PRODUCT MONOGRAPH

[Pr]PLEGRIDY™

peginterferon beta-1a

Liquid for injection 125 µg

Immunomodulator

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[Pr]PLEGRIDY™

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Liquid for subcutaneous injection in pre-filled syringe 125 µg per 0.5 mL	*For a complete listing see Dosage Forms, Composition and Packaging Section.*
	Liquid for subcutaneous injection in pre-filled pen 125 µg per 0.5 mL	

INDICATIONS AND CLINICAL USE

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.

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 "WARNINGS and PRECAUTIONS, Special population."

Pediatrics (< 18 years of age):
The safety and efficacy of PLEGRIDY in patients below 18 years of age has not been studied.

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.

For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Pregnant patients (see WARNING and PRECAUTIONS)
- Patients with current severe depression and/or suicidal ideation (see "WARNINGS and PRECAUTIONS").

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 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 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.
- 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 Part III Consumer 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.

Hepatic/Biliary/Pancreas

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 and hepatic injury have been observed with the use of PLEGRIDY. Patients should be monitored for signs of hepatic injury (see Adverse Reactions). Treatment with PLEGRIDY should be stopped if icterus or other clinical symptoms of hepatic dysfunction appear.

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 Adverse Reactions).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a rare complication of treatment with interferon beta, including PLEGRIDY. Discontinue peginterferon beta-1a if serious hypersensitivity reactions occur (see Adverse Reactions).

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 Adverse Reactions).

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 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.

Seizure

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 Adverse Reactions).

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 Adverse Reactions).

Immunogenicity

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

antibodies to the PEG moiety of peginterferon beta-1a.

Endocrine Disorders: hyperthyroidism

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

Special Populations

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 Adverse Reactions and Pharmacokinetics)

Pregnant Women:
There are no adequate and well-controlled studies in pregnant women. PLEGRIDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. PLEGRIDY has not been tested for developmental toxicity in pregnant animals. Administration of PLEGRIDY to mature female rhesus monkeys resulted in menstrual irregularities accompanied by decreases in serum progesterone and 17-beta estradiol, consistent with the known abortifacient effects of non-pegylated interferon beta-1a (see TOXICOLOGY).

Nursing Women:
It is not known whether PLEGRIDY is secreted in human milk.

Pediatrics (< 18 years of age):
The safety and effectiveness of PLEGRIDY in patients below the age of 18 have not been studied.

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.

ADVERSE REACTIONS

Adverse Drug 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%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of PLEGRIDY 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 1 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 1257 patients received at least 1 year, and 789 patients received at least 2 years of treatment with PLEGRIDY. 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 (Year 1). A total of 500 subjects were exposed to placebo.

The experience in Year 2 of the 105MS301 study (all patients received PLEGRIDY) was consistent with the experience in the 1-year placebo-controlled phase of the 105MS301 study.

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 177 weeks (41 months), with an overall exposure equivalent to 1932 person-years. The experience in the 105MS302 extension study has been 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 1 Adverse Reactions reported for PLEGRIDY 125 micrograms subcutaneously every 2 weeks at ≥ 1% higher incidence than placebo

MedDRA System Organ Class	MedDRA preferred term	PLEGRIDY (N=512) %	Placebo (N=500) %	PLEGRIDY Frequency category*	
				Very Common (≥1/10)	Common (≥1/100 - <1/10)
Infections and Infestation	Upper respiratory tract infection	29(6%)	27(5%)		Common
	Urinary Tract infection	28(5%)	21(4%)		Common
	Oral Herpes	12(2%)	7(1%)		Common
	Cystitis	9(2%)	2(<1%)		Common
Psychiatric Disorders	Insomnia	28(5%)	19(4%)		Common
	Anxiety	13(3%)	12(2%)		Common
Nervous System Disorders	Headache	224(44%)	165(33%)	Very Common	
	Dizziness	35(7%)	31(6%)		Common
	Somnolence	10(2%)	5(1%)		Common
	Balance disorder	9(2%)	7(1%)		Common
	Tremor	9(2%)	6(1%)		Common
	Dysgeusia	6(1%)	0		Common
Gastrointestinal disorders	Nausea	44(9%)	31 (6%)		Common
	Vomiting	26(5%)	11(2%)		Common
	Abdominal Pain	16(3%)	10(2%)		Common
	Toothache	16(3%)	11(2%)		Common
Eye Disorders	Visual Impairment	9(2%)	5(1%)		Common
Vascular Disorder	Hypertension	14(3%)	10(2%)		Common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal Pain	34(7%)	31(6%)		Common
Musculoskeletal and Connective Tissue Disorders	Myalgia	97(19%)	30(6%)	Very Common	
	Back Pain	61(12%)	57(11%)	Very Common	
	Arthralgia	57(11%)	35(7%)	Very Common	
	Musculoskeletal stiffness	15(3%)	9(2%)		Common
	Bone Pain	11(2%)	1(<1%)		Common
General Disorders and Administration Site Conditions	Injection site erythema	315(62%)	33(7%)	Very Common	
	Influenza like illness	239(47%)	63(13%)	Very Common	
	Pyrexia	228(45%)	76(15%)	Very Common	
	Chills	88(17%)	23(5%)	Very Common	
	Injection site pain	77(15%)	15(3%)	Very	

MedDRA System Organ Class	MedDRA preferred term	PLEGRIDY (N=512) %	Placebo (N=500) %	PLEGRIDY Frequency category*	
				Very Common (≥1/10)	Common (≥1/100 - <1/10)
				Common	
	Asthenia	68(13%)	38(8%)	Very Common	
	Injection site pruritus	68(13%)	6(1%)	Very Common	
	Hyperthermia	21(4%)	6(1%)		Common
	Pain	25(5%)	16(3%)		Common
	Injection site oedema	15(3%)	0		Common
	Injection site warmth	16(3%)	0		Common
	Injection site hematoma	15(3%)	7(1%)		Common
	Feeling Cold	9(2%)	2(<1%)		Common
	Injection site swelling	9(2%)	1(<1%)		Common
	Injection site inflammation	7(1%)	0		Common
	Injection site rash	8(2%)	0		Common
	Injection site reaction	6(1%)	0		Common
Investigations	Body temperature increased	31(6%)	14(3%)		Common
	Alanine aminotransferase increased	29(6%)	13(3%)		Common
	Aspartate aminotransferase increased	18(4%)	8(2%)		Common
	Gamma-glutamyl-transferase increased	15(3%)	7(1%)		Common
	Blood glucose increased	10(2%)	4(<1%)		Common
	Haemoglobin decreased	10(2%)	3(<1)		Common
Skin and Subcutaneous Tissue Disorder	Pruritus	19(4%)	6(1%)		Common
	Alopecia	8(2%)	6(1%)		Common
	Erythema	8(2%)	1(<1%)		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) (≤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 PLEGRDY (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received PLEGRDY in the 105MS301 study.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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 , carpel 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, quadriparesis, 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, hypoaethesia 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, cholelthiasis, 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, patallofemoral 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 sire 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

Post-Market Adverse Drug Reactions

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

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.

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

DOSAGE AND ADMINISTRATION

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 *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. *Part III, Consumer 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.

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 2).

Table 2 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 every 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).

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.

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.

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.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

A definitive mechanism of action of PLEGRIDY 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.

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 to14 days compared to 5 days observed for non-pegylated interferon beta-1a. The neopterin response was still observed when PLEGRIDY level was undetectable.

Pharmacokinetics

Following a single SC dose from 63 to 188 micrograms in healthy subjects, serum PLEGRIDY peak concentration (Cmax) 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 Cmax 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, Cmax, and half-life was high. At Week 24 following 125 µg at Q2W, %CV of 50%, 89%, and 57% for AUC_{tau}, Cmax, $t_{1/2}$, respectively, was observed.

Absorption: In healthy subjects, Cmax was reached from 1 to 1.5 days (Tmax) post dose and then declined. Following subcutaneous administration of 125 microgram PLEGRIDY every two weeks in multiple sclerosis patients, the peak concentration Cmax of 280 ± 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 ± SE).

Metabolism and Excretion: PLEGRIDY is not extensively metabolized in the liver. 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 (t1/2) 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 ± 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 µg in subjects with various degrees of renal impairment, there was an increase in AUC (30-53%) and Cmax (26-42%) in subjects with mild (creatinine clearance 50 to ≤ 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 Cmax 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.

STORAGE AND STABILITY

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 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.

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pre-filled syringe
PLEGRIDY 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).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: peginterferon beta 1-a

Chemical name: peginterferon beta-1a

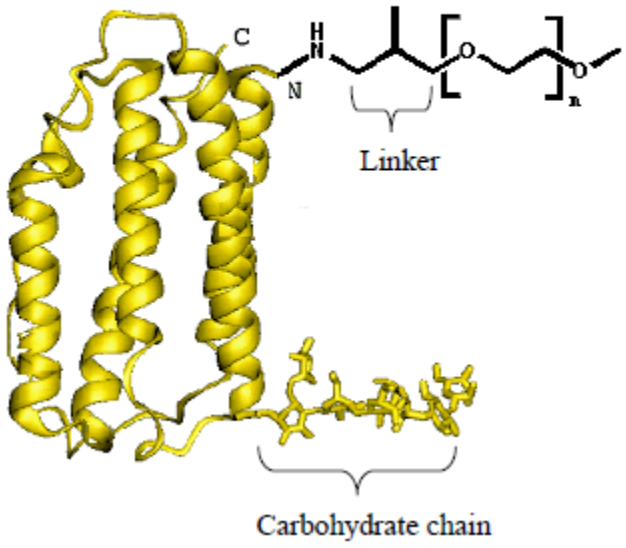
Glycosylated recombinant interferon beta-1a that is pegylated with a single, linear 20 kDa methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde moiety at the N-terminus.

CAS Index Number: 1211327-92-2

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.

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.

CLINICAL TRIALS

Study demographics and trial design

Table 3 Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
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%

The efficacy and safety of PLEGRIDY 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.

Study results

PLEGRIDY every 2 weeks reduced the ARR by 36% compared to placebo (p=0.0007) at one year (Table 4). Complete results for this study are shown in Table 4 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 4 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).

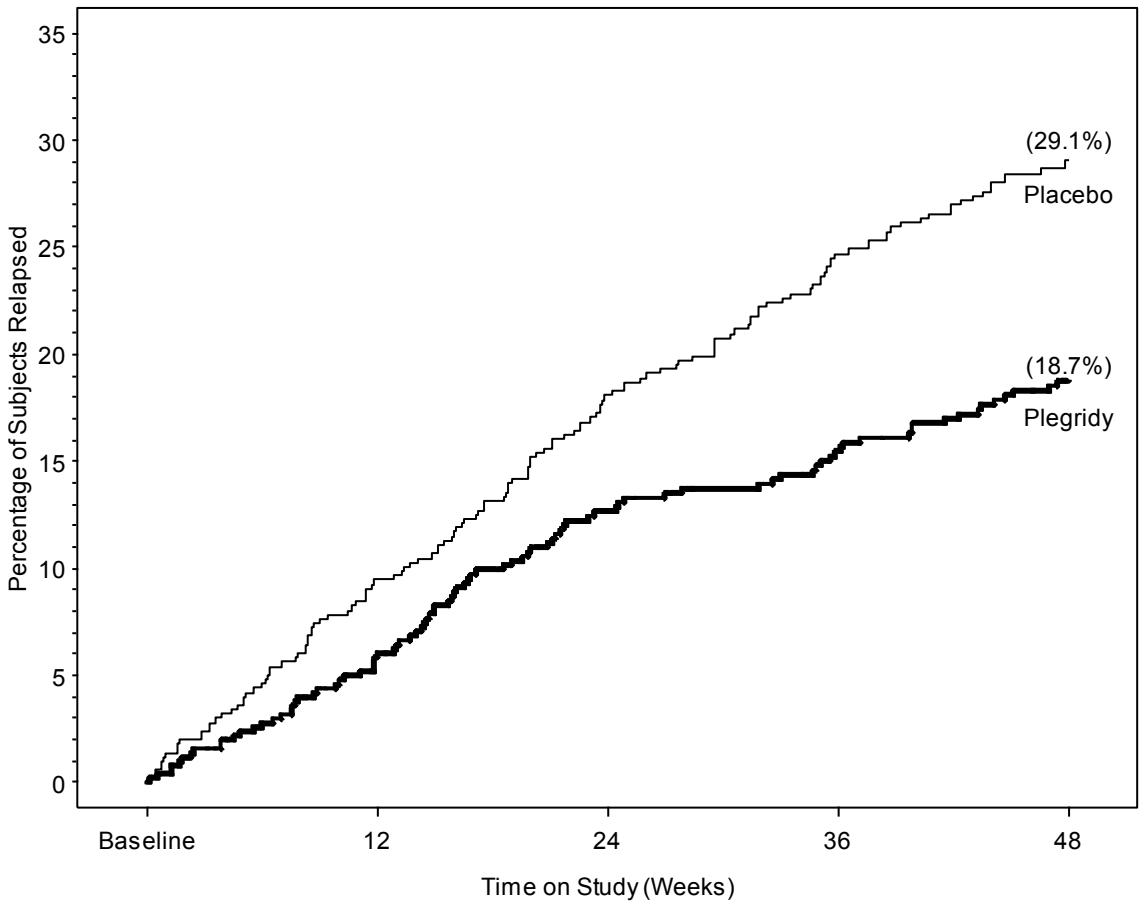
c Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. >=4), age (<40 vs. >=40).

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

DETAILED PHARMACOLOGY

See "Action and Clinical Pharmacology."

MICROBIOLOGY

Not applicable.

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 interfereon 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.

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

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.

Impairment of Fertility
The weekly subcutaneous administration of PLEGRIDY 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.

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PART III: CONSUMER INFORMATION

PLEGRIDY™ (pronounced PLEGG-rih-dee)
PLEGRIDY™ PS (peginterferon beta- 1a) pre-filled syringe
PLEGRIDY™ PEN (peginterferon beta- 1a) pre-filled pen

This leaflet is part III of a three-part "Product Monograph" published when PLEGRIDY was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PLEGRIDY. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is 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.

What it does:
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.

When it should not be used:
Do not use PLEGRIDY:

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

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.

What the medicinal ingredient is:
The medicinal/active ingredient in PLEGRIDY is peginterferon beta 1a.

What the important nonmedicinal ingredients are:
L-Arginine Hydrochloride, Glacial Acetic Acid, Polysorbate 20 in Water for Injection, and Sodium Acetate Trihydrate.

What dosage forms it comes in:
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.

WARNINGS AND PRECAUTIONS

BEFORE you use PLEGRIDY talk to your doctor or pharmacist if:

- you have ever experienced:
    - 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 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.

Pregnancy and breast-feeding

- If you could get pregnant, you need to use contraception while you use PLEGRIDY.
- If you are planning a baby or if you do become pregnant while you are using PLEGRIDY, tell your doctor. You and your doctor can discuss if you should carry on with treatment.
- If you are already pregnant, or think that you might be, talk to a doctor as soon as you can.
- If you want to breastfeed, talk to your doctor first.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes any medicines obtained without a prescription.
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.

PROPER USE OF THIS MEDICATION

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 a 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.

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.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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 get less.

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

1. Use your PLEGRIDY injection just before bedtime. This may allow you to sleep through the effects.
2. Take acetaminophen or ibuprofen half an hour before your PLEGRIDY injection and continue taking it for up to a day(24 hours). Speak to your doctor or pharmacist about a suitable dose.
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 get less 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.

Changes to levels of liver enzymes
These changes will show up in blood tests. You may not experience any symptoms or you may notice:
- 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, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Common		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
Symptom / Effect		Only if severe	In all cases	
Flu-like symptoms	headache, muscle aches, chills or a fever	X		
Injection site reactions	redness, itching or pain	X		
	swelling, bruising, warmth or rash at injection site	X		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Changes to levels of liver enzymes	Yellowing of your skin or the whites of your eyes (jaundice		X	
	Itching all over		X	
	Feeling sick, being sick (nausea and vomiting)		X	
	Easy bruising of the skin		X	
Other	headache	X		
	Muscle pain (myalgia)	X		
	Pain in your joints, arms, legs or neck (arthralgia)	X		
	Chills, feeling cold	X		
	Feeling weak and tired (asthenia)	X		
	Feeling sick or being sick (nausea or vomiting)	X		
	Itchy skin (pruritus)	X		
	Increase in body temperature	X		

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

HOW TO INJECT PLEGRIDY PRE-FILLED SYRINGE

HOW TO STORE IT

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.

Disposal

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.

WHAT IS IN YOUR PLEGRIDY PACK

The PLEGRIDY pre-filled syringe Starter Pack holds 2 ready to use syringes. Each Starter Pack for PLEGRIDY syringe contains clear, colourless liquid (0.5ml) containing one syringe with- 63 and one syringe with 94 micrograms of peginterferon- beta-1a. Every syringe has a pre-attached needle and is ready to inject.

The PLEGRIDY pre-filled syringe Administration Dose Pack holds 2 or 6 ready to use syringes. Each Administration Dose Pack syringe contains a clear, colourless liquid (0.5ml) containing 125 micrograms of peginterferon beta-1a. Every syringe has a pre-attached needle and is ready to inject.

The PLEGRIDY pre-filled pen Starter Pack holds 2 ready to use pens. Each Starter Pack for PLEGRIDY pen contains clear, colourless liquid (0.5ml) containing one pen with 63 and one pen with 94 micrograms of peginterferon- beta-1a. Every pen has a pre-attached needle and is ready to inject.

The PLEGRIDY pre-filled pen Administration Dose Pack holds 2 or 6 ready-to-use pens. Each Administration Dose Pack pen contains clear, colourless liquid (0.5ml) containing 125 micrograms of peginterferon beta-1a. Every pen has a pre-attached needle and is ready to inject.

BEFORE YOU START
Read the Instructions for Use before you start using PLEGRIDY and each time you get a refill. 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.

STORAGE
Once removed from the refrigerator, allow PLEGRIDY to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm.

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 (36 °F to 77 °F), protected from light.

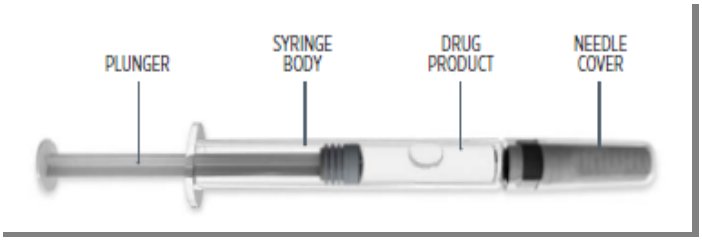
DOSE SCHEDULE
Choose the correct PLEGRIDY pre-filled syringe from a pack. PLEGRIDY pre-filled syringe Starter Pack contains your first two injections to gradually adjust your dose.

WHEN	WHICH DOSE	WHICH PACK
Day 0* (63 micrograms)	First injection: 63 micrograms, choose orange labelled syringe	
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	

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

PREPARING FOR INJECTION

KNOW THE PRE-FILLED SYRINGE FEATURES



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

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

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

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

CHECK THE PACK AND THE PRE-FILLED SYRINGE
Check the expiration date printed on the PLEGRDY pre-filled syringe, PLEGRIDY pre-filled syringe carton, and the outer carton. Do not use the PLEGRIDY pre-filled syringe past the expiration date.

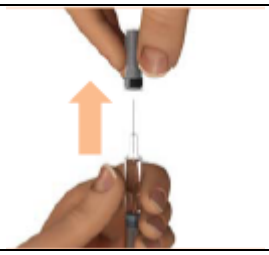
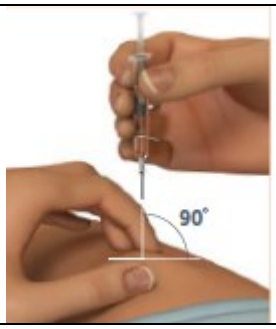
Let the pre-filled syringe sit for 30 minutes before injecting the PLEGRIDY dose to allow the medication to reach room temperature. A room temperature solution is more comfortable to inject. Do not use external heat sources such as hot water to warm the PLEGRIDY pre-filled syringe.

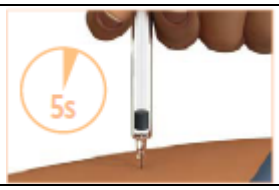
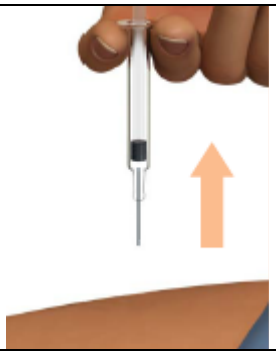
Check that the medication is clear and colourless	
Do not use PLEGRIDY pre-filled syringe if the liquid is coloured, cloudy, or contains floating particles.	

PLEGRIDY in pre-filled syringe is for subcutaneous injection. PLEGRIDY should be injected exactly as your healthcare professional has shown you. PLEGRIDY should not be injected into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way. Do not remove the Needle Cover until ready to inject.

Wash your hands with soap and water.

GIVING THE INJECTION

1. CHOOSE THE INJECTION SITE	
Choose an injection site and wipe the skin with an alcohol wipe. Let the injection site dry before injecting the dose. . Do not touch this area again before giving the injection. PLEGRIDY should be injected into the thigh, abdomen or upper arm.	
2. FIRMLY REMOVE NEEDLE COVER	
Pull the Needle Cover straight off the needle and dispose of the Needle Cover. Do not touch the needle. Do not recap the PLEGRIDY pre-filled syringe.	
3. PREPARE INJECTION SITE AND POSITION PRE-FILLED SYRINGE	
Pinch the skin around the cleaned injection site using thumb and forefinger.	
Hold the PLEGRIDY syringe at a 90° angle to the injection site.	
4. INJECT MEDICATION	
Quickly insert the needle straight into the skin fold until the needle is fully under the skin. The skin fold can be released after needle insertion.	

Slowly push the Plunger in one smooth motion until syringe is empty. This should take about 5 seconds. Do not lift the pre-filled syringe off the injection site.	
5. WAIT 5 SECONDS	
Keep the needle inserted for 5 seconds.	
6. REMOVE PRE-FILLED SYRINGE FROM SITE	
Pull the needle straight out. Do not recap the PLEGRIDY pre-filled syringe. Do not reuse the PLEGRIDY pre-filled syringe.	

AFTER THE INJECTION

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

DISPOSE OF PRE-FILLED SYRINGE
Discard the used PLEGRIDY pre-filled syringe 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 professional about the right way to throw away the container. There may be local laws about how dispose of used PLEGRIDY pre-filled syringes. Do discard used PLEGRIDY pre-filled syringe in household trash or recycling bins.

RECORD DATE AND INJECTION SITE LOCATION
Record the date and injection site location of each injection and alternate sites between your injections. Do not use the same injection site for consecutive injections.

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 healthcare professional.

GENERAL WARNINGS
Do not reuse your PLEGRIDY pre-filled syringe. Do not share your PLEGRIDY pre-filled syringe. Keep PLEGRIDY pre-filled syringe out of reach of children.

HOW TO INJECT PLEGRIDY PRE-FILLED PEN

BEFORE YOU START
Read the Instructions for Use before you start using PLEGRIDY and each time you get a refill. 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.

STORAGE
Once removed from the refrigerator, allow PLEGRIDY to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm.

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 (36°F to 77°F), protected from light

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	
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	

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

PREPARING FOR INJECTION

KNOW THE PEN FEATURES

Before use (Figure A)

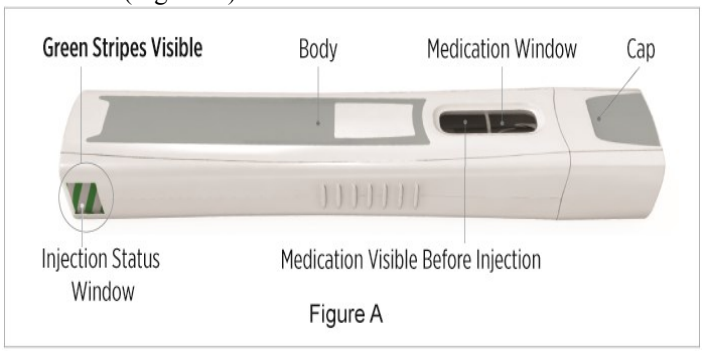


Figure A

After use (Figure B)

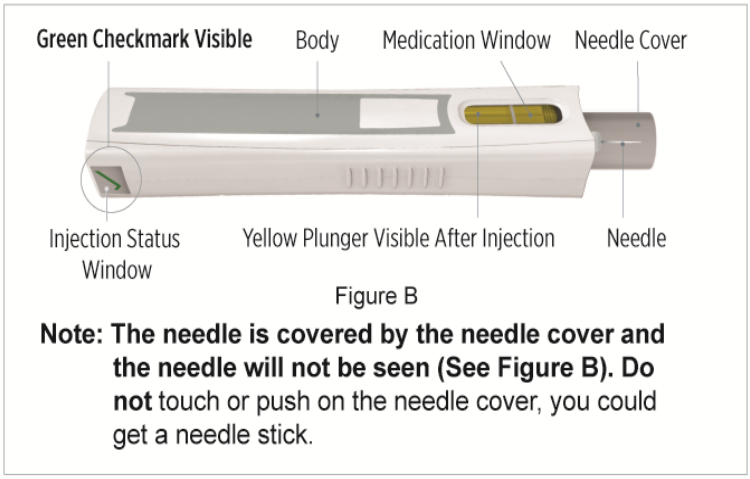


Figure B

Note: The needle is covered by the needle cover and the needle will not be seen (See Figure B). Do not touch or push on the needle cover, you could get a needle stick.

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

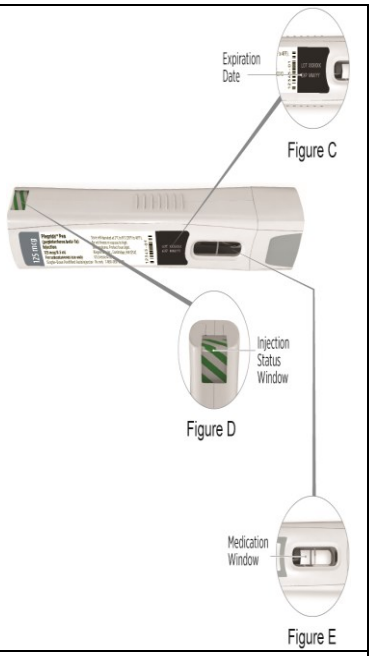
Collect supplies. You will need the following supplies to perform the injection:
- Alcohol wipe
- Gauze pad
- Adhesive bandage
- A puncture resistant container for disposal of used pens

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.

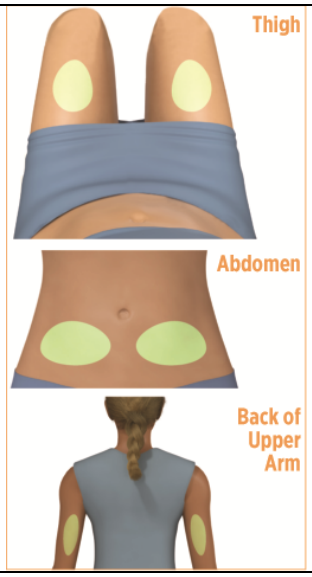
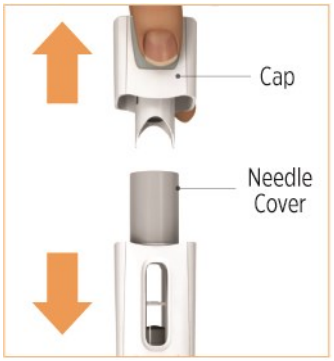
Check your PLEGRIDY Pen

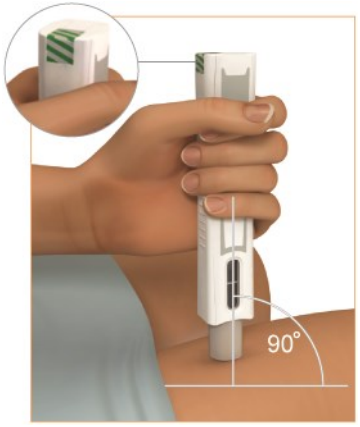
Check injection status. Make sure that green stripes are visible (Figure D). • Do not use the pen unless injection status window shows green stripes.	
• Check that the medication is clear and colourless in the medication window (Figure E). Do not use the PLEGRIDY Pen if the liquid is coloured, cloudy, or contains floating particles. • You may see a bubble. This is normal	

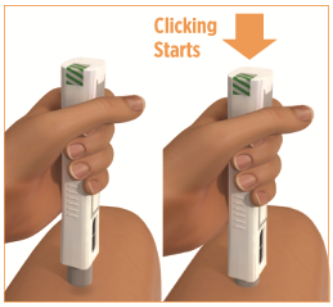
PLEGRIDY in pre-filled Pen is for subcutaneous injection.
PLEGRIDY should be injected exactly as your healthcare professional has shown you. PLEGRIDY should not be injected into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.
Do not remove the cap until ready to inject.
Wash your hands with soap and water.

GIVING THE INJECTION

1. CHOOSE THE INJECTION SITE (Figure F)	
Choose an injection site and wipe the skin with an alcohol wipe. Let the injection site dry before injecting the dose. Do not touch this area again before giving the injection. PLEGRIDY should be injected into the thigh, abdomen or upper arm.	

	
2. REMOVE CAP (Figure G)	
Pull the Cap off and dispose of the Cap. • Do not recap your PLEGRIDY Pen • The needle is covered by the needle cover and will not be visible. • Do not touch or push down on the needle cover, you could get a needle stick injury. Your PLEGRIDY Pen is ready to inject after the cap is removed.	

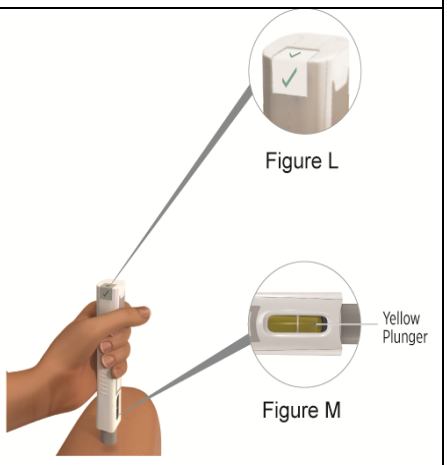
3. POSITION PEN AND CHECK (Figure H)	
Place your PLEGRIDY Pen on your chosen injection site. You should hold your PLEGRIDY Pen at a 90º angle to your injection site so that you can see the green stripes in the injection status window. Do not use your PLEGRIDY pen unless you see green stripes in the injection status window.	

4. INJECT MEDICATION (Figure I)	
Press into site and hold until clicking stops and green checkmarks appear. Pressing down will insert the needle and automatically start the injection. Do not lift the pen off the injection site. Do not make any movements until injection is completed. Continue to firmly press down, hold the Pen at a 90° angle and keep your hand steady until the injection is completed.	
During the injection process: PLEGRIDY Pen will "click" several times. Green stripes pattern will be moving in the injection status window. The pen's clicking sounds will stop when the injection is complete.	
Check for completion. Make sure the green check marks have appeared in the injection status window.	

5. REMOVE PEN FROM SITE (Figure K)	
Lift the PLEGRIDY Pen from the injection site. The needle cover will extend covering the needle completely.	

AFTER THE INJECTION

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

VERIFY DOSE DELIVERY	
Check the injection status window. You should see green checkmarks in the injection status window (Figure L). Check the medication window. You should see a yellow plunger in the medication window (Figure M) An extended yellow plunger indicates that the entire dose has been successfully administered. Do not reuse the PLEGRIDY Pen.	 Figure L Figure M

DISPOSE OF PEN
Discard the used PLEGRIDY Pen 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 professional about the right way to dispose of the container. There may be local laws about how to discard used Pens. Do not discard used PLEGRIDY Pen in household trash or recycling bins.

RECORD DATE AND INJECTION SITE LOCATION
Record the date and injection site location of each injection and alternate sites between your injections. Do not use the same injection site for consecutive injections.

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

GENERAL WARNINGS

Do not reuse your PLEGRIDY Pen. Do not share your PLEGRDY Pen. Keep PLEGRIDY Pen out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Biogen Canada Inc. at: 1-855-676-6300.

This leaflet was prepared by Biogen Canada Inc.