

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

RECENT MAJOR CHANGES

Indications and Usage (1) 07/2019

INDICATIONS AND USAGE

PLEGRIDY is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (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)
- Thrombotic Microangiopathy: Cases of thrombotic microangiopathy have been reported with interferon beta products. Discontinue PLEGRIDY if clinical symptoms and laboratory findings consistent with TMA occur (5.8)
- Autoimmune disorders: consider discontinuation of PLEGRIDY if a new autoimmune disorder occurs (5.9)

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 at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Epidemiological data do not suggest a clear relationship between interferon beta use and major congenital malformations, but interferon beta may cause fetal harm based on animal data (8.1)
- Severe Renal Impairment: monitor for adverse reactions (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2020

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PLEGRIDY is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

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

Dose	Time*	Amount (micrograms)	Color of Pen or Syringe Label
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 and 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 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, some fatal, have been reported with interferon beta products. Cases have been reported several weeks to years after starting interferon beta products. Discontinue PLEGRIDY if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

5.9 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)*]
- Thrombotic Microangiopathy [*see Warnings and Precautions (5.8)*]
- Autoimmune Disorders [*see Warnings and Precautions (5.9)*]

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

	PLEGRIDY (N=512) %	Placebo (N=500) %
Nervous System Disorders		
Headache	44	33
Gastrointestinal Disorders		
Nausea	9	6
Vomiting	5	2
Musculoskeletal and Connective Tissue Disorders		
Myalgia	19	6
Arthralgia	11	7
General Disorders and Administration Site Conditions		
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
Investigations		
Body temperature increased	6	3
Alanine aminotransferase increased	6	3
Aspartate aminotransferase increased	4	2
Gamma-glutamyl-transferase increased	3	1
Skin and Subcutaneous Tissue Disorder		
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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PLEGRIDY during pregnancy. Encourage patients to enroll by calling 1-866-810-1462 or visiting <https://www.plegridypregnancyregistry.com/>.

Risk Summary

Data from a large population-based cohort study, as well as other published studies over several decades, have not identified a drug-associated risk of major birth defects with the use of interferon beta products during early pregnancy. Findings regarding a potential risk for low birth weight or miscarriage with the use of interferon beta products in pregnancy have been inconsistent (*see Data*). In a study in pregnant monkeys, administration of interferon beta during pregnancy resulted in an increased rate of abortion (*see Data*).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Human Data

The majority of observational studies reporting on pregnancies exposed to interferon beta products did not identify an association between the use of interferon beta products during early pregnancy and an increased risk of major birth defects.

In a population-based cohort study conducted in Finland and Sweden, data were collected from 1996--2014 in Finland and 2005--2014 in Sweden on 2,831 pregnancy outcomes from women

with MS. 797 pregnancies were in women exposed to interferon beta only. No evidence was found of an increased risk of major birth defects among women with MS exposed to interferon beta products compared to women with MS that were unexposed to any non-steroid therapy for MS (n=1,647) within the study. No increased risks were observed for miscarriages and ectopic pregnancies, though there were limitations in obtaining complete data capture for these outcomes, making the interpretation of the findings more difficult.

Two small cohort studies that examined pregnancies exposed to interferon beta products (without differentiating between subtypes of interferon beta products) suggested that a decrease in mean birth weight may be associated with interferon beta exposure during pregnancy, but this finding was not confirmed in larger observational studies. Two small studies observed an increased prevalence of miscarriage, although the finding was only statistically significant in one study. Most studies enrolled patients later in pregnancy, which made it difficult to ascertain the true percentage of miscarriages. In one small cohort study, a significantly increased risk of preterm birth following interferon beta exposure during pregnancy was observed.

Animal Data

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 adverse effects on embryofetal development were observed. Abortifacient activity was evident following 3 to 5 doses.

8.2 Lactation

Risk Summary

Limited published literature has described the presence of interferon beta-1a products in human milk at low levels. There are no data on the effects of interferon beta-1a on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PLEGRIDY and any potential adverse effects on the breastfed infant from PLEGRIDY or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of PLEGRIDY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

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, L-arginine HCl (15.8 mg), glacial acetic acid (0.25 mg), polysorbate 20 (0.025 mg), and sodium acetate trihydrate (0.79 mg). 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, L-arginine HCl (15.8 mg), glacial acetic acid (0.25 mg), polysorbate 20 (0.025 mg), and sodium acetate trihydrate (0.79 mg). 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%).

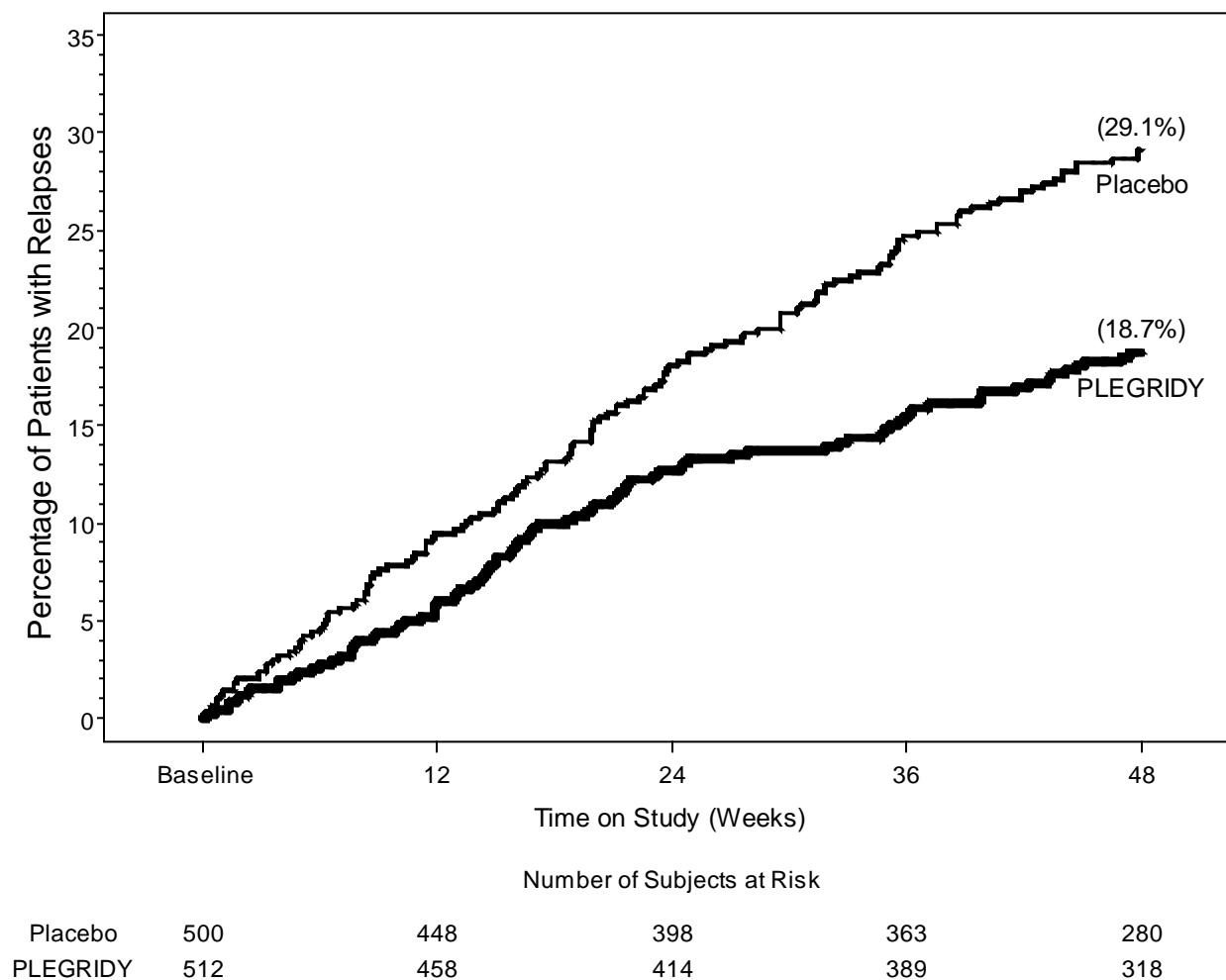
The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48.

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

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

Figure 1: Time to first relapse



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

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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 and Pregnancy Registry

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant.

Encourage patients to enroll in the PLEGRIDY Pregnancy Registry if they become pregnant while taking PLEGRIDY [*see Use in Specific Populations (8.1)*].

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 [*see Warnings and Precautions (5.1)*].

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 [*see Warnings and Precautions (5.2)*].

Seizure

Advise patients that seizures have been reported in patients using PLEGRIDY. Instruct patients to report seizures immediately to their physician [*see Warnings and Precautions (5.3)*].

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 [*see Warnings and Precautions (5.4)*].

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 [*see Warnings and Precautions (5.5)*].

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 [*see Warnings and Precautions (5.6)*].

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 [*see Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

43643-0X

Manufactured by:

Biogen 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 relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- It is not known if PLEGRIDY is safe and effective in people under 18 or over 65 years of age.

Do not take PLEGRIDY if you:

- are allergic to interferon beta or peginterferon, 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 about all of your medical conditions, including 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.
- have or had low blood cell counts.
- have or had bleeding problems.
- have or had heart problems.
- have or had seizures (epilepsy).
- have or had thyroid problems.
- have or had any kind of autoimmune disease (where the body's immune system attacks the body's own cells).
- are pregnant or plan to become pregnant. It is not known if PLEGRIDY can harm your unborn baby.
 - If you become pregnant while taking PLEGRIDY, talk to your healthcare provider about enrolling in the PLEGRIDY Pregnancy Registry. You can enroll in this registry by calling 1-866-810-1462 or visiting <https://www.plegridypregnancyregistry.com/>. The purpose of this registry is to collect information about the safety of Plegridy during pregnancy.
- are breastfeeding or plan to breastfeed. PLEGRIDY may pass into your breastmilk. Talk to your healthcare provider about the best way to feed your baby if you use PLEGRIDY.

Tell your healthcare provider about all the medicines you take, including prescription and over the counter medicines, vitamins, and herbal supplements.

How should I use PLEGRIDY?

- See the detailed **Instructions for Use** for instructions on how to prepare and 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.

- Your healthcare provider will tell you how much PLEGRIDY to inject and how often to inject PLEGRIDY. Do not inject more than your healthcare provider tells you to.
- When you use PLEGRIDY for the first time, your healthcare provider may tell you to slowly increase your dose.
- 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.
- After 2 hours check your 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 provider.
- Always use a new, PLEGRIDY prefilled pen or new, unopened single dose prefilled syringe for each injection.

What are the possible side effects of PLEGRIDY?

PLEGRIDY may cause serious side effects, including:

- **See “What is the most important information I should know about PLEGRIDY?”**
- **seizures.** Some people have had seizures while taking PLEGRIDY, including people who have never had seizures before.
- **serious allergic reactions.** Serious allergic reactions can happen if you take PLEGRIDY. Symptoms may include: itching, swelling of the face, eyes, lips, tongue, or throat, trouble breathing, feeling faint, anxiousness, skin rash, hives, skin bumps. Get emergency help right away if you have any of these symptoms. Talk to your healthcare provider before taking another dose of PLEGRIDY
- **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.** 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).
- **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 will do tests to monitor for side effects while you use PLEGRIDY.
- **thrombotic microangiopathy (TMA).** TMA is a condition that involves injury to the smallest blood vessels in your body. TMA can also cause injury to your red blood cells (the cells that carry oxygen to your organs and tissues) and your platelets (cells that help your blood clot) and can sometimes lead to death. Your healthcare provider may tell you to stop taking PLEGRIDY if you develop TMA.
- **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.

The most common side effects of PLEGRIDY include:

- **flu-like symptoms.** Many people who use PLEGRIDY have flu-like symptoms, especially early in the course of therapy. These symptoms are not really the flu. You cannot pass it on to anyone else.
 - You may be able to manage these flu-like symptoms by taking over-the-counter pain and fever reducers and drinking plenty of water.

Flu like symptoms or other common side effects OF PLEGRIDY may include: headache, muscle and joint aches, fever, chills, or tiredness.

Talk with your healthcare provider about ways to help if you develop flu-like symptoms while taking PLEGRIDY.

These are not all of the possible side effects of PLEGRIDY.

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 a Medication Guide. 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. You can ask your pharmacist or healthcare provider for information about PLEGRIDY that is written for health professionals.

What are the ingredients in PLEGRIDY?

Active ingredient: peginterferon beta-1a

Inactive ingredients:

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

For more information, go to www.plegridy.com or call 1-800-456-2255

Manufactured by: Biogen Inc., Cambridge, MA 02142, U.S. License # 1697

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This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 03/2020

INSTRUCTIONS FOR USE
PLEGRIDY® (PLEGG-rih-dee)
(peginterferon beta-1a) injection, for Subcutaneous Use
Single-Dose Prefilled Pen
125 mcg

Important: Do not remove the Plegridy Pen cap until you are ready to inject.

How to Inject your Plegridy Pen

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

Note:

- **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 experience difficulty or 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.
- **Take your Plegridy Pen out of the refrigerator and let it come to room temperature for at least 30 minutes before your injection.**
- **Do not** use more than 1 Plegridy Pen every 14 days.
- **Do not** use your Plegridy Pen if it has been dropped or is visibly damaged.

How should I store Plegridy?

- Store Plegridy in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If a refrigerator is not available, PLEGRIDY may be stored at room temperature up to 77°F (25°C) for up to 30 days in total.
- Keep Plegridy in the original carton to protect it from light.
- **Do not** freeze Plegridy.
- **Keep Plegridy Pens, needles, and all medicines out of the reach of children.**

Supplies needed for your Plegridy Pen injection:

- 1 Plegridy 125 mcg Pen (see Figure A)

Before Use – Parts of your Plegridy Pen (Figure A)

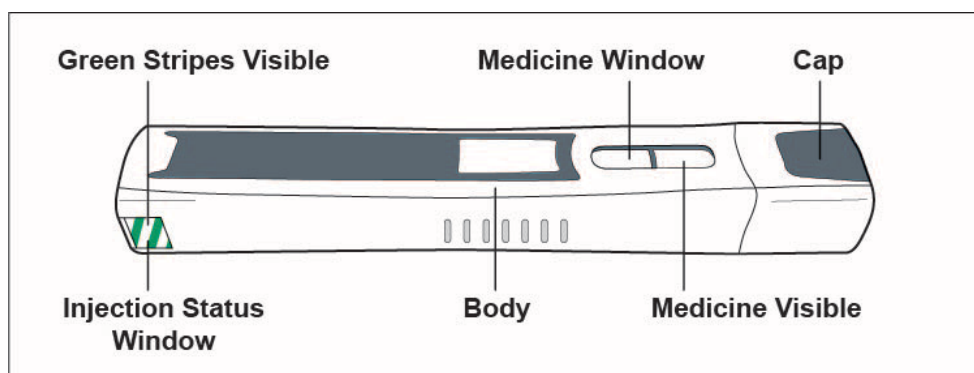


Figure A

Important: Do not remove the Plegridy Pen cap until you are ready to inject. If you remove the cap before you are ready to inject, do not re-cap the pen. Re-capping could cause the pen to lock.

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

- alcohol wipe
- gauze pad
- adhesive bandage
- 1 sharps container for throwing away used needles and Plegridy Pens. See “**Disposing of your used Plegridy Pens**” at the end of these instructions.
- a well-lit area and a clean, flat surface to work on, like a table

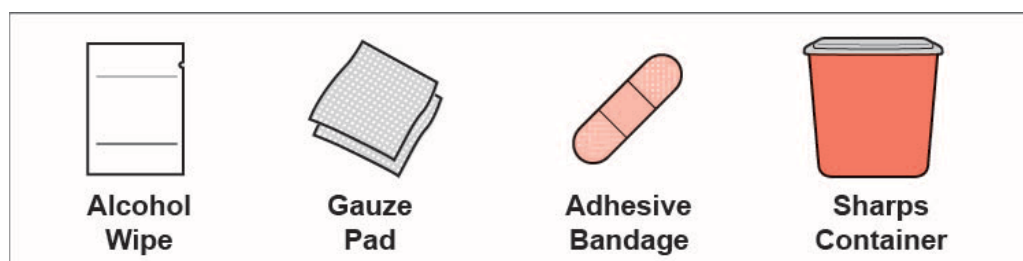


Figure B

Preparing for your injection:

Step 1: 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.

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 Pen (see Figure C)

- Check the injection status window on your Plegridy Pen. Before you give your injection, you should see green stripes in the injection status window.
 - **Do not** use Plegridy Pen if you do not see the green stripes in the injection status window.

- Check the expiration date printed on your Plegridy Pen.
 - **Do not** use Plegridy Pen past the expiration date.

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

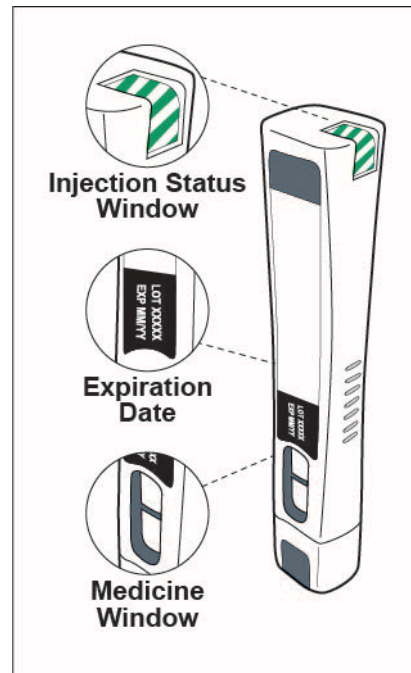
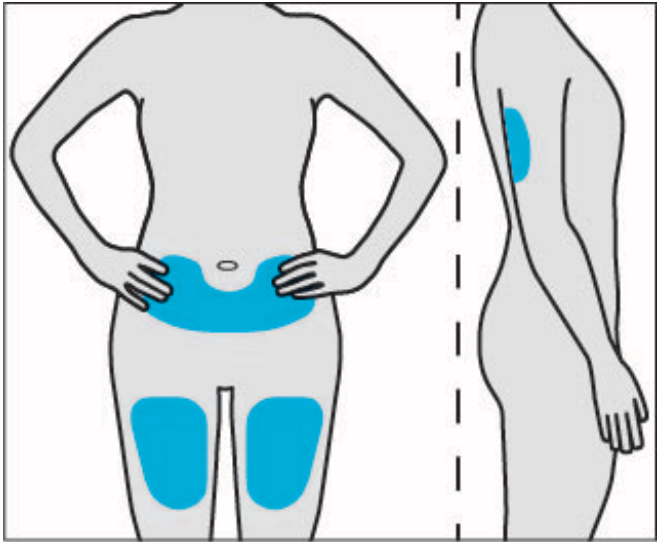


Figure C

Step 4: Choose and clean 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 D).
 - **Do not** inject into an area of your body where the

<p>skin is irritated, reddened, bruised, infected or scarred.</p> <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ Do not touch this area again before giving your injection. • Let your injection site dry on its own before injecting your dose. 	 <p>The diagram shows two views of a human body. On the left, a back view of a person with hands on hips, showing blue shaded injection sites on the upper buttocks and lower back. On the right, a side view of a person with a blue shaded injection site on the upper buttock. A vertical dashed line separates the two views.</p> <p>Figure D</p>
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Giving your injection:

Step 5: Remove the Plegridy Pen cap

<ul style="list-style-type: none"> • Pull the Plegridy Pen cap straight off and set it aside (See Figure E). <ul style="list-style-type: none"> ○ The needle is covered by the needle cover and the needle will not be seen. • Important information: <ul style="list-style-type: none"> ○ Do not touch or clean the needle cover. You could get a needle stick injury or the pen may lock. ○ Do not recap your Plegridy Pen. This could lock the pen. • Your Plegridy Pen is ready to inject after the cap is 	
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removed.

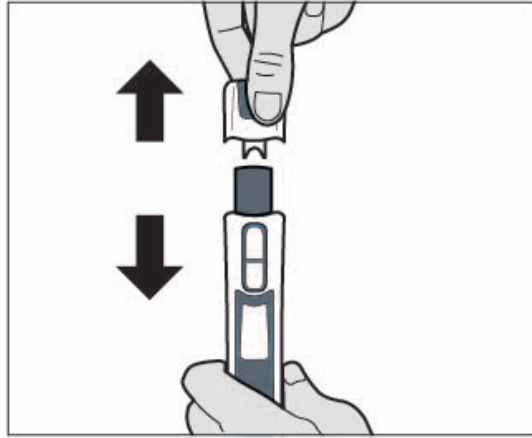


Figure E

Step 6: Give your injection

- 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 F).
 - **Do not** use your Plegridy Pen unless you see green stripes in the injection status window.

Note: Be ready to inject before you start pressing your Plegridy Pen down on your injection site. After you start pressing, the needle cover will lock when it is lifted from the site.

- **Firmly press and hold down your Plegridy Pen on your injection site.** This will insert the needle and start your injection (See Figure G).
 - **You will hear a clicking sound.**
- Continue to hold your Plegridy Pen firmly down on your injection site until the clicking sound has stopped (see Figure H).
 - **Do not** lift your Plegridy Pen off your injection site until the clicking sound stops and you see green checkmarks in the injection status window.

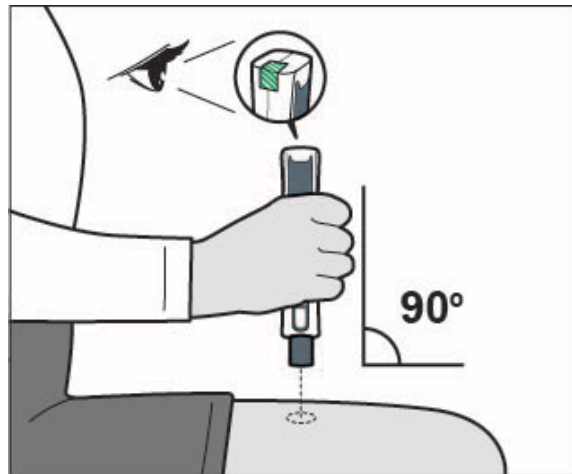
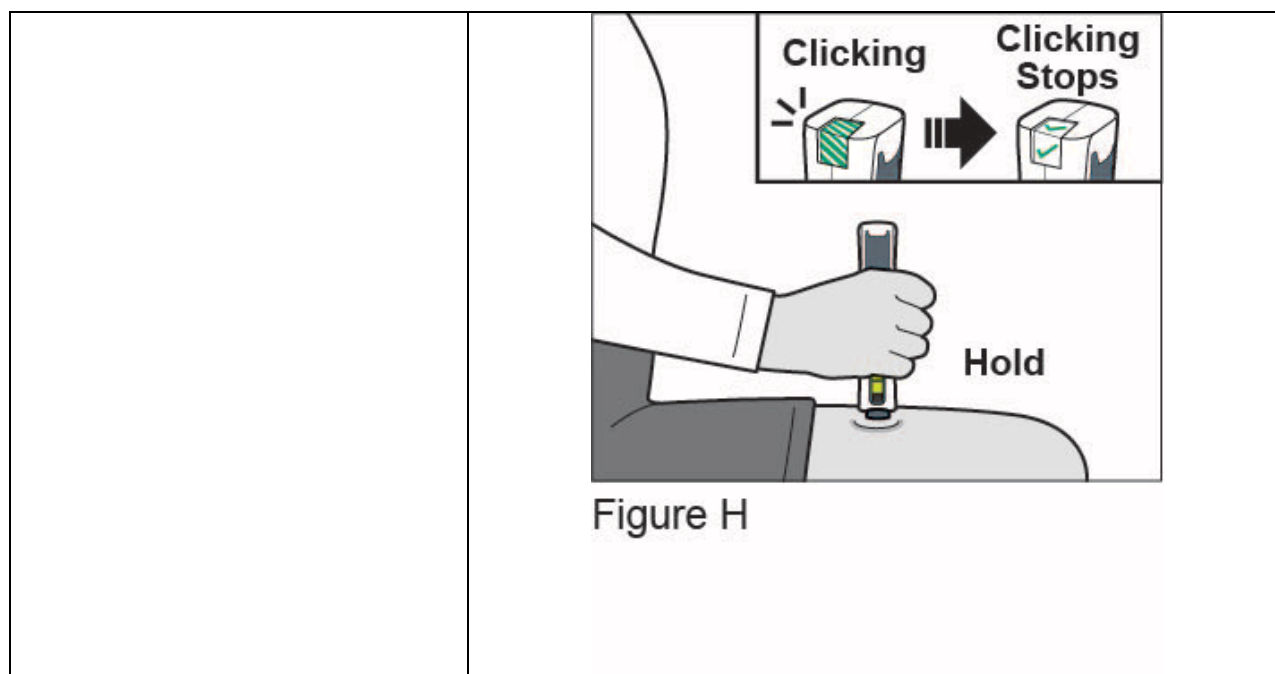


Figure F



Figure G



If you do not hear clicking sounds or you do not see green checkmarks in the injection status window after trying to give your injection, your Plegridy Pen may have locked and you should call 1-800-456-2255.

Step 7: Remove your Plegridy Pen from your injection site

- After the clicking sound has stopped, lift your Plegridy Pen from your injection site. The needle will be covered and it will lock (see Figure I).

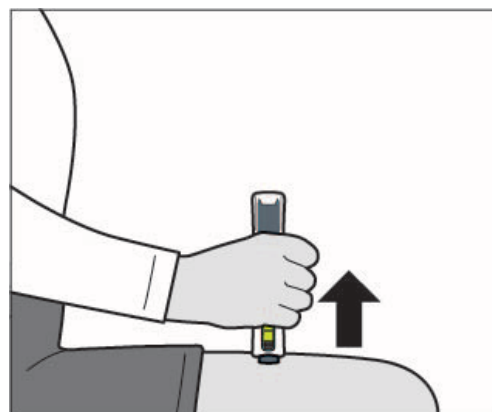


Figure I

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

- Check the injection status window. You should see green checkmarks in the injection status window.
- Check the medicine window. You should see a yellow plunger in the medicine window.
 - If you see blood at your injection site, wipe it off with gauze and apply an adhesive bandage.

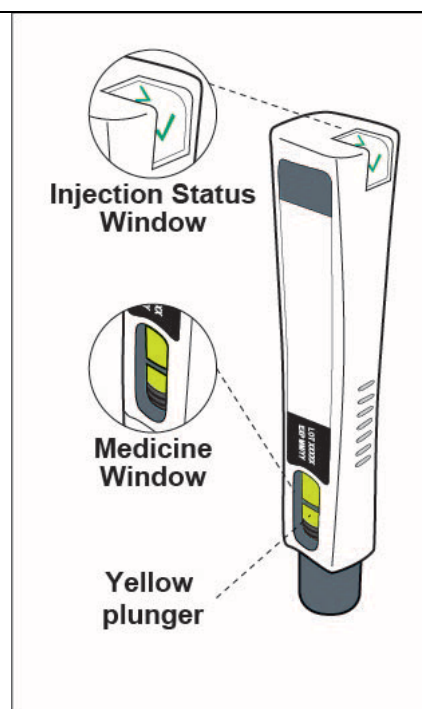


Figure J

After your injection:

After Use – Parts of your Plegridy Pen (Figure K)

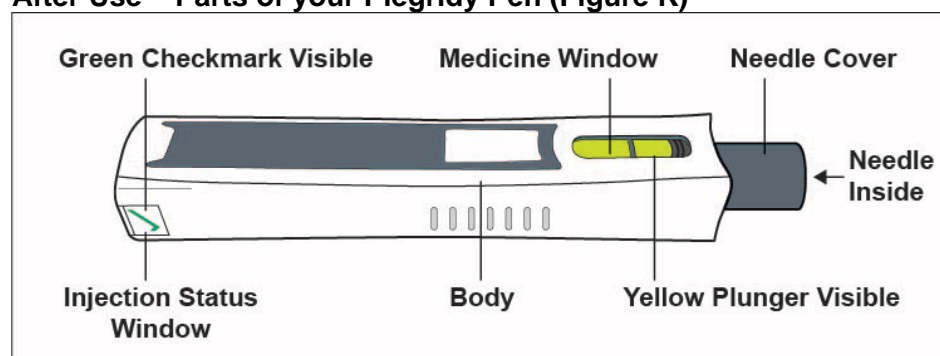


Figure K

Important: **Do not** touch the needle cover in any way. You could get a needle stick injury.

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

Step 9: Disposing of your used Plegridy Pens

- Put your used Plegridy Pens in an FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) Plegridy Pens in your household trash.**
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- **Do not** recap your Plegridy Pen.

Step 10: Check your injection site

- Plegridy may commonly cause redness, pain or swelling of your skin at the injection site.
- After 2 hours, check your injection site for redness, swelling or tenderness. Call your healthcare provider right away if your injection site becomes swollen and painful or the area looks infected and does not heal within a few days.

Questions?

For product or service-related questions, call 1-800-456-2255 or go to www.plegridy.com.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Issued: 03/2020

43644-0X

INSTRUCTIONS FOR USE
PLEGRIDY® (PLEGG-rih-dee)
(peginterferon beta-1a) injection, for Subcutaneous Use
Single-Dose Prefilled Syringe
125 mcg

How to Inject your Plegridy Prefilled Syringe

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

Note:

- **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 right way.
- If you experience difficulty or have questions, call 1-800-456-2255.
- Plegridy Prefilled Syringe is for use under the skin only (subcutaneous).
- **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 infection from them.
- **Take your Plegridy Prefilled Syringe out of the refrigerator and let it come to room temperature for at least 30 minutes before your injection.**
- **Do not** use more than 1 Plegridy Prefilled Syringe every 14 days.
- **Do not** use your Plegridy Prefilled Syringe if it has been dropped or is visibly damaged.

How should I store Plegridy?

- Store Plegridy in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If a refrigerator is not available, PLEGRIDY may be stored at room temperature up to 77°F (25°C) for up to 30 days in total.
- Keep Plegridy in the original carton to protect it from light.
- **Do not** freeze Plegridy.
- **Keep Plegridy Prefilled Syringes, needles, and all medicines out of the reach of children.**

Supplies needed for your Plegridy Prefilled Syringe injection:

- 1 Plegridy 125 mcg Prefilled Syringe (See Figure A)



Figure A

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

- alcohol wipe
- gauze pad
- adhesive bandage
- 1 sharps container for throwing away used needles and Plegridy Prefilled Syringes. See **“Disposing of your used Plegridy Prefilled Syringes”** at the end of these instructions.
- a well-lit area and a clean, flat surface to work on, like a table



Figure B

Preparing for your injection:

Step 1: Take your Plegridy Prefilled Syringe out of the refrigerator and let it come to room temperature for at least 30 minutes.

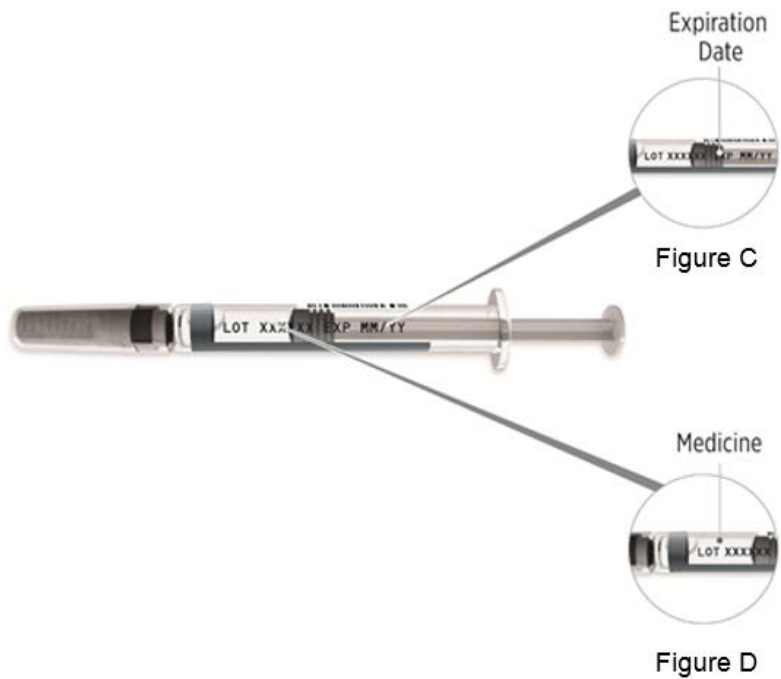
- **Do not** use external heat sources such as hot water to warm your Plegridy Prefilled Syringe.

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 C).
 - **Do not** use Plegridy Prefilled Syringe past the expiration date.
- Check that your Plegridy medicine is clear and colorless (See Figure D).
 - **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.



Step 4: Choose and clean 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 E).
 - **Do not** inject directly into your belly button.
 - **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.
 - Do not touch this area again before giving your injection.
- Let your injection site dry on its own before injecting your dose.
- **Do not** take off the Plegridy Prefilled Syringe needle cover until you are ready to inject.



Figure E

Giving Your Injection:

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 F).
 - **Be careful** when removing the needle cover to avoid getting a needle stick injury.
 - **Do not** touch the needle.
 - **Important: Do not** recap the Plegridy Prefilled Syringe. You could get a needle stick injury.
 - Throw away the needle cover after your injection.

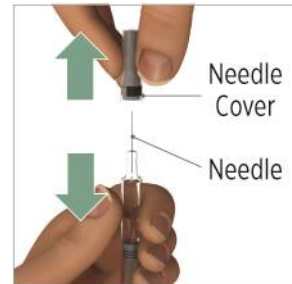


Figure F

Step 6: Gently pinch the injection site

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



Figure G

Step 7: Give your Plegridy Prefilled Syringe injection

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

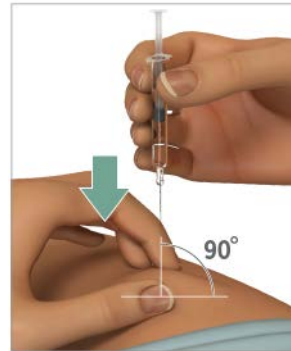


Figure H

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



Figure I

- Pull the needle straight out of your skin (See Figure J).
 - If you see blood at your injection site, wipe it off with gauze and apply an adhesive bandage.
- **Important: Do not** recap your Plegridy Prefilled Syringe. You could get a needle stick injury.
- **Do not** reuse your Plegridy Prefilled Syringe.

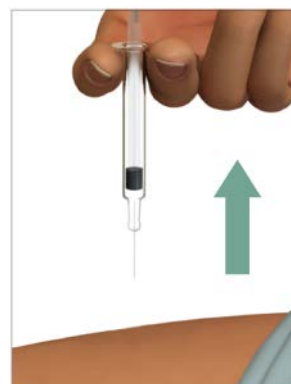


Figure J

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After Your Injection:

Step 8: Disposing of your used Plegridy Prefilled Syringes

- Put your used Plegridy Prefilled Syringes in an FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) Plegridy Prefilled Syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Step 9: Check your injection site

- Plegridy may commonly cause redness, pain or swelling of your skin at the injection site.
- After 2 hours, check your injection site for redness, swelling or tenderness.
- Call your healthcare provider right away if your injection site becomes swollen and painful or the area looks infected and does not heal within a few days.

Questions?

For product or service-related questions, call 1-800-456-2255 or go to www.plegridy.com.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Issued: 03/2020

43654-0X

INSTRUCTIONS FOR USE
PLEGRIDY® (PLEGG-rih-dee)
(peginterferon beta-1a) injection, for Subcutaneous Use
Single-Dose Prefilled Pen
Starter Pack

Important: Do not remove the Plegridy Pen cap until you are ready to inject.

How to Inject your Plegridy Pen

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

Note:

- **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 experience difficulty or 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.
- **Take your Plegridy Pen out of the refrigerator and let it come to room temperature for at least 30 minutes before your injection.**
- **Do not** use more than 1 Plegridy Pen every 14 days.
- **Do not** use your Plegridy Pen if it has been dropped or is visibly damaged.

How should I store Plegridy?

- Store Plegridy in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If a refrigerator is not available, PLEGRIDY may be stored at room temperature up to 77°F (25°C) for up to 30 days in total.
- Keep Plegridy in the original carton to protect it from light.
- **Do not** freeze Plegridy.
- **Keep Plegridy Pens, needles, and all medicines out of the reach of children.**

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

- 1 Starter Pack for Plegridy Pen which contains:
 - 1 Plegridy 63 mcg Pen (orange pen)
 - 1 Plegridy 94 mcg Pen (blue pen)



Figure A

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

- alcohol wipe
- gauze pad
- adhesive bandage
- 1 sharps container for throwing away used needles and Plegridy Pens. See “**Disposing of your used Plegridy Pens**” at the end of these instructions.
- a well-lit area and a clean, flat surface to work on, like a table

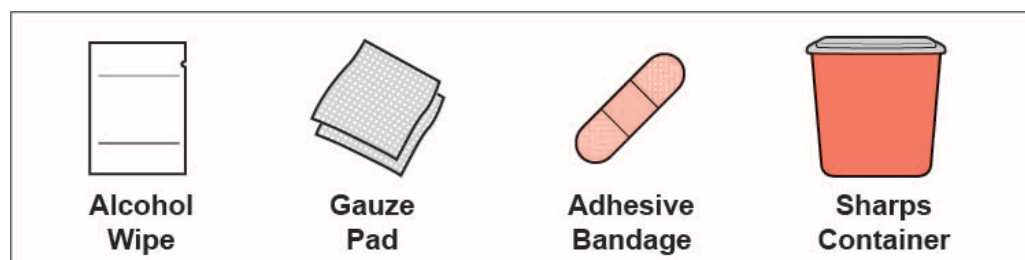



Figure B

Dose Schedule

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

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



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

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

Before Use – Parts of your Plegridy Pen before use (See Figure E):

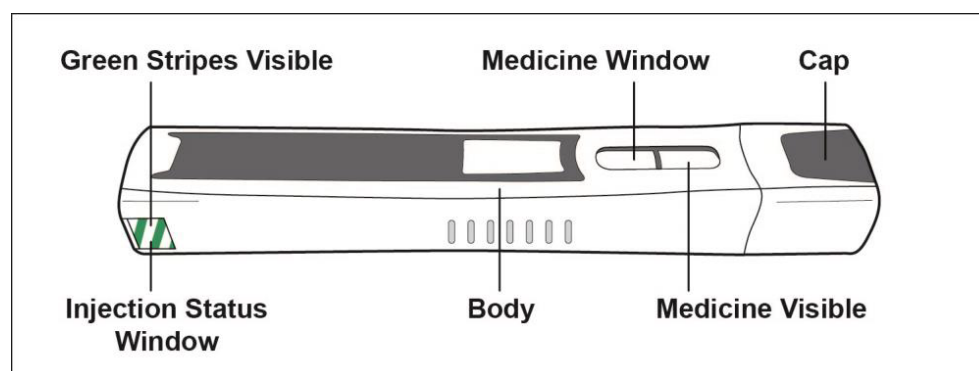


Figure E

Important: Do not remove the Plegridy Pen cap until you are ready to inject. If you remove the cap before you are ready to inject, do not re-cap the pen. Re-capping could cause the pen to lock.

Preparing for your injection:

Step 1: 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.

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 Pen (see Figure F)

- Check the injection status window on your Plegridy Pen. Before you give your injection, you should see green stripes in the injection status window.
 - **Do not** use Plegridy Pen if you do not see the green stripes in the injection status window.
- Check the expiration date printed on your Plegridy Pen.
 - **Do not** use Plegridy Pen past the expiration date.
- Check the medicine window on your Plegridy Pen and make sure the Plegridy medicine is clear and colorless.
 - **Do not** use Plegridy Pen if the liquid is colored, cloudy, or has floating particles in it.
 - You might see air bubbles in the medicine window. This is normal and will not affect your dose.

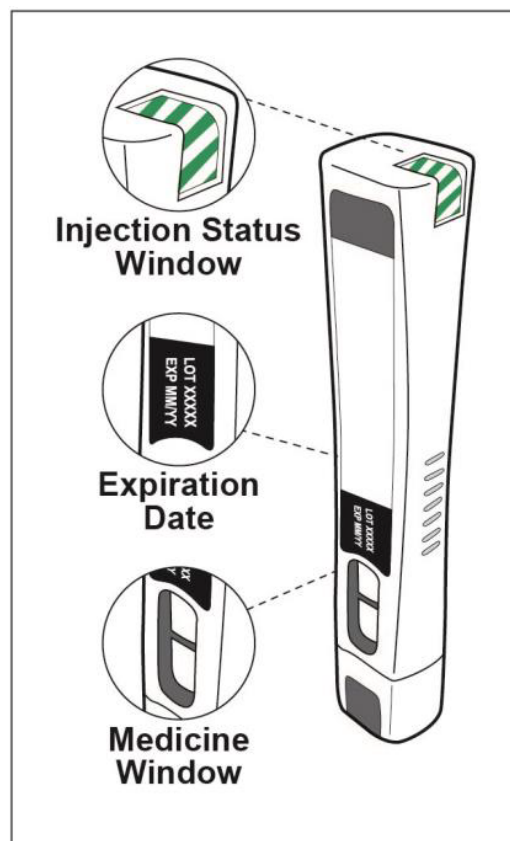


Figure F

Step 4: Choose and clean your injection site

- Plegridy Pen is for use under the skin only (subcutaneous).
- Plegridy Pen should be injected into your thigh, stomach area (abdomen) or the back of your upper arm (See Figure G).
 - **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.

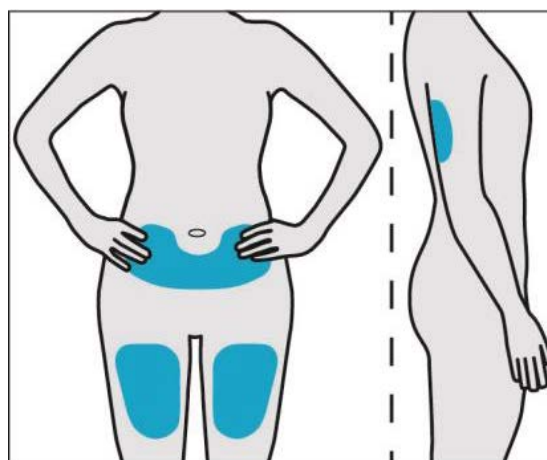
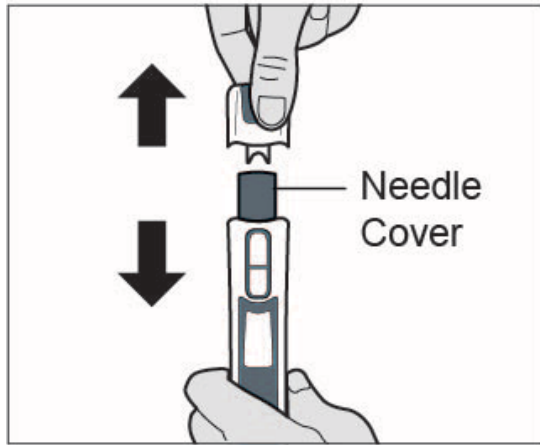


Figure G

- | | |
|---|--|
| <ul style="list-style-type: none">• Choose an injection site and wipe your skin with an alcohol wipe.<ul style="list-style-type: none">○ Do not touch this area again before giving your injection.• Let your injection site dry on its own before injecting your dose. | |
|---|--|

Giving your injection:

Step 5: Remove the Plegridy Pen cap

- | | |
|---|---|
| <ul style="list-style-type: none">• Pull the Plegridy Pen cap straight off and set it aside (See Figure H).<ul style="list-style-type: none">○ The needle is covered by the needle cover and the needle will not be seen.• Important information:<ul style="list-style-type: none">○ Do not touch or clean the needle cover. You could get a needle stick injury or the pen may lock.○ Do not recap your Plegridy Pen. This could lock the pen.• Your Plegridy Pen is ready to inject after the cap is removed. |  <p>Figure H</p> |
|---|---|

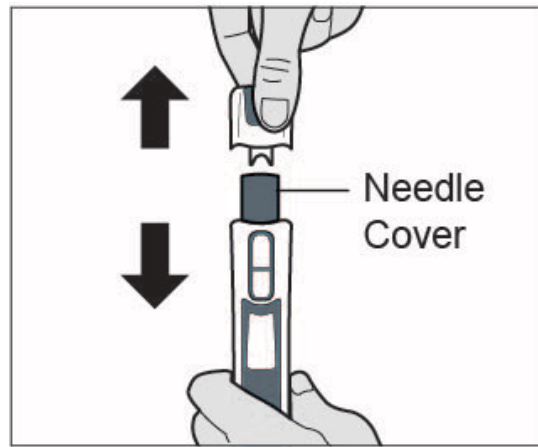


Figure H

Step 6: Give your injection

- 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 I).
 - **Do not** use your Plegridy Pen unless you see green stripes in the injection status window.

Note: Be ready to inject before you start pressing your Plegridy Pen down on your injection site. After you start pressing, the needle cover will lock when it is lifted from the site.

- **Firmly press and hold down your Plegridy Pen on your injection site.** This will insert the needle and start your injection (See Figure J).
- **You will hear a clicking sound.**
- Continue to hold your Plegridy Pen firmly down on your injection site until the clicking sound has stopped (See figure K).
- **Do not** lift your Plegridy Pen off your injection site until the clicking sound stops and you see green checkmarks in the injection status window.

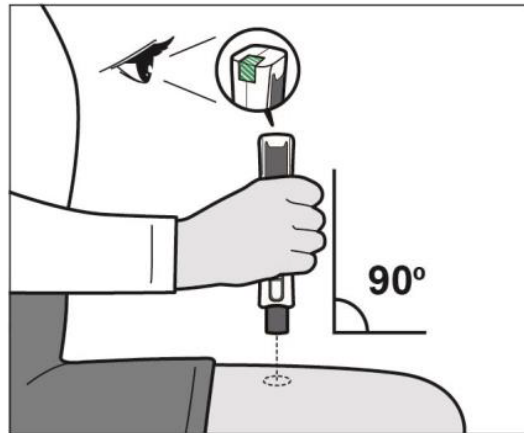


Figure I

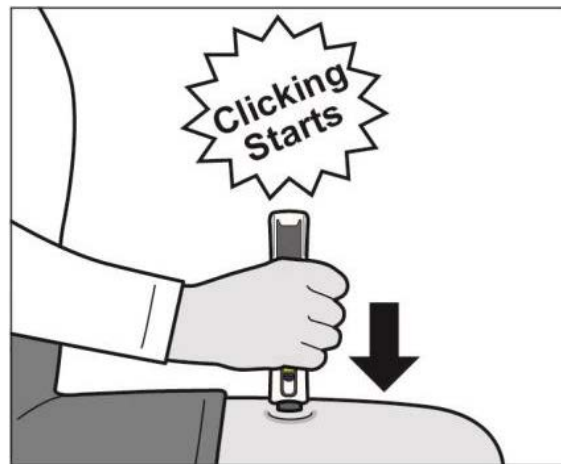


Figure J

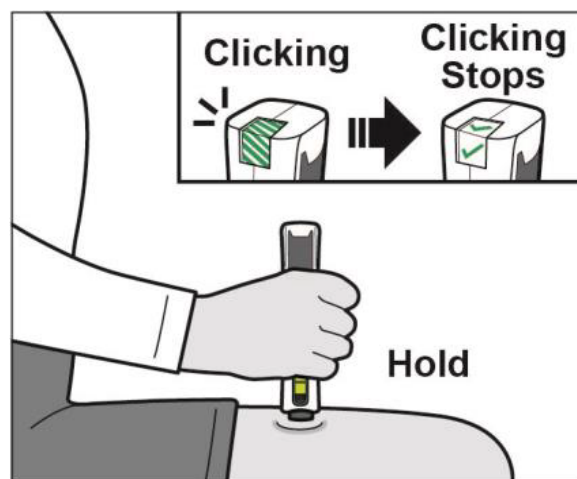


Figure K

If you do not hear clicking sounds, or you do not see green checkmarks in the injection status window after trying to give your injection, your Plegridy Pen may have locked and you should call 1-800-456-2255 for help.

Step 7: Remove your Plegridy Pen from your injection site

- After the clicking sound has stopped, lift your Plegridy Pen from your injection site. The needle will be covered by the needle cover and it will lock (see Figure L).

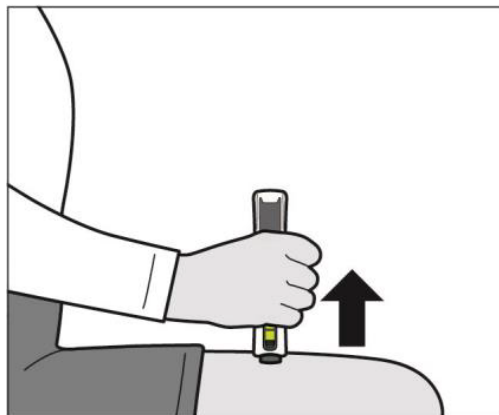


Figure L

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

- Check the injection status window. You should see green checkmarks in the injection status.
- Check the medicine window. You should see a yellow plunger in the medicine.
 - If you see blood at your injection site, wipe it off with the gauze pad and apply an adhesive bandage.

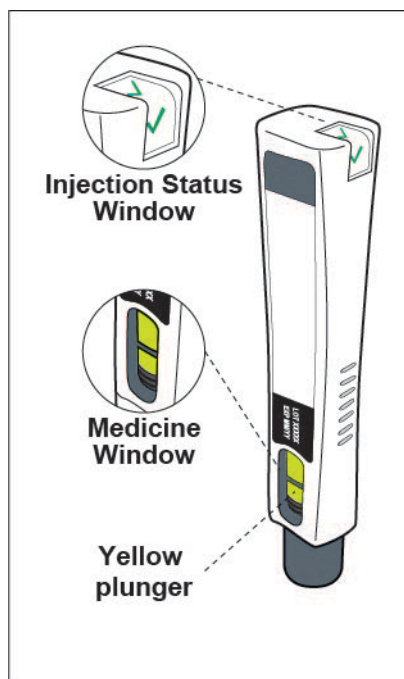


Figure M

After your injection:

After Use – Parts of your Plegridy Pen (Figure N)

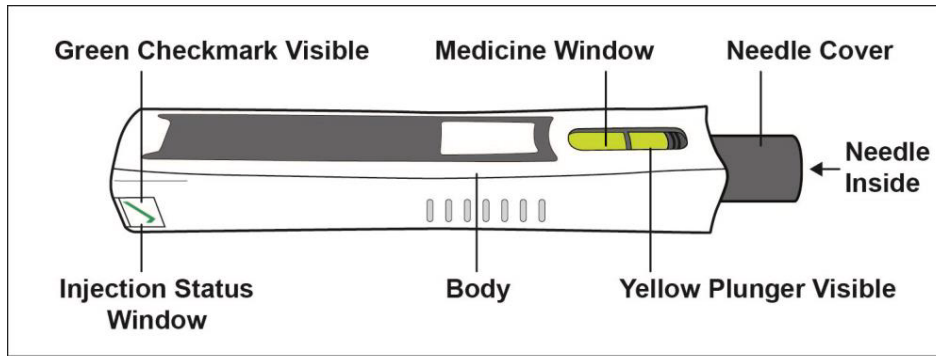


Figure N

Important: **Do not** touch the needle cover in any way. You could get a needle stick injury.

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

Step 9: Disposing of your used Plegridy Pens

- Put your used Plegridy Pens in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) Plegridy Pens in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- **Do not** recap your Plegridy Pen.

Step 10: Check your injection site

- Plegridy may commonly cause redness, pain or swelling of your skin at the injection site.
- After 2 hours check your injection site for redness, swelling or tenderness.
- Call your healthcare provider right away if your injection site becomes swollen and painful or the area looks infected and does not heal within a few days.

Questions?

For product or service-related questions, call 1-800-456-2255 or go to www.plegridy.com.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Issued: 03/2020

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INSTRUCTIONS FOR USE
PLEGRIDY® (PLEGG-rih-dee)
(peginterferon beta-1a) injection for Subcutaneous Use
Single-Dose Prefilled Syringe
Starter Pack

How to Inject your Plegridy Prefilled Syringe

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

Note:

- **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 right way.
- If you experience difficulty or have questions, call 1-800-456-2255.
- Plegridy Prefilled Syringe is for use under the skin only (subcutaneous).
- **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 infection from them.
- **Take your Plegridy Prefilled Syringe out of the refrigerator and let it come to room temperature for at least 30 minutes before your injection.**
- **Do not** use more than 1 Plegridy Prefilled Syringe every 14 days.
- **Do not** use your Plegridy Prefilled Syringe if it has been dropped or is visibly damaged.

How should I store Plegridy?

- Store Plegridy in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If a refrigerator is not available, PLEGRIDY may be stored at room temperature up to 77°F (25°C) for up to 30 days in total.
- Keep Plegridy in the original carton to protect it from light.
- **Do not** freeze Plegridy.
- **Keep Plegridy Prefilled Syringes, needles, and all medicines out of the reach of children.**

Supplies needed for your Starter Pack for Plegridy Prefilled Syringe injection (See Figure A):

- 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)



Figure A

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



- alcohol wipe
- gauze pad
- adhesive bandage
- 1 sharps container for throwing away used needles and Plegridy Prefilled Syringes. See **“Disposing of your used Plegridy Prefilled Syringes”** at the end of these instructions.
- a well-lit area and a clean, flat surface to work on, like a table



Figure B

Dose Schedule

- **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
Day 1 (63 mcg)	First Dose: 63 mcg	Orange Syringe (See Figure C)  Figure C
When	Which Dose	Choose
Day 15 (94 mcg)	Second Dose: 94 mcg	Blue Syringe (See Figure D)  Figure D

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

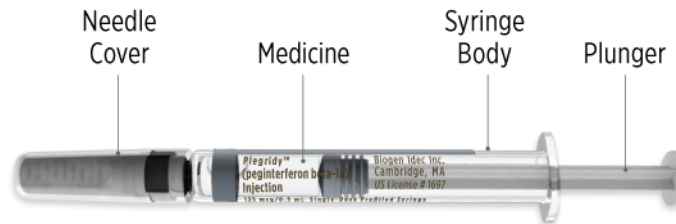


Figure E

Preparing for your injection:

Step 1: Take your Plegridy Prefilled Syringe out of the refrigerator and let it come to room temperature for at least 30 minutes.

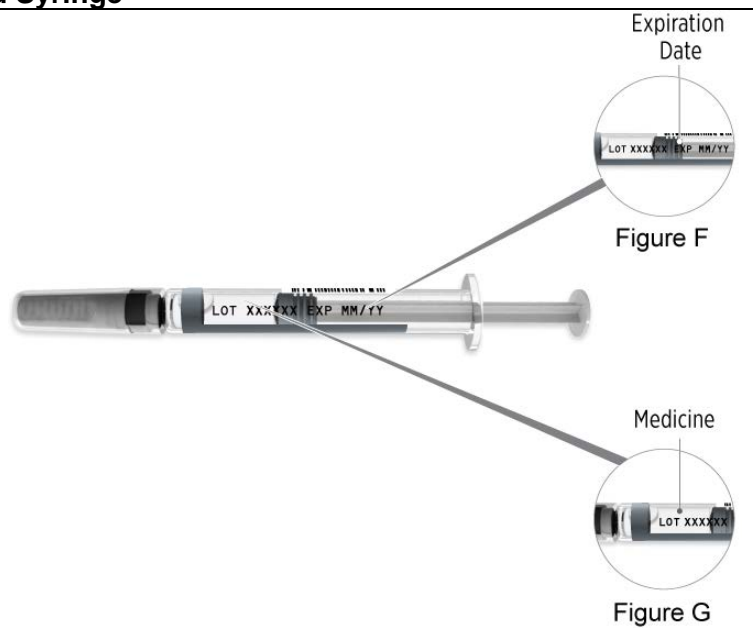
- **Do not** use external heat sources such as hot water to warm your Plegridy Prefilled Syringe.

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.
- 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.



Step 4: Choose and clean your injection site

- Plegridy Prefilled Syringe is for use under the skin only (subcutaneous).
- Plegridy Prefilled Syringe should be injected into your thigh, stomach area (abdomen) or the back of your upper arm (See Figure H).
 - **Do not** inject directly into your belly button.
 - **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.
 - Do not touch this area again before giving your injection.
- Let your injection site dry on its own before injecting the dose.
- **Do not** take off the Plegridy Prefilled Syringe needle cover until you are ready

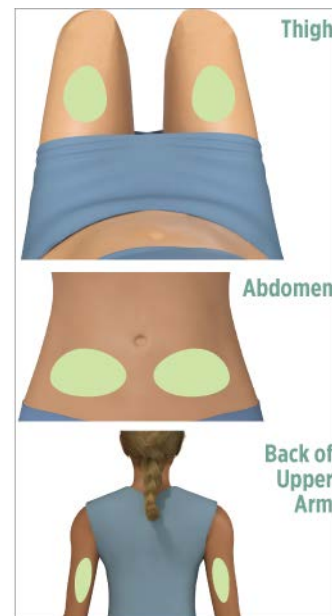


Figure H

to inject.	
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Giving Your Injection:

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).
 - **Be careful** when removing the needle cover to avoid getting a needle stick injury.
 - **Do not** touch the needle.
 - **Important: Do not** recap the Plegridy Prefilled Syringe. You could get a needle stick injury.
 - Throw away the needle cover after your injection.

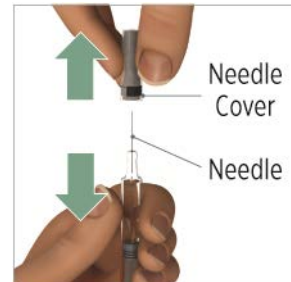


Figure I

Step 6: Gently pinch the injection site

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



Figure J

Step 7: Give your Plegridy Prefilled Syringe injection

- With your other hand, hold your Plegridy Prefilled Syringe like a pencil. **Use a quick 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.

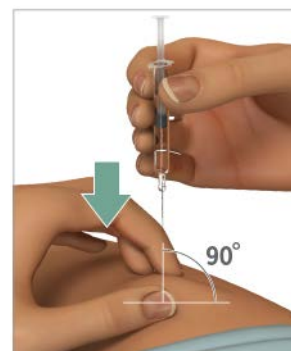

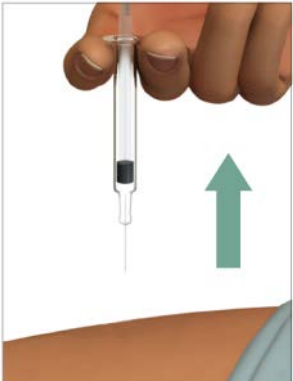


Figure K

<ul style="list-style-type: none"> • Slowly push the plunger down until the syringe is empty (See Figure L). <ul style="list-style-type: none"> ○ Do not take your Plegridy Prefilled Syringe out of your injection site until you have slowly pushed the plunger all the way down. 	 <p>Figure L</p>
<ul style="list-style-type: none"> • Pull the needle straight out of your skin (See Figure M). <ul style="list-style-type: none"> ○ If you see blood at your injection site, wipe it off with the gauze pad and apply an adhesive bandage. • Important: Do not recap your Plegridy Prefilled Syringe. You could get a needle stick injury. • Do not reuse your Plegridy Prefilled Syringe. 	 <p>Figure M</p>

After Your Injection:

Step 8: Disposing of your used Plegridy Prefilled Syringes

- Put your used Plegridy Prefilled Syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) Plegridy Prefilled Syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak resistant, and
 - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Step 9: Check your injection site

- Plegridy may commonly cause redness, pain or swelling of your skin at the injection site.
- After 2 hours check your injection site for redness, swelling or tenderness.
- Call your healthcare provider right away if your injection site becomes swollen and painful or the area looks infected and does not heal within a few days.

Questions?

For product or service-related questions, call 1-800-456-2255 or go to www.plegridy.com.

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