Do not use the PLEGRIDY Pen past the expiration date.

Let the pen sit for 30 minutes before injecting the PLEGRIDY dose to allow the medication to reach room temperature. Do not use external heat sources such as hot water to warm the PLEGRIDY Pen. A room temperature solution is more comfortable to inject.

Supplies Needed for Your PLEGRIDY Injection:

1 PLEGRIDY Pen (See Figure A).

Before Use – Parts of your PLEGRIDY Pen (See Figure A):

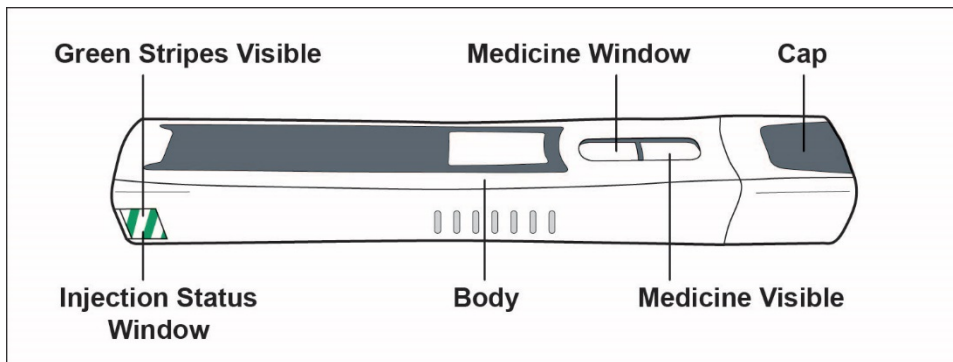


Figure A

⚠ 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): Alcohol wipe

- Gauze pad
- Adhesive bandage
- 1 sharps container for throwing away used PLEGRIDY pens. (See Disposing of Your Used PLEGRIDY pen at the end of these instructions).



Figure B

Preparing for your injection:

Step 1. Remove your pen from the refrigerator.

- a. Remove your PLEGRIDY pen from the refrigerator and select the appropriate pen (dosage) from the pack.
- b. Close the pack and put back in the refrigerator after removing one pen.
- c. **Let the PLEGRIDY pen come 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 area and a clean, flat surface to work on, like a table. Collect all the supplies you will need to give yourself, or to receive, an injection.
- b. Wash your hands with soap and water and dry thoroughly.

Step 3. Check your PLEGRIDY Pen (See *Figure C*)

- a. Check the injection status window. You should see green stripes.
- b. Check the expiration date.
- c. Check the medication window and make sure the PLEGRIDY medicine is colourless.

⚠ Do not use your pen if:

- You do not see the green stripes in the injection status window.
- It is past the expiration date.
- The liquid is cloudy or has floating particles in it.

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

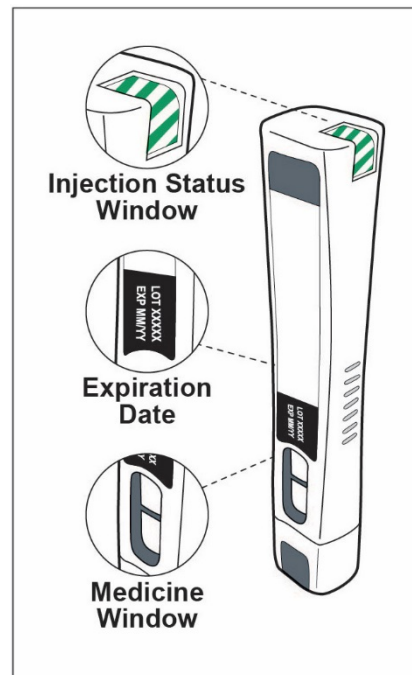


Figure C

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 *Figure D*).

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

- b. Wipe your skin with an alcohol wipe.

⚠ 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.

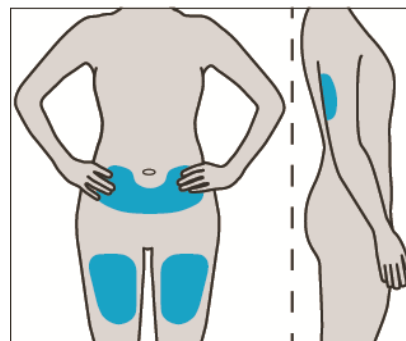


Figure D

Giving your injection:

Step 5. Remove the PLEGRIDY Pen cap

- a. Pull the pen cap straight off and set it aside for disposal after your injection (See *Figure E*). Your pen is ready to inject.

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

⚠ Caution! Do not recap your pen. This could lock the pen.

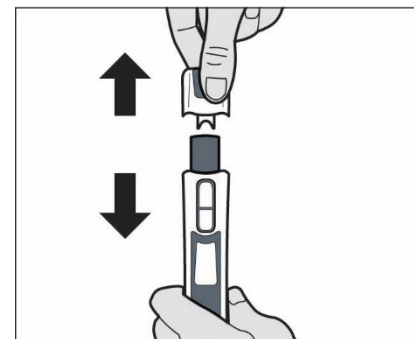


Figure E

Step 6. Give your injection

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

Note: Be ready to inject prior to pressing your pen down on your injection site, as the needle cover will lock when it is lifted from the site.

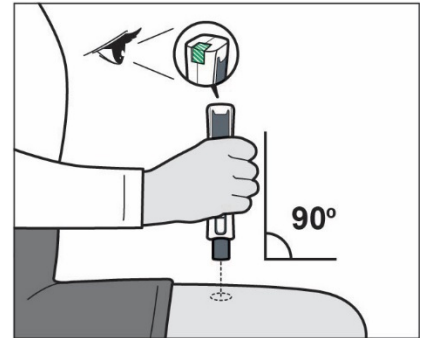


Figure F

- b. Firmly press and hold down your pen on your injection site until you hear the clicking sounds start (See *Figure G*).

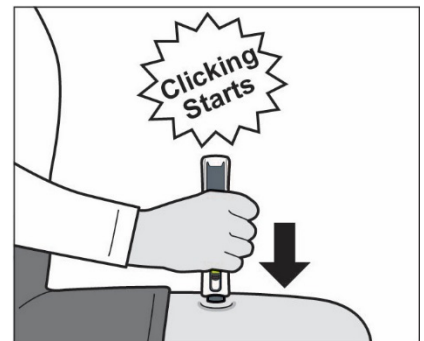


Figure G

- c. Continue to hold your 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 checkmarks in the injection status window.



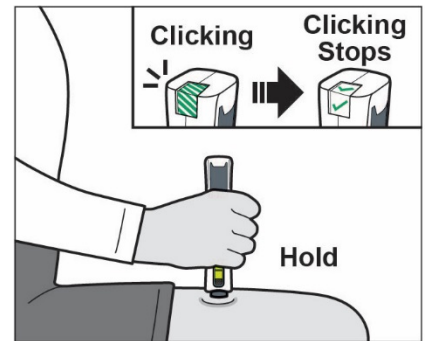


Figure H

If you do not hear clicking sounds and/or you do not see green checkmarks in the injection status window after attempting to inject, your pen may have locked and you should call the Biogen ONE® Support Program at 1-855-676-6300.

Step 7. Remove your PLEGRIDY Pen from your injection site

- a. After the clicking sound has stopped, lift your pen from your injection site. The needle cover will extend to cover the needle and will lock (See *Figure I*).

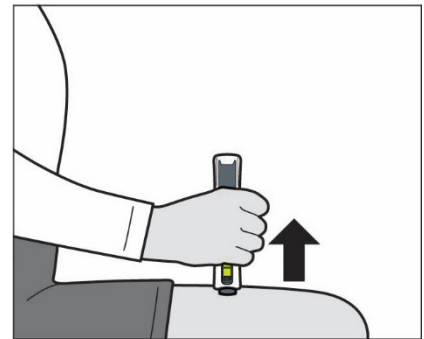


Figure I

Step 8. Check to make sure you have received your full dose of PLEGRIDY (see *Figure J*)

- a. Check the injection status window. You should see green checkmarks.
- b. Check the medication window. You should see a yellow plunger.

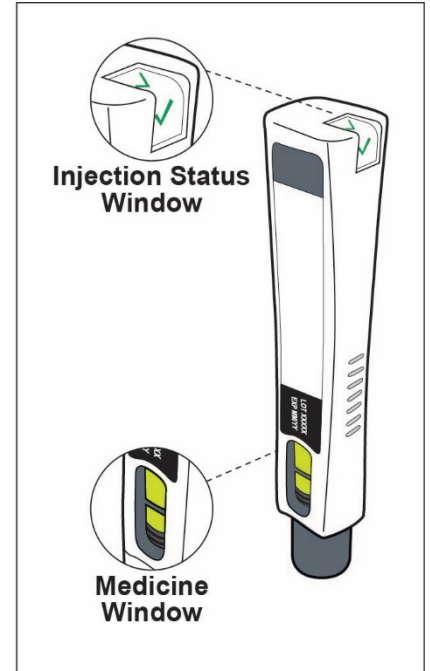


Figure J

After Your Injection

After Use – Parts of your PLEGRIDY Pen (see Figure K):

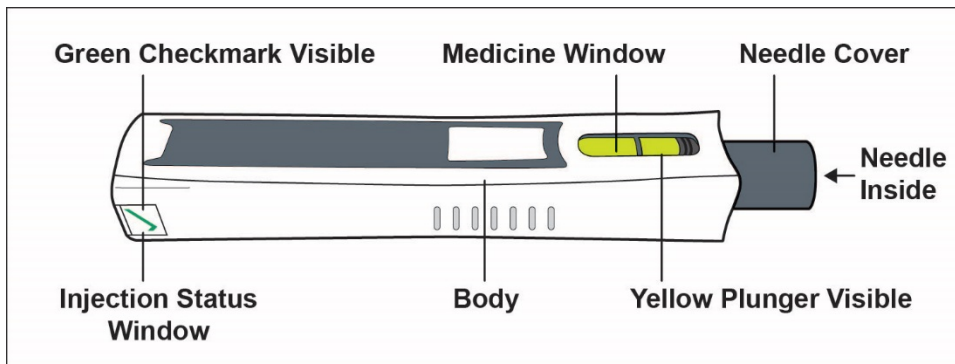


Figure K


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

After your injection:

Step 9. Dispose of your used PLEGRIDY Pens

- a. Throw away the used PLEGRIDY pens into a special secure container, such as a sharps bin, or according to community guidelines. Check with your doctor, pharmacist or nurse about the right way to throw away the container.

⚠ Do not dispose of your used pens or disposal container in your household trash unless your community guidelines permit this.

 **Do not** recap your PLEGRIDY Pen.

Step 10. Care for injection site

- a. Apply a gauze pad or adhesive bandage to the injection site, if needed.

Step 11. Check your injection site


- a. Apply a gauze pad or adhesive bandage to the injection site, if needed.
- b. 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

- a) Record the date and location of each injection and alternate sites between your injections.
- b) Do not use the same injection site for consecutive injections.

Storage

- Recommended storage is controlled refrigeration 2°C to 8°C (36°F to 46°F) 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 (up to 77°F) for up to 30 days.

 **Do not** freeze or expose to high temperatures.

If you want more information about PLEGRIDY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>; the manufacturer's website www.biogen.ca, or by calling 1-800-477-3462.

This leaflet was prepared by Biogen Canada Inc.

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