

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 or intramuscular use

Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Warnings and Precautions (5.8)

7/2023

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 or intramuscular 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 or intramuscular injections using the prefilled syringe (2.2)
- Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms (2.3)

DOSAGE FORMS AND STRENGTHS

Subcutaneous Administration:

- Injection: 125 mcg/0.5 mL in a single-dose prefilled pen or single-dose prefilled syringe (3)
- Injection: 63 mcg/0.5 mL in a single-dose prefilled pen or single-dose prefilled syringe (3)
- Injection: 94 mcg/0.5 mL in a single-dose prefilled pen or single-dose prefilled syringe (3)

Intramuscular Administration:

- Injection: 125 mcg/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 PLEGRIDY (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)
- Anaphylaxis and other allergic reactions: Discontinue PLEGRIDY if a serious allergic reaction occurs (5.3)
- Injection site reactions: Do not administer PLEGRIDY into affected area until fully healed; if multiple lesions occur, change injection site or discontinue PLEGRIDY until healing of skin lesions (5.4)
- Congestive heart failure: monitor patients with pre-existing significant cardiac disease for worsening of cardiac symptoms (5.5)
- Decreased peripheral blood counts: monitor complete blood counts (5.6)
- 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 (5.7)
- Pulmonary Arterial Hypertension: Cases of pulmonary arterial hypertension (PAH) have been reported in patients treated with interferon beta products, including PLEGRIDY. Discontinue PLEGRIDY if PAH is diagnosed (5.8)
- Autoimmune disorders: consider discontinuation of PLEGRIDY if a new autoimmune disorder occurs (5.9)

ADVERSE REACTIONS

The most common adverse reactions in clinical trials of subcutaneous PLEGRIDY (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 <http://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: 7/2023

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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 may only be administered subcutaneously (SC) or intramuscularly (IM).

Recommended Maintenance Dosage

After initial titration (see Table 1 and Table 2), the recommended dosage of PLEGRIDY is 125 micrograms injected every 14 days.

For subcutaneous injection:

Patients may rotate injection sites between the abdomen, back of the upper arm, or thigh.

For intramuscular injection:

Patients may rotate injection sites between the left and right thighs.

Treatment Initiation

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms sometimes experienced during treatment with PLEGRIDY.

Switching between the subcutaneous and intramuscular routes of administration and vice versa has not been studied. It is not expected that dose titration should be repeated to ameliorate flu-like symptoms if switching between subcutaneous and intramuscular routes of administration, or vice versa based upon bioequivalence demonstrated between the two routes of administration.

Subcutaneous Administration of PLEGRIDY

Patients using PLEGRIDY for the first time 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 Subcutaneous Dose Titration

Dose	Time ^a	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

^a Dosed every 14 days

Intramuscular Administration of PLEGRIDY

For patients using PLEGRIDY injected intramuscularly for the first time, PLEGRIDY should be titrated using the PLEGRIDY Titration Kit designed for use with the prefilled syringe. The PLEGRIDY Titration Kit is supplied separately and contains two titration devices to be used only with PLEGRIDY prefilled syringes for intramuscular use.

Patients should start treatment with 63 micrograms (yellow clip) on day 1. On day 15 (14 days later), the dose is increased to 94 micrograms (purple clip), 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 2](#)).

Table 2: Schedule for Intramuscular Dose Titration

Dose	Time ^a	Amount (micrograms)	Titration Clip
Dose 1	On day 1	63	Yellow
Dose 2	On day 15	94	Purple
Dose 3	On day 29 and every 14 days thereafter	125 (full dose)	No Clips Needed

^a 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 or intramuscular injections using the prefilled syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Advise patients and caregivers to rotate injection sites with

each administration to minimize the likelihood of severe injection site reactions, including necrosis or localized infection [*see Warnings and Precautions (5.4)*].

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.

Each PLEGRIDY pen and syringe for subcutaneous injection is provided with the needle pre-attached. PLEGRIDY prefilled syringe for intramuscular injection is supplied as a prefilled syringe with a separate needle. Both intramuscular and subcutaneous prefilled syringes and subcutaneously administered prefilled pens are for one-time use in one patient 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

PLEGRIDY is a clear to slightly opalescent and colorless to slightly yellow solution.

Subcutaneous Administration:

- Injection: 125 mcg/0.5 mL in a single-dose prefilled pen or single-dose prefilled syringe
- Injection: 63 mcg/0.5 mL in a single-dose prefilled pen or a single-dose prefilled syringe
- Injection: 94 mcg/0.5 mL in a single-dose prefilled pen or a single-dose prefilled syringe

Intramuscular Administration:

- Injection: 125 mcg/0.5 mL 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 PLEGRIDY [*see Warnings and Precautions (5.3)*].

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.

Cases of noninfectious hepatitis have been reported in the postmarketing setting with use 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 Anaphylaxis and Other Allergic Reactions

Serious allergic reactions are rare complications of treatment with interferon beta; anaphylaxis has been reported with use of PLEGRIDY in the postmarketing setting.

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.

The protective rubber cover of the PLEGRIDY prefilled syringe for intramuscular administration contains natural rubber latex which may cause allergic reactions and should not be handled by latex-sensitive individuals. The safe use of PLEGRIDY prefilled syringe in latex-sensitive individuals has not been studied.

5.4 Injection Site Reactions Including Necrosis

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

In clinical studies of subcutaneous PLEGRIDY, 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.

In Study 3, which compared single doses of intramuscular and subcutaneous PLEGRIDY [*see Adverse Reactions (6.1)*], the incidence of injection site reactions (e.g., injection site erythema, pain, pruritus, or edema) was 14% in the intramuscular PLEGRIDY group and 32% in the subcutaneous PLEGRIDY group.

Injection site abscesses and cellulitis have been reported in the postmarketing setting with use of interferon beta. Some cases required treatment with hospitalization for surgical drainage and intravenous antibiotics.

Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred.

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, change injection site or discontinue PLEGRIDY until healing occurs.

5.5 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.

5.6 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.

5.7 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.

5.8 Pulmonary Arterial Hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported in patients treated with interferon beta products, including PLEGRIDY. PAH has occurred in patients treated with interferon beta products in the absence of other contributory factors. Many of the reported cases required hospitalization, including one case with interferon beta in which the patient underwent a lung transplant. PAH has developed at various time points after initiating therapy with interferon beta products and may occur several years after starting treatment.

Patients who develop unexplained symptoms (e.g., dyspnea, new or increasing fatigue) should be assessed for PAH. If alternative etiologies have been ruled out and a diagnosis of PAH is confirmed, discontinue treatment 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.

5.10 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.

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)]
- Anaphylaxis and Other Allergic Reactions [see Warnings and Precautions (5.3)]
- Injection Site Reactions Including Necrosis [see Warnings and Precautions (5.4)]
- Congestive Heart Failure [see Warnings and Precautions (Section 5.5)]
- Decreased Peripheral Blood Counts [see Warnings and Precautions (5.6)]
- Thrombotic Microangiopathy [see Warnings and Precautions (5.7)]
- Pulmonary Arterial Hypertension [see Warnings and Precautions (5.8)]
- Autoimmune Disorders [see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]

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.

PLEGRIDY Via Subcutaneous Administration

In clinical studies (Study 1 and Study 2), a total of 1468 patients with relapsing multiple sclerosis received PLEGRIDY by subcutaneous injection 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 3 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 3: 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

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.

Comparison Between Subcutaneous and Intramuscular Administration

An open-label, crossover study analyzed findings from 130 healthy volunteers to assess the bioequivalence of single doses of 125 micrograms of PLEGRIDY administered as a subcutaneous and intramuscular injection (Study 3).

The most commonly reported adverse reactions (with >10% incidence in either arm) across both treatment periods were chills (36% in IM vs 27% in SC), pain (22% in IM vs 14% in SC), headache (36% in IM vs 41% in SC), injection site pain (11% in IM vs 15% in SC), and injection site erythema (2% in IM vs 25% in SC). Overall, injection site reactions were reported in 14% via IM route as compared to 32% via SC route.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

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 in the studies described below with the incidence of antibodies in other studies or to other interferon beta-1a products may be misleading.

In Study 1, fewer than 1% of patients treated with PLEGRIDY SC every 14 days for 1 year developed neutralizing antibodies. Approximately 7% of PLEGRIDY SC-treated patients developed antibodies to the polyethylene glycol moiety.

No formal studies have been conducted with regards to immunogenicity of the intramuscular route of administration of PLEGRIDY.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PLEGRIDY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylactic reactions

In post marketing experience, serious hypersensitivity reactions, including cases of anaphylaxis, have been reported following PLEGRIDY administration [*see Warnings and Precautions (5.3)*].

Hepatic injury

In post marketing experience, noninfectious hepatitis (including serious hepatitis) cases have been reported following PLEGRIDY administration [*see Warnings and Precautions (5.1)*].

Pulmonary Arterial Hypertension

In postmarketing experience, pulmonary arterial hypertension has been reported following PLEGRIDY administration [*see Warnings and Precautions (5.8)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Peginterferon beta-1a is a covalent conjugate of recombinant interferon beta-1a (approximate molecular weight [MW] 20,000 daltons) with a single, linear methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde molecule (approximate MW 20,000 daltons). Interferon beta-1a 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 recombinant interferon beta-1a is identical to that of the human interferon beta counterpart.

The molecular weight of peginterferon beta-1a is approximately 44,000 daltons, consistent with the mass of the protein, the carbohydrate moieties (approximately 2,500 daltons), and the attached poly(ethylene glycol).

Peginterferon beta-1a 125 mcg contains 125 mcg of interferon beta-1a plus 125 mcg of poly(ethylene glycol). Using the World Health Organization International Standard for interferon beta, peginterferon beta-1a 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. Peginterferon beta-1a 125 mcg contains approximately 12 MIU of antiviral activity.

Subcutaneous Administration

PLEGRIDY (peginterferon beta-1a) injection is a sterile, preservative-free solution in a single-dose prefilled pen or single-dose prefilled syringe with a 29-gauge, 0.5-inch needle for subcutaneous use. Each prefilled pen or prefilled syringe delivers 0.5 mL. Each 0.5 mL contains 63 mcg, 94 mcg, or 125 mcg of peginterferon beta-1a, and L-arginine HCl (15.8 mg), glacial acetic acid (0.25 mg), polysorbate 20 (0.025 mg), and sodium acetate trihydrate (0.79 mg) in Water for Injection, USP. The pH is approximately 4.8.

Intramuscular Administration

PLEGRIDY (peginterferon beta-1a) injection is a sterile, preservative-free solution in a single-dose prefilled syringe with a 23-gauge, 1.25-inch needle for intramuscular use. Each prefilled syringe delivers 0.5 mL. Each 0.5 mL contains 125 mcg of peginterferon beta-1a, and L-arginine HCl (15.8 mg), glacial acetic acid (0.25 mg), polysorbate 20 (0.025 mg), and sodium acetate trihydrate (0.79 mg) in Water for Injection, USP. 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.

The pharmacokinetics of 125 µg single dose of PLEGRIDY administered subcutaneously and intramuscularly were similar.

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%).

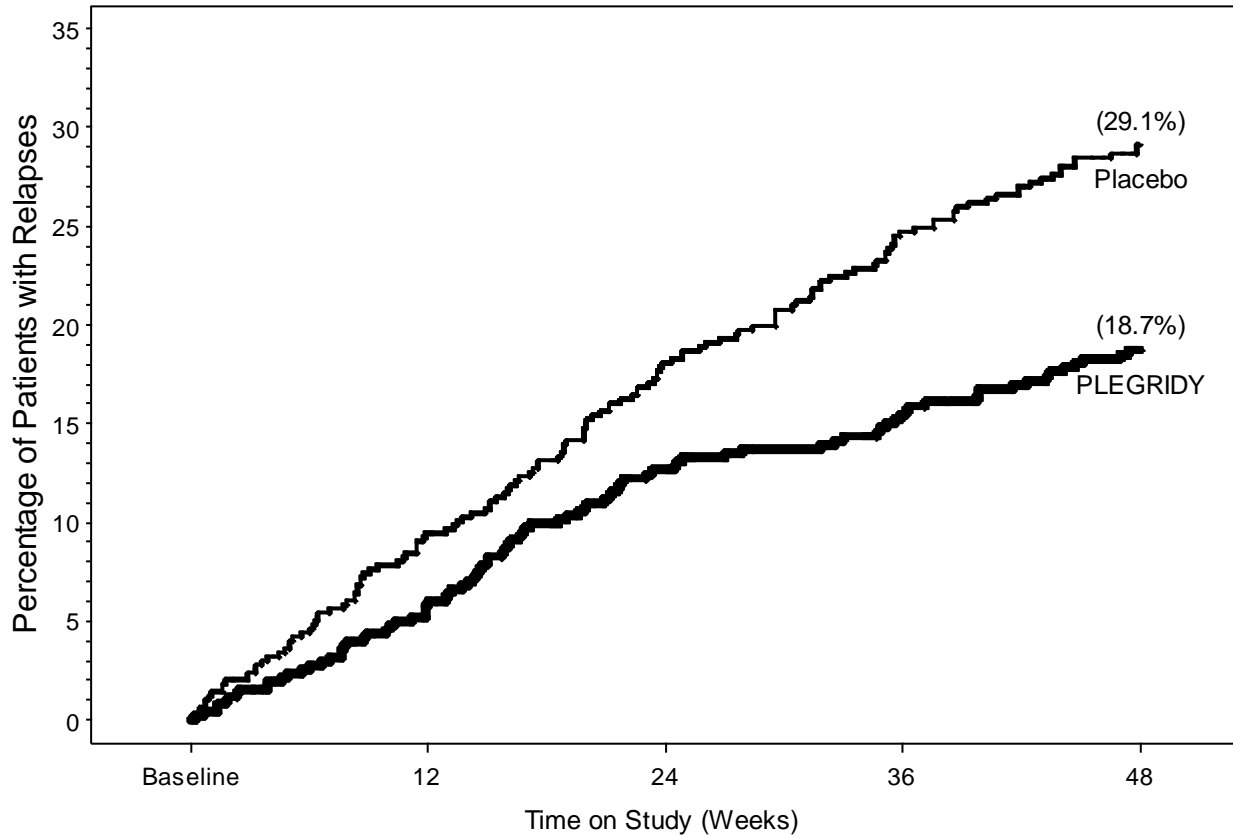
The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48.

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 4](#) and [Figure 1](#) show the results of Study 1.

Table 4: 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



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

16.1 How Supplied

PLEGRIDY (peginterferon beta-1a) injection is a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution supplied as a 0.5 mL single-dose prefilled pen or a 0.5 mL single-dose prefilled syringe.

Subcutaneous Administration

PLEGRIDY (peginterferon beta-1a) injection for subcutaneous use is supplied as a single-dose prefilled pen or single-dose prefilled syringe with a rubber stopper and a 29-gauge, 0.5-inch staked needle with a rigid needle shield in the following packaging configurations:

- Carton containing two-125 mcg/0.5 mL single-dose prefilled pens of PLEGRIDY (NDC 64406-011-01).
- Starter Pack carton containing two single-dose prefilled pens; dose 1 provides 63 mcg/0.5 mL of PLEGRIDY and dose 2 provides 94 mcg/0.5 mL of PLEGRIDY (NDC 64406-012-01).
- Carton containing two-125 mcg/0.5 mL single-dose prefilled syringes of PLEGRIDY (NDC 64406-015-01).
- Starter Pack carton containing two single-dose prefilled syringes; dose 1 provides 63 mcg/0.5 mL of PLEGRIDY, and dose 2 provides 94 mcg/0.5 mL of PLEGRIDY (NDC 64406-016-01).

Intramuscular Administration

PLEGRIDY (peginterferon beta-1a) injection for intramuscular use is supplied as a single-dose prefilled syringe with a rubber stopper and a 23-gauge, 1.25-inch staked needle provided separately with the syringe in the following packaging configurations:

- Carton containing two-125 mcg/0.5 mL single-dose prefilled syringes of PLEGRIDY (NDC 64406-017-01).
- The PLEGRIDY Titration Kit must be prescribed and dispensed separately for treatment initiation. The Titration Kit contains two titration clips: The yellow clip (for dose 1) allows a delivered dose of 63 mcg of PLEGRIDY, and the purple clip (for dose 2) allows a delivered dose of 94 mcg of PLEGRIDY.

16.2 Storage and Handling

Store PLEGRIDY prefilled pens and prefilled syringes in a refrigerator between 2°C to 8°C (36°F to 46°F) in the closed original carton to protect from light until ready for injection. Do not freeze. Discard if frozen.

If refrigeration is unavailable, PLEGRIDY may be stored at room temperature up to 25°C (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 should not exceed 30 days.

PLEGRIDY prefilled syringe for intramuscular administration contains natural rubber latex which may cause allergic reactions.

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 [*see Warnings and Precautions (5.4)*]. For subcutaneous administration, the usual injection sites are the abdomen, back of the upper arm, and thigh. For intramuscular administration, alternate injections between the left and right thigh.
- 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 to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant [*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)*].

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. Inform latex-sensitive patients that

the PLEGRIDY prefilled syringe for intramuscular administration contains natural rubber latex [see *Warnings and Precautions (5.3)*].

Injection Site Reactions Including Necrosis

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 (5.4)*].

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 (5.5)*].

Pulmonary Arterial Hypertension

Inform patients that PAH has occurred in patients treated with interferon beta products, including PLEGRIDY. Instruct patients to promptly report any new symptoms such as new or increasing fatigue or shortness of breath to their healthcare provider [see *Warnings and Precautions (5.8)*].

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 (5.10)*].

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)*].

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

injection, for subcutaneous or intramuscular 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).
- have or had an allergic reaction to rubber or latex. The tip of the cap of the PLEGRIDY prefilled syringe for intramuscular use is made of natural rubber latex.
- are pregnant or plan to become pregnant. It is not known if PLEGRIDY can harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with PLEGRIDY.
- 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.

- If you are prescribed PLEGRIDY for injection under the skin (subcutaneous injection):
 - you should use a PLEGRIDY Starter Pack to slowly adjust your dose when you begin treatment.
 - inject PLEGRIDY under the skin of your stomach (abdomen), back of upper arm, or thigh 1 time every 14 days.
- If you are prescribed PLEGRIDY for injection into the muscle (intramuscular injection):
 - you should use a PLEGRIDY Titration Kit to slowly adjust your dose when you begin treatment.
 - inject PLEGRIDY into your thigh 1 time every 14 days.
- If your healthcare provider changes where you are injecting PLEGRIDY (under the skin or into the muscle), you do not need to slowly increase your dose again.
- 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, pain, itching, swelling, tenderness, a break in your skin that becomes blue and black, or drains fluid. 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?

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

PLEGRIDY may cause serious side effects, including:

- **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, itching, 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. 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 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.
- **pulmonary arterial hypertension.** Pulmonary arterial hypertension can occur with interferon beta products, including PLEGRIDY. Symptoms may include new or increasing fatigue or shortness of breath. Contact your healthcare provider right away if you develop these symptoms.
- **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.
- **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, 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.

These are not all 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 (subcutaneous injection only):** L-arginine hydrochloride, glacial acetic acid, polysorbate 20, and sodium acetate trihydrate in sterile water for injection.
- **Single-dose Prefilled Syringe (subcutaneous and intramuscular injection):** L-arginine hydrochloride, glacial acetic acid, polysorbate 20, and 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.

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