

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PLEGRIDY™ safely and effectively. See full prescribing information for PLEGRIDY.

**PLEGRIDY (peginterferon beta-1a) injection, for subcutaneous injection**  
**Initial U.S. Approval: 2014**

### INDICATIONS AND USAGE

PLEGRIDY is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis (1)

### DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1)
- Recommended dose: 125 micrograms every 14 days (2.1)
- PLEGRIDY dose should be titrated, starting with 63 micrograms on day 1, 94 micrograms on day 15, and 125 micrograms (full dose) on day 29 (2.1)
- A healthcare professional should train patients in the proper technique for self-administering subcutaneous injections using the prefilled pen or syringe (2.2)
- Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms (2.3)

### DOSAGE FORMS AND STRENGTHS

- Injection: 125 micrograms per 0.5 mL solution in a single-dose prefilled pen (3)
- Injection Starter Pack: 63 micrograms per 0.5 mL solution in a single-dose prefilled pen and 94 micrograms per 0.5 mL solution in a single-dose prefilled pen (3)
- Injection: 125 micrograms per 0.5 mL solution in a single-dose prefilled syringe (3)
- Injection Starter Pack: 63 micrograms per 0.5 mL solution in a single-dose prefilled syringe and 94 micrograms per 0.5 mL solution in a single-dose prefilled syringe (3)

### CONTRAINDICATIONS

History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation (4)

### WARNINGS AND PRECAUTIONS

- Hepatic injury: monitor liver function tests; monitor patients for signs and symptoms of hepatic injury; consider discontinuation of PLEGRIDY if hepatic injury occurs (5.1)
- Depression and suicide: advise patients to report immediately any symptom of depression or suicidal ideation to their healthcare provider; consider discontinuation of PLEGRIDY if depression occurs (5.2)
- Seizure: Seizures are associated with the use of interferon beta. Exercise caution when administering PLEGRIDY to patients with a seizure disorder (5.3)
- Anaphylaxis and other allergic reactions: serious allergic reactions have been reported as a rare complication of treatment with interferon beta. Discontinue PLEGRIDY if a serious allergic reaction occurs (5.4)
- Injection site reactions: change injection site or consider discontinuation of PLEGRIDY if there is necrosis (5.5)
- Congestive heart failure: monitor patients with pre-existing significant cardiac disease for worsening of cardiac symptoms (5.6)
- Decreased peripheral blood counts: monitor complete blood counts (5.7)
- Autoimmune disorders: consider discontinuation of PLEGRIDY if a new autoimmune disorder occurs (5.8)

### ADVERSE REACTIONS

The most common adverse reactions (incidence  $\geq 10\%$  and at least 2% more frequent on PLEGRIDY than on placebo) were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec at 1-800-456-2255 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: based on animal data, may cause fetal harm (8.1)
- Severe Renal Impairment: monitor for adverse reactions (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2014

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# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

PLEGRIDY (peginterferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing Information

PLEGRIDY is administered subcutaneously.

The recommended dosage of PLEGRIDY is 125 micrograms injected subcutaneously every 14 days.

#### Treatment initiation

Patients should start treatment with 63 micrograms on day 1. On day 15 (14 days later), the dose is increased to 94 micrograms, reaching the full dose of 125 micrograms on day 29 (after another 14 days). Patients continue with the full dose (125 micrograms) every 14 days thereafter (see [Table 1](#)). A PLEGRIDY Starter Pack is available containing two prefilled pens or syringes: 63 micrograms (dose 1) and 94 micrograms (dose 2).

**Table 1: Schedule for Dose Titration**

<b>Dose</b>	<b>Time*</b>	<b>Amount (micrograms)</b>	<b>Color of Pen or Syringe Label</b>
Dose 1	On day 1	63	Orange
Dose 2	On day 15	94	Blue
Dose 3	On day 29 and every 14 days thereafter	125 (full dose)	Grey

\*Dosed every 14 days

### 2.2 Important Administration Instructions (All Dosage Forms)

Healthcare professionals should train patients in the proper technique for self-administering subcutaneous injections using the prefilled pen or syringe. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections are abdomen, back of the upper arm, and thigh.

Each PLEGRIDY pen and syringe is provided with the needle pre-attached. Prefilled pens and syringes are for a single dose only and should be discarded after use.

## 2.3 Premedication for Flu-like Symptoms

Prophylactic and concurrent use of analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms sometimes experienced during treatment with PLEGRIDY.

## 3 DOSAGE FORMS AND STRENGTHS

### *Pen*

- Injection: 125 micrograms of PLEGRIDY per 0.5 mL of solution in a single-dose prefilled pen
- Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled pen and 94 micrograms per 0.5 mL solution in a single-dose prefilled pen

### *Prefilled Syringe*

- Injection: 125 micrograms of PLEGRIDY per 0.5 mL of solution in a single-dose prefilled syringe
- Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled syringe and 94 micrograms per 0.5 mL of solution in a single-dose prefilled syringe

## 4 CONTRAINDICATIONS

PLEGRIDY is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation [*see Warnings & Precautions (5.4)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hepatic Injury

Severe hepatic injury, including hepatitis, autoimmune hepatitis, and rare cases of severe hepatic failure, have been reported with interferon beta. Asymptomatic elevation of hepatic transaminases has also been reported, and in some patients has recurred upon rechallenge with interferon beta.

Elevations in hepatic enzymes and hepatic injury have been observed with the use of PLEGRIDY in clinical studies. The incidence of increases in hepatic transaminases was greater in patients taking PLEGRIDY than in those taking placebo. The incidence of elevations of alanine aminotransferase above 5 times the upper limit of normal was 1% in placebo-treated patients and 2% in PLEGRIDY-treated patients. The incidence of elevations of aspartate aminotransferase above 5 times the upper limit of normal was less than 1% in placebo-treated patients and less than 1% in PLEGRIDY-treated patients. Elevations of serum hepatic

transaminases combined with elevated bilirubin occurred in 2 patients. Both cases resolved following discontinuation of PLEGRIDY.

Monitor patients for signs and symptoms of hepatic injury.

## **5.2 Depression and Suicide**

Depression, suicidal ideation, and suicide occur more frequently in patients receiving interferon beta than in patients receiving placebo.

In clinical studies, the overall incidence of adverse events related to depression and suicidal ideation in multiple sclerosis patients was 8% in both the PLEGRIDY and placebo groups. The incidence of serious events related to depression and suicidal ideation was similar and less than 1% in both groups.

Advise patients to report immediately any symptom of depression or suicidal ideation to their healthcare provider. If a patient develops depression or other severe psychiatric symptoms, consider stopping treatment with PLEGRIDY.

## **5.3 Seizures**

Seizures are associated with the use of interferon beta.

The incidence of seizures in multiple sclerosis clinical studies was less than 1% in patients receiving PLEGRIDY and placebo.

Exercise caution when administering PLEGRIDY to patients with a seizure disorder.

## **5.4 Anaphylaxis and Other Allergic Reactions**

Anaphylaxis and other serious allergic reactions are rare complications of treatment with interferon beta.

Less than 1% of PLEGRIDY-treated patients experienced a serious allergic reaction such as angioedema or urticaria. Those who did have serious allergic reactions recovered promptly after treatment with antihistamines or corticosteroids.

Discontinue PLEGRIDY if a serious allergic reaction occurs.

## **5.5 Injection Site Reactions**

Injection site reactions, including injection site necrosis, can occur with the use of subcutaneous interferon beta.

In clinical studies, the incidence of injection site reactions (e.g., injection site erythema, pain, pruritus, or edema) was 66% in the PLEGRIDY group and 11% in the placebo group; the incidence of severe injection site reactions was 3% in the PLEGRIDY group and 0% in the placebo group. One patient out of 1468 patients who received PLEGRIDY in clinical studies experienced injection site necrosis. The injury resolved with standard medical treatment.

Decisions to discontinue therapy following necrosis at a single injection site should be based on the extent of the necrosis. For patients who continue therapy with PLEGRIDY after injection

site necrosis has occurred, avoid administration of PLEGRIDY near the affected area until it is fully healed. If multiple lesions occur, discontinue PLEGRIDY until healing occurs.

## **5.6 Congestive Heart Failure**

Congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure occur in patients receiving interferon beta.

In clinical studies, the incidence of cardiovascular events was 7% in both PLEGRIDY and placebo treatment groups. No serious cardiovascular events were reported in the PLEGRIDY group.

Monitor patients with significant cardiac disease for worsening of their cardiac condition during initiation and continuation of treatment with PLEGRIDY.

## **5.7 Decreased Peripheral Blood Counts**

Interferon beta can cause decreased peripheral blood counts in all cell lines, including rare instances of pancytopenia and severe thrombocytopenia.

In clinical studies, decreases in white blood cell counts below  $3.0 \times 10^9/L$  occurred in 7% of patients receiving PLEGRIDY and in 1% receiving placebo. There is no apparent association between decreases in white blood cell counts and an increased risk of infections or serious infections. The incidence of clinically significant decreases in lymphocyte counts (below  $0.5 \times 10^9/L$ ), neutrophil counts (below  $1.0 \times 10^9/L$ ), and platelet counts (below  $100 \times 10^9/L$ ) were all less than 1% and similar in both placebo and PLEGRIDY groups. Two serious cases were reported in patients treated with PLEGRIDY: one patient (less than 1%) experienced severe thrombocytopenia (defined as a platelet count less than or equal to  $10 \times 10^9/L$ ), and another patient (less than 1%) experienced severe neutropenia (defined as a neutrophil count less than or equal to  $0.5 \times 10^9/L$ ). In both patients, cell counts recovered after discontinuation of PLEGRIDY. Compared to placebo, there were no significant differences in red blood cell counts in patients treated with PLEGRIDY.

Monitor patients for infections, bleeding, and symptoms of anemia. Monitor complete blood cell counts, differential white blood cell counts, and platelet counts during treatment with PLEGRIDY. Patients with myelosuppression may require more intensive monitoring of blood cell counts.

## **5.8 Autoimmune Disorders**

Autoimmune disorders of multiple target organs including idiopathic thrombocytopenia, hyper- and hypothyroidism, and autoimmune hepatitis have been reported with interferon beta.

In clinical studies, the incidence of autoimmune disorders was less than 1% in both PLEGRIDY and placebo treatment groups.

If patients develop a new autoimmune disorder, consider stopping PLEGRIDY.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of labeling:

- Hepatic Injury [*see Warnings and Precautions (5.1)*]
- Depression and Suicide [*see Warnings and Precautions (5.2)*]
- Seizures [*see Warnings and Precautions (5.3)*]
- Anaphylaxis and Other Allergic Reactions [*see Warnings and Precautions (5.4)*]
- Injection Site Reactions [*see Warnings and Precautions (5.5)*]
- Congestive Heart Failure [*see Warnings and Precautions (5.6)*]
- Decreased Peripheral Blood Counts [*see Warnings and Precautions (5.7)*]
- Autoimmune Disorders [*see Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of PLEGRIDY cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

In clinical studies (Study 1 and Study 2), 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. A total of 1093 patients received at least 1 year, and 415 patients at least 2 years of treatment with PLEGRIDY. A total of 512 and 500 patients, respectively, received PLEGRIDY 125 micrograms every 14 days or every 28 days during the placebo-controlled phase of Study 1 (year 1). The experience in year 2 of Study 1 and in the 2-year safety extension study (Study 2) was consistent with the experience in the 1-year placebo-controlled phase of Study 1.

In the placebo-controlled phase of Study 1, the most common adverse drug reactions for PLEGRIDY 125 micrograms subcutaneously every 14 days were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia (all had incidence more than 10% and at least 2% more than placebo). The most commonly reported adverse event leading to discontinuation in patients treated with PLEGRIDY 125 micrograms subcutaneously every 14 days was influenza-like illness (in less than 1% of patients).

[Table 2](#) summarizes adverse reactions reported over 48 weeks from patients treated in the placebo-controlled phase of Study 1 who received subcutaneous PLEGRIDY 125 micrograms (n=512), or placebo (n=500), every 14 days.

**Table 2: Adverse reactions in the 48-week placebo-controlled phase of Study 1 with an incidence 2% higher for PLEGRIDY than for placebo**

	<b>PLEGRIDY (N=512) %</b>	<b>Placebo (N=500) %</b>
<b>Nervous System Disorders</b>		
Headache	44	33
<b>Gastrointestinal Disorders</b>		
Nausea	9	6
Vomiting	5	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Myalgia	19	6
Arthralgia	11	7
<b>General Disorders and Administration Site Conditions</b>		
Injection site erythema	62	7
Influenza like illness	47	13
Pyrexia	45	15
Chills	17	5
Injection site pain	15	3
Asthenia	13	8
Injection site pruritus	13	1
Hyperthermia	4	1
Pain	5	3
Injection site edema	3	0
Injection site warmth	3	0
Injection site hematoma	3	1
Injection site rash	2	0
<b>Investigations</b>		
Body temperature increased	6	3
Alanine aminotransferase increased	6	3
Aspartate aminotransferase increased	4	2
Gamma-glutamyl-transferase increased	3	1
<b>Skin and Subcutaneous Tissue Disorder</b>		
Pruritus	4	1

### *Immunogenicity*

For therapeutic proteins, there is a potential for immunogenicity. In Study 1, fewer than 1% of patients treated with PLEGRIDY every 14 days for 1 year developed neutralizing antibodies. Approximately 7% of PLEGRIDY-treated patients developed antibodies to PEG.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PLEGRIDY with the incidence of antibodies to other products may be misleading.

### *Flu-Like Symptoms*

Influenza-like illness was experienced by 47% of patients receiving PLEGRIDY 125 micrograms every 14 days and 13% of patients receiving placebo. Fewer than 1% of PLEGRIDY-treated patients in Study 1 discontinued treatment due to flu-like symptoms.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C

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. In monkeys given interferon beta by subcutaneous injection every other day during early pregnancy, no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses.

### **8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PLEGRIDY is administered to a nursing woman.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **8.5 Geriatric Use**

Safety and effectiveness in geriatric patients have not been established.

### **8.6 Renal Impairment**

Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment [*see Clinical Pharmacology (12.3)*].



## 11 DESCRIPTION

PLEGRIDY (peginterferon beta-1a) is an interferon beta-1a to which a single, linear 20,000 dalton (Da) methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde molecule is covalently attached to the alpha amino group of the N-terminal amino acid residue.

The interferon beta-1a portion of PLEGRIDY is produced as a glycosylated protein using genetically-engineered Chinese hamster ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of the recombinant interferon beta-1a is identical to that of the human interferon beta counterpart. The molecular mass of PLEGRIDY is approximately 44,000 Da, consistent with the mass of the protein (approximately 20,000 Da), the carbohydrate moieties (approximately 2,500 Da), and the attached poly(ethylene glycol). However, because of 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 interferon beta, 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. PLEGRIDY contains no preservative.

### 11.1 PLEGRIDY PEN Single-Dose Prefilled Pen

PLEGRIDY PEN is composed of an autoinjector that surrounds a prefilled glass syringe containing 0.5 mL of a sterile solution in water for injection of 63, 94, or 125 micrograms of peginterferon beta-1a, 15.8 mg of L-arginine HCl, 0.79 mg of sodium acetate trihydrate, 0.25 mg of glacial acetic acid, and 0.025 mg of polysorbate 20. The pH is approximately 4.8.

### 11.2 PLEGRIDY Single-Dose Prefilled Syringe

A prefilled syringe of PLEGRIDY for subcutaneous injection contains 0.5 mL of a sterile solution in water for injection of 63, 94, or 125 micrograms of peginterferon beta-1a, 15.8 mg of L-arginine HCl, 0.79 mg of sodium acetate trihydrate, 0.25 mg of glacial acetic acid, and 0.025 mg of polysorbate 20. The pH is approximately 4.8.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism by which PLEGRIDY exerts its effects in patients with multiple sclerosis is unknown.

### 12.2 Pharmacodynamics

There is no biochemical or physiologic effect known to relate directly to the clinical effect of PLEGRIDY.

## 12.3 Pharmacokinetics

After single-dose or multiple-dose subcutaneous administration of PLEGRIDY to healthy subjects, serum PLEGRIDY peak concentration ( $C_{\max}$ ) and total exposure over time (area under the curve, or AUC) increased in proportion to doses from 63 to 188 micrograms. PLEGRIDY did not accumulate in the serum after multiple doses of 125 micrograms every 14 days. 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 between individual patients for AUC,  $C_{\max}$ , and half-life was high (41% to 68%, 74% to 89%, and 45% to 93%, respectively).

### *Absorption*

After 125 microgram subcutaneous doses of PLEGRIDY in multiple sclerosis patients, the maximum concentration occurred between 1 and 1.5 days, the mean  $C_{\max}$  was 280 pg/mL, and the AUC over the 14 day dosing interval was 34.8 ng.hr/mL.

### *Distribution*

In multiple sclerosis patients taking 125 microgram subcutaneous doses of PLEGRIDY every 14 days, the estimated volume of distribution was 481 liters.

### *Metabolism and Elimination*

Clearance mechanisms for PLEGRIDY include catabolism and excretion. The major pathway of elimination is renal. The half-life is approximately 78 hours in multiple sclerosis patients. The mean steady state clearance of PLEGRIDY is approximately 4.1 L/hr. PLEGRIDY is not extensively metabolized in the liver.

### *Specific Populations*

Body weight, gender, and age do not require dosage adjustment.

Renal impairment can increase the  $C_{\max}$  and AUC for PLEGRIDY. Results of a pharmacokinetic study in patients with mild, moderate, and severe renal impairment (creatinine clearance 50 to 80, 30 to 50, and less than 30 mL/minute, respectively) showed increases above normal for  $C_{\max}$  of 27%, 26%, and 42%, and for AUC, increases of 30%, 40%, and 53%. The half-life was 53, 49, and 82 hours in patients with mild, moderate, and severe renal impairment, respectively, compared to 54 hours in normal subjects.

In the same study, subjects with end stage renal disease requiring hemodialysis two or three times weekly had AUC and  $C_{\max}$  of PLEGRIDY values that were similar to those of normal controls. Each hemodialysis session removed approximately 24% of circulating PLEGRIDY from the systemic circulation [see *Use in Specific Populations* (8.6)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

The carcinogenic potential of PLEGRIDY has not been tested in animals.

#### *Mutagenesis*

PLEGRIDY 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*

In monkeys administered interferon beta by subcutaneous injection over the course of one menstrual cycle, menstrual irregularities, anovulation, and decreased serum progesterone levels were observed. These effects were reversible after discontinuation of drug.

## **14 CLINICAL STUDIES**

The efficacy of PLEGRIDY was demonstrated in the randomized, double-blind, and placebo-controlled phase (year 1) of Study 1. The trial compared clinical and MRI outcomes at 48 weeks in patients who received PLEGRIDY 125 micrograms (n=512) or placebo (n=500) by the subcutaneous route, once every 14 days.

Study 1 enrolled patients who had a baseline Expanded Disability Status Scale (EDSS) score from 0 to 5, who had experienced at least 2 relapses within the previous three years, and had experienced at least 1 relapse in the previous year. The trial excluded patients with progressive forms of multiple sclerosis. The mean age of the study population was 37 years, the mean disease duration was 3.6 years, and the mean EDSS score at baseline was 2.46. The majority of the patients were women (71%).

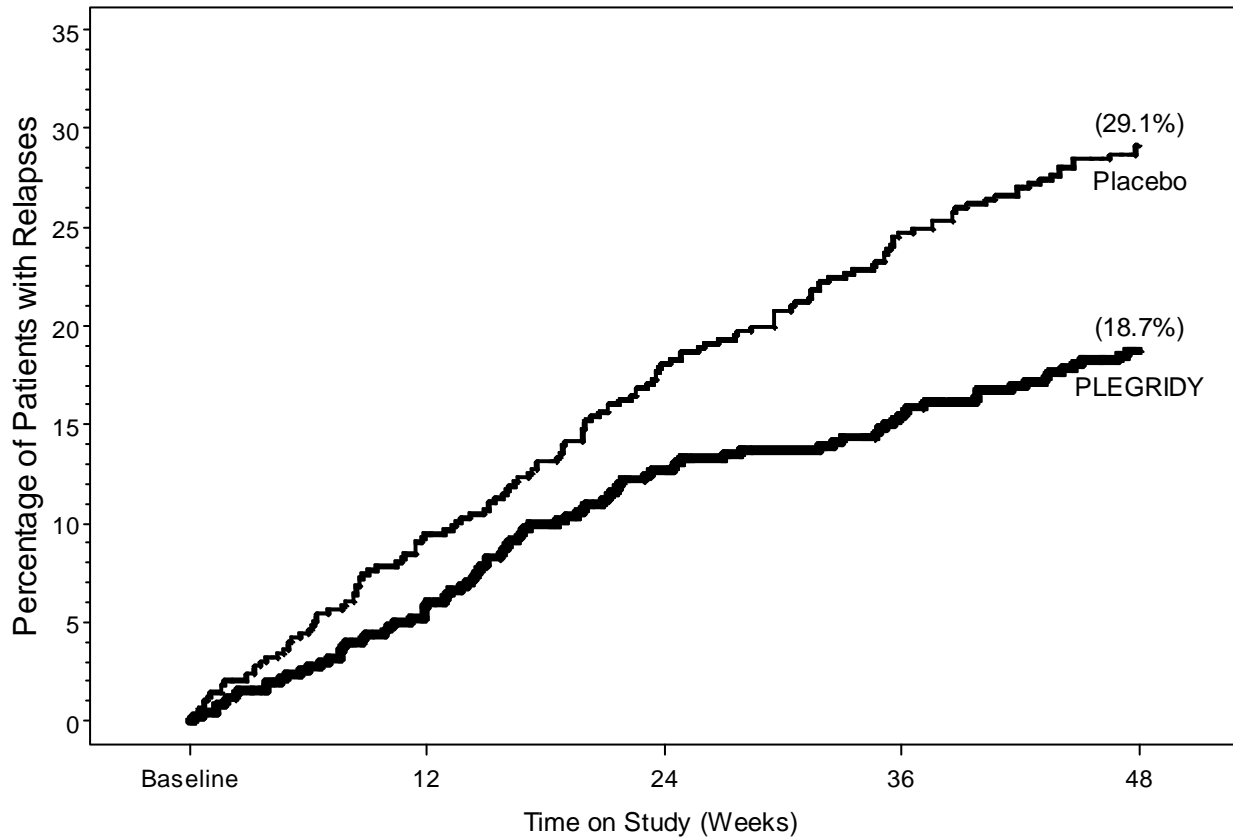
The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48.

The primary outcome was the annualized relapse rate over 1 year. Secondary outcomes included the proportion of patients relapsing, number of new or newly enlarging T2 hyperintense lesions, and time to confirmed disability progression. Confirmed disability progression was defined as follows: if the baseline EDSS score was 0, a sustained 12-week increase in EDSS score of 1.5 points was required; if the baseline EDSS score was greater than 0, a sustained 12-week increase in EDSS score of 1 point was required. [Table 3](#) and [Figure 1](#) show the results of Study 1.

**Table 3: Clinical and MRI Results of Study 1**

<b>Endpoint</b>	<b>PLEGRIDY 125 micrograms every 14 days</b>	<b>Placebo</b>	<b>p-value</b>
<b>Clinical outcomes at 48 weeks</b>	<b>N=512</b>	<b>N=500</b>	
Annualized relapse rate Relative reduction	0.26 36%	0.40	0.0007
Proportion of patients with relapses Relative risk reduction	0.19 39%	0.29	0.0003
Proportion of patients with disability progression Relative risk reduction	0.07 38%	0.11	0.0383
<b>MRI outcomes at 48 weeks</b>	<b>N=457</b>	<b>N=476</b>	
Mean number of new or newly enlarging T2 hyperintense lesions Relative reduction	3.6 67%	10.9	<0.0001
Mean number of Gd enhancing lesions Relative reduction	0.2 86%	1.4	<0.0001

**Figure 1: Time to first relapse**



Number of Subjects at Risk

Placebo	500	448	398	363	280
PLEGRIDY	512	458	414	389	318

PLEGRIDY 125 mcg every 14 days (n=512) versus placebo (n=500) Hazard Ratio (95% CI)=0.61(0.47, 0.80), p=0.0003

## 16 HOW SUPPLIED/STORAGE AND HANDLING

PLEGRIDY is supplied as a sterile, clear liquid for subcutaneous injection in two presentations, a prefilled pen and a prefilled syringe.

### 16.1 PLEGRIDY PEN Single-Dose Prefilled Pen

Each dose of PLEGRIDY is stored in a 1 mL capacity glass syringe with a rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single prefilled syringe contains 0.5 mL of solution of PLEGRIDY containing 63 micrograms, 94 micrograms, or 125 micrograms of peginterferon beta-1a. The glass syringe is contained within

a single-dose, disposable, injection device (prefilled pen). The following packaging configurations are available:

- A carton containing two single-dose prefilled pens, each providing 125 micrograms of PLEGRIDY. The NDC is 64406-011-01.
- A Starter Pack carton containing two single-dose prefilled pens; dose 1 provides 63 micrograms of PLEGRIDY, and dose 2 provides 94 micrograms of PLEGRIDY. The NDC is 64406-012-01.

## **16.2 PLEGRIDY Single-Dose Prefilled Syringe**

Each dose of PLEGRIDY is stored in a 1 mL capacity glass syringe with a rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single prefilled syringe contains 0.5 mL of solution of PLEGRIDY containing 63 micrograms, 94 micrograms, or 125 micrograms of peginterferon beta-1a. The following packaging configurations are available:

- A carton containing two single-dose prefilled syringes, each providing 125 micrograms of PLEGRIDY. The NDC is 64406-015-01.
- A Starter Pack carton containing two single-dose prefilled syringes; dose 1 provides 63 micrograms of PLEGRIDY, and dose 2 provides 94 micrograms of PLEGRIDY. The NDC is 64406-016-01.

## **16.3 Storage and Handling**

Store in the closed original carton to protect from light until ready for injection.

Store in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Discard if frozen. 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.

If refrigeration is unavailable, PLEGRIDY may be stored between 2°C to 25°C (36°F to 77°F) for a period up to 30 days, protected from light. PLEGRIDY can be removed from, and returned to, a refrigerator if necessary. The total combined time out of refrigeration, within a temperature range of 2°C to 25°C (36°F to 77°F), should not exceed 30 days.

## **16.4 Instructions for Disposal**

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

## **17 PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

Instruct patients to carefully read the supplied PLEGRIDY Medication Guide and Instructions for Use, and caution patients not to change the PLEGRIDY dose or schedule of administration without medical consultation.

### **Instructions for Self-Injection Technique and Procedures**

Provide appropriate instruction for methods of self-injection, including careful review of the PLEGRIDY Medication Guide and Instructions for Use. Instruct patients in the use of aseptic technique when administering PLEGRIDY.

Inform patients that a healthcare provider should show them or their caregiver how to prepare to inject PLEGRIDY before administering the first dose. Tell patients not to re-use needles or syringes, and instruct patients on safe disposal procedures. Inform patients to dispose of used needles and syringes in a puncture-resistant container, and instruct patients regarding safe disposal of full containers.

### **Advise patients:**

- to rotate areas of injection with each dose to minimize the likelihood of injection site reactions
- NOT to inject into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way
- to check the injection site after 2 hours for redness, swelling, and tenderness
- to contact their healthcare professional if they have a skin reaction and it does not clear up in a few days

### **Pregnancy**

Advise patients that PLEGRIDY should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

### **Liver Disease**

Advise patients that severe hepatic injury, including rare cases of hepatic failure, has been reported during the use of interferon beta. Advise patients of symptoms of hepatic dysfunction, and instruct patients to report them immediately to their physician.

### **Depression and Suicide**

Advise patients that depression, suicidal ideation, and suicide have been reported with the use of interferon beta. Instruct patients to report symptoms of depression or thoughts of suicide to their physician immediately.

**Seizure**

Advise patients that seizures have been reported in patients using PLEGRIDY. Instruct patients to report seizures immediately to their physician.

**Anaphylaxis and Other Allergic Reactions**

Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur.

**Injection Site Reactions**

Advise patients that injection site reactions can occur and that the reactions can include injection site necrosis. Instruct patients to report promptly any break in the skin that is associated with blue-black discoloration, swelling, or drainage of fluid from the injection site.

**Cardiac Disease**

Advise patients that worsening of significant cardiac disease has been reported in patients using interferon beta. Advise patients of symptoms of worsening cardiac condition, and instruct patients to report them immediately to their physician.

**Flu-like Symptoms**

Inform patients that flu-like symptoms are common following initiation of therapy with PLEGRIDY. Prophylactic and concurrent use of analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment.

43643-D

Manufactured by:

Biogen Idec Inc.

Cambridge, MA 02142

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**Medication Guide**  
**PLEGRIDY™ (PLEGG-rih-dee)**  
**(peginterferon beta-1a) injection for subcutaneous use**

Read this Medication Guide 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 with your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about PLEGRIDY?**

**PLEGRIDY can cause serious side effects, including:**

- Liver problems or worsening of liver problems, including liver failure and death. Symptoms may include: yellowing of your skin or the white part of your eye, nausea, loss of appetite, tiredness, bleeding more easily than normal, confusion, sleepiness, dark colored urine, and pale stools.
- During your treatment with PLEGRIDY you will need to see your healthcare provider and have regular blood tests to check for these possible side effects.
- Depression or suicidal thoughts. Symptoms may include: new or worsening depression (feeling hopeless or bad about yourself), thoughts of hurting yourself or suicide, irritability (getting upset easily), nervousness, or new or worsening anxiety.

**Call your healthcare provider right away if you have any of the symptoms listed above.**

**What is PLEGRIDY?**

- PLEGRIDY is a prescription medicine used to treat people with relapsing forms of multiple sclerosis (MS).
- It is not known if PLEGRIDY is safe and effective in people under 18 or over 65 years of age.

**Who should not use PLEGRIDY?**

**Do not take PLEGRIDY if you:**

- are allergic to interferon beta or peginterferon beta-1a, or any of the other ingredients in PLEGRIDY. See the end of this Medication Guide for a complete list of ingredients in PLEGRIDY.

**Before using PLEGRIDY, tell your healthcare provider if you:**

- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and suicidal behavior
- have or had liver problems, low blood cell counts, bleeding problems, heart problems, seizures (epilepsy), thyroid problems, or any kind of autoimmune disease
- take prescription and over-the-counter medicines, vitamins, and herbal supplements
- are pregnant or plan to become pregnant. It is not known if PLEGRIDY will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with PLEGRIDY.
- are breastfeeding or plan to breastfeed. It is not known if PLEGRIDY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use PLEGRIDY.

**How should I use PLEGRIDY?**

- See the **Instructions for Use** for detailed instructions to prepare for and to inject your dose of PLEGRIDY.
- Use PLEGRIDY exactly as your healthcare provider tells you. A healthcare provider should show you how to inject your PLEGRIDY before you use it for the first time.
- When you first use PLEGRIDY, your healthcare provider may tell you to slowly increase your dose so that you can adjust to the effects of PLEGRIDY before using the full dose. You should use a PLEGRIDY starter pack to slowly adjust your dose when you begin treatment.
- PLEGRIDY is given by injection under the skin (subcutaneous injection) of your stomach (abdomen), back of upper arm, or thigh 1 time every 14 days.
- Change (rotate) the site you choose with each injection to help decrease the chance that you will have an injection site reaction. **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way.
- Always use a new, PLEGRIDY prefilled pen or new, unopened single-use prefilled syringe for each injection.

**What are the possible side effects of PLEGRIDY?**

See **“What is the most important information I should know about PLEGRIDY?”**

**PLEGRIDY may cause additional serious side effects, including:**

- **serious allergic reactions.** Serious allergic reactions can happen quickly. Symptoms may include: itching, swelling of the face, eyes, lips, tongue, or throat, trouble breathing, feeling faint, anxiousness, skin rash, hives, skin bumps.
- **injection site reactions.** PLEGRIDY may commonly cause redness, pain, or swelling at the place where your injection was given. Call your healthcare provider right away if an injection site becomes swollen and painful or the area looks infected and it does not heal within a few days. You may have a skin infection or an area of severe skin damage (necrosis) requiring treatment by a healthcare provider.
- **heart problems, including congestive heart failure.** While PLEGRIDY is not known to have any direct effects on the heart, some people who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking interferon beta. If you already have heart failure, PLEGRIDY may cause your heart failure to get worse. Call your healthcare provider right away if you have worsening symptoms of heart failure such as shortness of breath or swelling of your lower legs or feet while using PLEGRIDY.
  - Some people using PLEGRIDY may have other heart problems, including low blood pressure, fast or abnormal heart beat, chest pain, heart attack, or a heart muscle problem (cardiomyopathy).
- **autoimmune diseases.** Problems with easy bleeding or bruising (idiopathic thrombocytopenia), thyroid gland problems (hyperthyroidism and hypothyroidism), and autoimmune hepatitis have happened in some people who use interferon beta.
- **blood problems and changes in your blood tests.** PLEGRIDY can decrease your white blood cells or platelets, which can cause an increased risk of infection, bleeding, or anemia and can cause changes in your liver function tests. Your healthcare provider should do blood tests while you use PLEGRIDY to check for side effects.
- **seizures.** Some people have had seizures while taking PLEGRIDY, including people who have never had seizures before.

**The most common side effects of PLEGRIDY include:**

- **flu-like symptoms.** Many people who use PLEGRIDY have flu-like symptoms early in the course of therapy. These symptoms are not really the flu. You cannot pass it on to anyone else. **Symptoms may include:** headache, muscle and joint aches, fever, chills, or tiredness.
  - You may be able to manage these flu-like symptoms by taking over-the-counter pain and fever reducers and drinking plenty of water. For many people, these symptoms lessen or go away over time.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General Information about the safe and effective use of PLEGRIDY.**

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. If you would like more information, talk to your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about PLEGRIDY that is written for health professionals. Do not use PLEGRIDY for a condition for which it was not prescribed. Do not give PLEGRIDY to other people, even if they have the same symptoms that you have. It may harm them. For more information, go to [www.plegridy.com](http://www.plegridy.com) or call 1-800-456-2255

**What are the ingredients in PLEGRIDY?**

**Active ingredient:** peginterferon beta-1a

**Inactive ingredients:**

- **Single-Use Prefilled Pen:** sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, polysorbate 20 in water for injection
- **Single-Use Prefilled Syringe:** sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, polysorbate 20 in water for injection

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## INSTRUCTIONS FOR USE (PLEGG-rh-dee)

Injection, for Subcutaneous Use  
Single-Use Prefilled Pen

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Read this Instructions for Use before you start using Plegridy and 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.

**Before you use your Plegridy Pen for the first time**, your healthcare provider should show you or your caregiver how to prepare and inject your Plegridy Pen the right way. If you have questions, call 1-800-456-2255. 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.** By sharing the Pen, you may give an infection to them or get an infection from them.

Supplies needed for your Plegridy Pen injection (See Figure A):



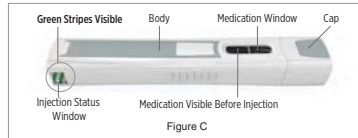
Additional supplies which are not included in the pack (See Figure B):

1 sharps container for throwing away used needles and  
**Disposing of your used Plegridy Pens\***

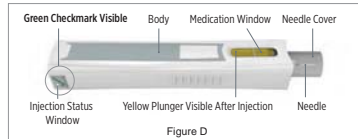
a well-lit area and a clean, flat surface to work on, like a table



Parts of your Plegridy Pen before use (See Figure C):



Parts of your Plegridy Pen after use (See Figure D):



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

**Note:**

• Before you prepare your injection, take your Plegridy Pen out of the refrigerator and let it come to room temperature for at least 30 minutes.

- Do not use external heat sources such as hot water to warm your Plegridy Pen.
- Do not remove the cap until you are ready to inject.
- Do not use more than 1 Plegridy Pen every 14 days.

Preparing for your injection:

Step 1: Collect your supplies and wash your hands

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

Step 2: Check your Plegridy Pen

- If you experience difficulty or have questions, call 1-800-456-2255.
- Check the expiration date printed on your Plegridy Pen (See Figure E).
- Do not use Plegridy Pen past the expiration date.

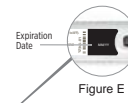


Figure E

- Check the injection status window on your Plegridy Pen. You should see green stripes in the injection status window (See Figure F).
- Do not use Plegridy Pen if you do not see the green stripes in the injection status window.



Figure F

- Check the medication window on your Plegridy Pen and make sure the Plegridy medicine is clear and colorless (See Figure G).
- Do not use Plegridy Pen if the liquid is colored, cloudy, or has floating particles in it.
- You might see air bubbles in the medication window. This is normal and will not affect your dose.

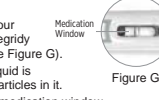


Figure G

Giving your injection:

Step 3: Choose your injection site

- Plegridy Pen is for use under the skin only (subcutaneous).
- Plegridy Pen should be injected into your thigh, abdomen or the back of your upper arm (See Figure H).
- Do not inject into an area of your body where the skin is irritated, reddened, bruised, infected or scarred.
- Change (rotate) your injection site for each injection. Do not use the same injection site for each injection.
- Choose an injection site and wipe your skin with an alcohol wipe.
- Let your injection site dry on its own before injecting your dose.
- Do not touch this area again before giving your injection.
- Do not take off the Plegridy Pen cap until you are ready to inject.



Figure H

Step 4: Remove the Plegridy Pen cap

- Pull the Plegridy Pen cap straight off and set it aside (See Figure I).
- Do not recap your Plegridy Pen.
- The needle is covered by the needle cover and the needle will not be seen (See Figure I).
- Do not touch or push down on the needle cover, you could get a needle stick.
- Your Plegridy Pen is ready to inject after the cap is removed.

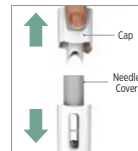


Figure I

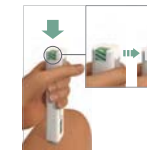
Step 5: Place your Plegridy Pen on your injection site

- Place your Plegridy Pen on your chosen injection site.
- You should hold your Plegridy Pen at a 90° angle to your injection site so that you can see the green stripes in the injection status window (See Figure J).
- Do not use your Plegridy Pen unless you see green stripes in the injection status window



Step 6: Give your Plegridy Pen injection

- Firmly press and hold down your Plegridy Pen on your injection site. This will insert the needle and start your injection (See Figure K).
- You will hear a "clicking" sound.
- Hold your Plegridy Pen firmly down on your injection site until the "clicking" sound has stopped.
- Do not lift your Plegridy Pen of your injection site until the "clicking" sound stops and you see green checkmarks in the injection status window.
- After the "clicking" sound has stopped, check the injection status window should see green checkmarks in the injection status window (See Figure L).



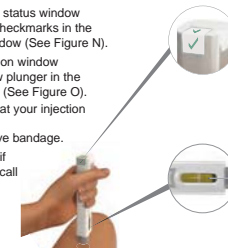
Step 7: Remove your Plegridy Pen from your injection site

- Lift your Plegridy Pen from your injection site. The needle cover will be covering all of the needle (See Figure M).



Step 8: Check to make sure you have received your full dose of Plegridy

- Check the injection status window should see green checkmarks in the injection status window (See Figure N).
- Check the medication window should see a yellow plunger in the medication window (See Figure O).
- If you see blood at your injection site, wipe it off and apply an adhesive bandage.
- If you experience difficulty or have questions, call 1-800-456-2255.



**INSTRUCTIONS FOR USE**  
(PLEGG-rih-dee)  
Injection, for Subcutaneous Use  
Single-Use Prefilled Pen

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Read this Instructions for Use before you start using Plegriidry and 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.

**Before you use your Plegriidry Pen for the first time**, your healthcare provider should show you or your caregiver how to prepare and inject your Plegriidry Pen the right way. If you have questions, call 1-800-456-2255. Plegriidry Pen is for use under the skin only (subcutaneous). **Each Plegriidry Pen can be used 1 time only. Do not share your Plegriidry Pen with anyone else.** By sharing the Pen, you may give an infection to them or get an infection from them.

**Supplies needed for your Starter Pack for Plegriidry Pen**

1 Starter Pack for Plegriidry Pen which contains:



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

1 sharps container for throwing away used needles and disposing of your used Plegriidry Pens<sup>®</sup>



a well-lit area and a clean, flat surface to work on, like a table



Sharps Container

**Step 1: Choose your dose**

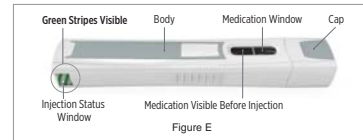
• **Choose the right Plegriidry Pen for your dose.** The Starter Pack for Plegriidry Pen contains your first 2 injections to slowly adjust your dose.

When	Which Dose	Choose
Day 1 (63 mcg)	First Dose: 63 mcg	<b>Orange Pen</b> (See Figure C)  Figure C
Day 15 (94 mcg)	Second Dose: 94 mcg	<b>Blue Pen</b> (See Figure D)  Figure D

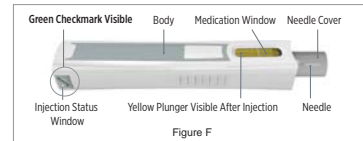
• **Make sure you use the 63 mcg orange pen for your first dose (day 1).**  
• **Make sure you use the 94 mcg blue pen for your second dose (day 15).**

Ask your healthcare provider which Plegriidry Pen you should use for your correct dose if you are not sure.

**Parts of your Plegriidry Pen before use (See Figure E):**



**Parts of your Plegriidry Pen after use (See Figure F):**



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

**Note:**

- **Before you prepare your injection, take your Plegriidry Pen out of the refrigerator and let it come to room temperature for at least 30 minutes.**
  - ▲ **Do not use external heat sources** such as hot water to warm your Plegriidry Pen.
  - ▲ **Do not remove the cap** until you are ready to inject.
  - ▲ **Do not use more than 1 Plegriidry Pen every 14 days.**

**Preparing for your injection:**

**Step 2: Collect your supplies and wash your hands**

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

**Step 3: Check your Plegriidry Pen**

- If you experience difficulty or have questions, call 1-800-456-2255.
- Check the expiration date printed on your Plegriidry Pen (See Figure G).
  - ▲ **Do not use Plegriidry Pen past the expiration date.**

- Check the injection status window on your Plegriidry Pen. You should see green stripes in the injection status window (See Figure H).
  - ▲ **Do not use Plegriidry Pen** if you do not see the green stripes in the injection status window.

- Check the medication window on your Plegriidry Pen and make sure the Plegriidry medicine is clear and colorless (See Figure I).
  - ▲ **Do not use Plegriidry Pen** if the liquid is colored, cloudy, or has floating particles in it.
  - You might see air bubbles in the medication window. This is normal and will not affect your dose.

**Giving your injection:**

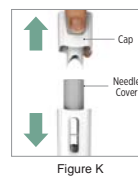
**Step 4: Choose your injection site**

- Plegriidry Pen is for use under the skin only (subcutaneous).
- Plegriidry Pen should be injected into your thigh, abdomen or the back of your upper arm (See Figure J).
  - ▲ **Do not inject** into an area of your body where the skin is irritated, reddened, bruised, infected or scarred.
- **Change (rotate) your injection site** for each injection. **Do not use** the same injection site for each injection.
- Choose an injection site and wipe your skin with an alcohol wipe.
- Let your injection site dry on its own before injecting your dose.
  - ▲ **Do not touch** this area again before giving your injection.
- **Do not take off the Plegriidry Pen cap** until you are ready to inject.



**Step 5: Remove the Plegriidry Pen cap**

- Pull the Plegriidry Pen cap straight off and set it aside (See Figure K).
  - ▲ **Do not recap your Plegriidry Pen.**
    - The needle is covered by the needle cover and the needle will not be seen (See Figure K).
  - ▲ **Do not touch or push down on the needle cover**, you could get a needle stick.
- Your Plegriidry Pen is ready to inject after the cap is removed.



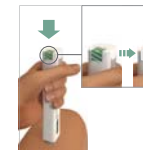
**Step 6: Place your Plegriidry Pen on your injection site**

- Place your Plegriidry Pen on your chosen injection site.
  - You should hold your Plegriidry Pen at a 90° angle to your injection site so that you can see the green stripes in the injection status window (See Figure L).
  - ▲ **Do not use your Plegriidry Pen** unless you see green stripes in the injection status window



**Step 7: Give your Plegriidry Pen injection**

- **Firmly press and hold down your Plegriidry Pen on your injection site.** This will insert the needle and start your injection (See Figure M).
  - **You will hear a “clicking” sound.**
- Hold your Plegriidry Pen firmly down on your injection site until the “clicking” sound has stopped.
  - ▲ **Do not lift your Plegriidry Pen** of your injection site until the “clicking” sound stops and you see green checkmarks in the injection status window.
- After the “clicking” sound has stopped, check the injection status window should see green checkmarks in the injection status window (See Figure N).



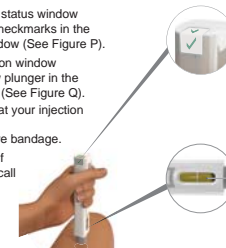
**Step 8: Remove your Plegriidry Pen from your injection site**

- Lift your Plegriidry Pen from your injection site. The needle cover will be covering all of the needle (See Figure O).



**Step 9: Check to make sure you have received your full dose of Plegriidry**

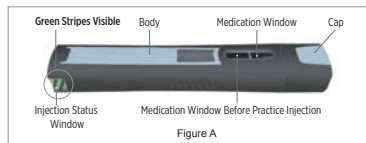
- Check the injection status window should see green checkmarks in the injection status window (See Figure P).
- Check the medication window should see a yellow plunger in the medication window (See Figure Q).
  - If you see blood at your injection site, wipe it off and apply an adhesive bandage.
- If you experience dizziness or have questions, call 1-800-456-2255.



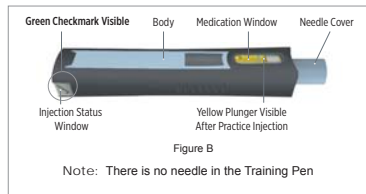
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#### Training Pen before use (See Figure A):



#### Training Pen after use (See Figure B):



#### Preparing for your injection:

##### Step 1: Collect your supplies and wash your hands

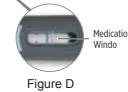
- Wash your hands with soap and water.
- Remove the Training Pen from the box.

#### Step 2: Check your Training Pen

- Check the injection status window on the Training Pen.
  - You should see green stripes in the injection status window (See Figure C).
  - ▲ **Do not use the Training Pen** if you do not see green stripes in the injection status window. Your healthcare provider may need to reset the device.



- Check the medication window on the Training Pen (See Figure D).
  - **The Training Pen does not contain a needle or active Plegridy medicine.**
  - Your healthcare provider should tell you and show you how to check your Plegridy Pen to make sure your Plegridy medicine is clear and colorless before you use it for the first time.



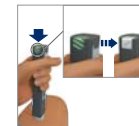
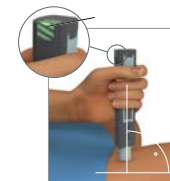
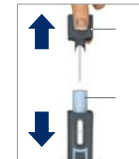
#### Practice giving your injection:

##### Step 3: Choose your practice injection site

- Choose your practice injection site. The recommended injection sites are under the skin (subcutaneously) of the thigh, abdomen or the back of the upper arm (See Figure E).
  - ▲ **Do not inject** into an area of the body where the skin is irritated, reddened, bruised, infected or scarred.
- Choose a practice injection site and wipe your skin with an alcohol wipe.
- Let your practice injection site dry on its own before injecting your dose.
  - ▲ **Do not touch** this area again before giving your practice injection.
  - ▲ **Do not take off** the Training Pen cap until you are ready to inject.



Figure E



**INSTRUCTIONS FOR USE**  
(PLEGG-rh-dee)

**Injection, for Subcutaneous Use**  
**Single-Use Prefilled Syringe**

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Read this Instructions for Use before you start using Plegridy and 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.

**Before you use your Plegridy Prefilled Syringe for the first time**, your healthcare provider should show you or your caregiver how to prepare and inject your Plegridy Prefilled Syringe the

first time. If you have any questions or need assistance, call 1-800-456-2255. Plegridy Prefilled Syringe is for use under the skin only.

**Each Plegridy Prefilled Syringe can be used 1 time only.** Do not share your Plegridy Prefilled Syringe with anyone else. By sharing the needle, you may give an infection to them or get an

**Supplies needed for your Plegridy Prefilled Syringe injection**

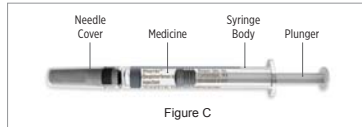


Additional supplies which are not included in the pack (See Figure B):

- 1 sharps container for throwing away used needles and Plegridy Prefilled Syringe
- Disposing of your used Plegridy Prefilled Syringe** at the end of these instructions.
- a well-lit area and a clean, flat surface to work on, like a table



**Parts of your Plegridy Prefilled Syringe (See Figure C):**



- **Before you prepare your injection, take your Plegridy Prefilled Syringe out of the refrigerator and let it come to room temperature for at least 30 minutes.**
  - ▲ **Do not** use external heat sources such as hot water to warm your Plegridy Prefilled Syringe.

▲ **Do not** use more than 1 Plegridy Prefilled Syringe every 14 days.

**Preparing for your injection:**

**Step 1: Collect your supplies and wash your hands**

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

**Step 2: Check your Plegridy Prefilled Syringe**

- Check the expiration date printed on your Plegridy Prefilled Syringe (See Figure D).
  - ▲ **Do not** use Plegridy Prefilled Syringe past the expiration date.



Figure D



- Check that your Plegridy medicine is clear and colorless (See Figure E).
  - ▲ **Do not** use Plegridy Prefilled Syringe if the liquid is colored, cloudy, or has floating particles in it.
  - o You might see air bubbles in your Plegridy medicine. This is normal and will not affect your dose.



Figure E

**Giving your injection:**

**Step 3: Choose your injection site**

- Plegridy Prefilled Syringe is for use under the skin only (subcutaneous).
- Plegridy Prefilled Syringe should be injected into your thigh, abdomen or the back of your upper arm (See Figure F).
  - ▲ **Do not** inject into an area of your body where the skin is irritated, reddened, bruised, infected or scarred.
- **Change (rotate) your injection site** for each injection. **Do not** use the same injection site for each injection.
- Choose an injection site and wipe your skin with an alcohol wipe.
- Let your injection site dry on its own before injecting your dose.



Figure F

- ▲ **Do not** touch this area again before giving your injection.
- ▲ **Do not** take off the Plegridy Prefilled Syringe needle cover until you are ready to inject.

**Step 4: Remove the Plegridy Prefilled Syringe needle cover**

- With 1 hand, hold your Plegridy Prefilled Syringe. With your other hand, firmly hold the needle cover and pull the needle cover straight off the needle (See Figure G).
  - o Throw away the needle cover after your injection. **Do not** recap your Plegridy Prefilled Syringe.
  - ▲ **Do not** touch the needle.

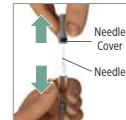


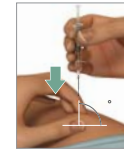
Figure G

**Step 5: Give your Plegridy Prefilled Syringe injection**

- With 1 hand, use your thumb and first finger and pinch the skin around your cleaned injection site (See Figure H).



- With your other hand, hold your Plegridy Prefilled Syringe like a pencil. **dart-like motion and insert the needle at a 90° angle into your skin (See Figure I).**
- After the needle is in, let go of your skin.



- Slowly push the plunger down until the syringe is empty (See Figure J).

- ▲ **Do not** Syringe out of your injection site until you have slowly pushed the plunger all the way down.



- Pull the needle straight out of your skin (See Figure K).
  - o If you see blood at your injection site, wipe it off adhesive bandage.

- ▲ **Do not** recap your Plegridy Prefilled Syringe.
- ▲ **Do not** reuse your Plegridy Prefilled Syringe.





## INSTRUCTIONS FOR USE (PLEGG-rh-dee)

### Injection, for Subcutaneous Use Single-Use Prefilled Syringe

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Cambridge, MA 02142

Read this Instructions for Use before you start using Plegridy and 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.

**Before you use your Plegridy Prefilled Syringe for the first time,** your healthcare provider should show you or your caregiver how to prepare and inject your Plegridy Prefilled Syringe the

correct way. If you have any questions or need help, call 1-800-456-2255. Plegridy Prefilled Syringe is for use under the skin only.

**Each Plegridy Prefilled Syringe can be used 1 time only.** Do not share your Plegridy Prefilled Syringe with anyone else. By sharing the needle, you may give an infection to them or get an

### Supplies needed for your Starter Pack for Plegridy Prefilled

- 1 Starter Pack for Plegridy Prefilled Syringe which contains:
  - 1 Plegridy 63 mcg Prefilled Syringe (orange syringe)
  - 1 Plegridy 94 mcg Prefilled Syringe (blue syringe)





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

- 1 sharps container for throwing away used needles and Plegridy Prefilled Syringes
- 1 disinfectant wipe for cleaning the injection site
- 1 alcohol wipe for cleaning the injection site
- 1 adhesive bandage
- 1 clean, flat surface to work on, like a table



### Step 1: Choose your dose

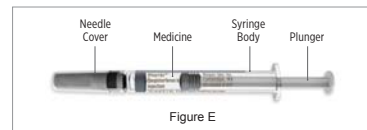
- Choose the right Plegridy Prefilled Syringe for your dose. The Starter Pack for Plegridy Prefilled Syringe contains your first 2 injections to slowly adjust your dose.

When	Which Dose	Choose
<b>Day 1</b> (63 mcg)	<b>First Dose:</b> 63 mcg	<b>Orange Syringe</b> (See Figure C)  Figure C
<b>Day 15</b> (94 mcg)	<b>Second Dose:</b> 94 mcg	<b>Blue Syringe</b> (See Figure D)  Figure D

- Make sure you use the 63 mcg orange syringe for your first dose (day 1).
- Make sure you use the 94 mcg blue syringe for your second dose (day 15).

Ask your healthcare provider which Plegridy Prefilled Syringe you should use for your correct dose if you are not sure.

### Parts of your Plegridy Prefilled Syringe (See Figure E):



- Before you prepare your injection, take your Plegridy Prefilled Syringe out of the refrigerator and let it come to room temperature for at least 30 minutes.
- Do not use external heat sources such as hot water to warm your Plegridy Prefilled Syringe.
- Do not use more than 1 Plegridy Prefilled Syringe every 14 days.

### Preparing for your injection:

#### Step 2: Collect your supplies and wash your hands

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

#### Step 3: Check your Plegridy Prefilled Syringe

- Check the expiration date printed on your Plegridy Prefilled Syringe (See Figure F).
- Do not use Plegridy Prefilled Syringe past the expiration date.

Expiration Date



Figure F



Medicine



Figure G

- Check that your Plegridy medicine is clear and colorless (See Figure G).
- Do not use Plegridy Prefilled Syringe if the liquid is colored, cloudy, or has floating particles in it.
- You might see air bubbles in your Plegridy medicine. This is normal and will not affect your dose.

### Giving your injection:

#### Step 4: Choose your injection site

- Plegridy Prefilled Syringe is for use under the skin only (subcutaneous).
- Plegridy Prefilled Syringe should be injected into your thigh, abdomen or the back of your upper arm (See Figure H).
- Do not inject into an area of your body where the skin is irritated, reddened, bruised, infected or scarred.
- Change (rotate) your injection site for each injection. Do not use the same injection site for each injection.
- Choose an injection site and wipe your skin with an alcohol wipe.
- Let your injection site dry on its own before injecting the dose.
- Do not touch this area again before giving your injection.

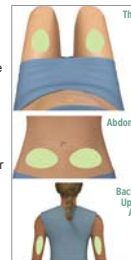


Figure H

- Do not take off the Plegridy Prefilled Syringe needle cover until you are ready to inject.

#### Step 5: Remove the Plegridy Prefilled Syringe needle cover

- With 1 hand, hold your Plegridy Prefilled Syringe. With your other hand, firmly hold the needle cover and pull the needle cover straight off the needle (See Figure I).
- Throw away the needle cover after your injection. Do not recap your Plegridy Prefilled Syringe.
- Do not touch the needle.

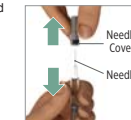


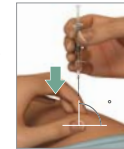
Figure I

### Step 6: Give your Plegridy Prefilled Syringe injection

- With 1 hand, use your thumb and first finger and pinch the skin around your cleaned injection site (See Figure J).



- With your other hand, hold your Plegridy Prefilled Syringe like a pencil. Use a dart-like motion and insert the needle at a 90° angle into your skin (See Figure K).
- After the needle is in, let go of your skin.



- Slowly push the plunger down until the syringe is empty (See Figure L).
- Do not syringe out of your injection site until you have slowly pushed the plunger all the way down.



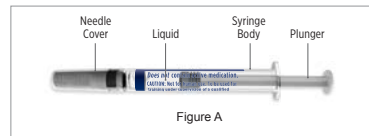
- Pull the needle straight out of your skin (See Figure M).
- If you see blood at your injection site, wipe it off with an adhesive bandage.
- Do not recap your Plegridy Prefilled Syringe.
- Do not reuse your Plegridy Prefilled Syringe.



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#### Parts of the Training Syringe (See Figure A):



#### Preparing for your injection:

##### Step 1: Collect your supplies and wash your hands

- Wash your hands with soap and water.
- Remove the Training Syringe from the box.

##### Step 2: Check your Training Syringe

- Check the expiration date printed on the Training Syringe (See Figure B).

▲ **Do not** use the Training Syringe past the expiration date.

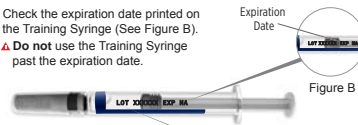


Figure B

- Check that the liquid in the Training Syringe is clear and colorless (See Figure C).

▲ **Do not** use the Training Syringe if the liquid is colored, cloudy, or has floating particles in it.

- You might see air bubbles in the Training Syringe liquid. This is normal and will not affect your dose.



Figure C

#### Practice giving your injection:

##### Step 3: Choose your practice injection site

- This Training Syringe will be injected into an injection site on a training pad that your healthcare provider will give you.
- Wipe the practice injection site with an alcohol wipe (See Figure D).
- Let the practice injection site dry on its own before injecting your practice dose.

▲ **Do not** touch this area again before injecting your practice dose.



Figure D

##### Step 4: Remove the needle cover

- With 1 hand, hold the Training Syringe. With your other hand, firmly hold the needle cover and pull the needle cover straight off the needle (See Figure E).
- Throw away the needle cover after the practice injection. **Do not** recap the Training Syringe.

▲ **Do not** touch the needle.

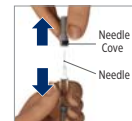
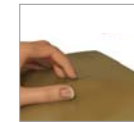


Figure E



▲

▲

▲