

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

Warnings and Precautions, Thrombotic Microangiopathy (5.8) 10/2015

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Hepatic injury: monitor liver function tests; monitor patients for signs and symptoms of hepatic injury; consider discontinuation of PLEGRIDY if hepatic injury occurs (5.1)
- Depression and suicide: advise patients to report immediately any symptom of depression or suicidal ideation to their healthcare provider; consider discontinuation of PLEGRIDY if depression occurs (5.2)
- Seizure: Seizures are associated with the use of interferon beta. Exercise caution when administering PLEGRIDY to patients with a seizure disorder (5.3)
- Anaphylaxis and other allergic reactions: serious allergic reactions have been reported as a rare complication of treatment with interferon beta. Discontinue PLEGRIDY if a serious allergic reaction occurs (5.4)
- Injection site reactions: change injection site or consider discontinuation of PLEGRIDY if there is necrosis (5.5)
- Congestive heart failure: monitor patients with pre-existing significant cardiac disease for worsening of cardiac symptoms (5.6)
- Decreased peripheral blood counts: monitor complete blood counts (5.7)
- 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: based on animal data, may cause fetal harm (8.1)
- Severe Renal Impairment: monitor for adverse reactions (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
2.1	Dosing Information
2.2	Important Administration Instructions (All Dosage Forms)
2.3	Premedication for Flu-like Symptoms
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
5.1	Hepatic Injury
5.2	Depression and Suicide
5.3	Seizures
5.4	Anaphylaxis and Other Allergic Reactions
5.5	Injection Site Reactions
5.6	Congestive Heart Failure
5.7	Decreased Peripheral Blood Counts
5.8	Thrombotic Microangiopathy
5.9	Autoimmune Disorders
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.3	Nursing Mothers
8.4	Pediatric Use

8.5	Geriatric Use
8.6	Renal Impairment
11	DESCRIPTION
11.1	PLEGRIDY PEN Single-Dose Prefilled Pen
11.2	PLEGRIDY Single-Dose Prefilled Syringe
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.2	Pharmacodynamics
12.3	Pharmacokinetics
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
14	CLINICAL STUDIES
16	HOW SUPPLIED/STORAGE AND HANDLING
16.1	PLEGRIDY PEN Single-Dose Prefilled Pen
16.2	PLEGRIDY Single-Dose Prefilled Syringe
16.3	Storage and Handling
16.4	Instructions for Disposal
17	PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

PLEGRIDY is administered subcutaneously.

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

Treatment initiation

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

Table 1: Schedule for Dose Titration

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 Category C

There are no adequate and well-controlled studies in pregnant women. PLEGRIDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PLEGRIDY has not been tested for developmental toxicity in pregnant animals. In monkeys given interferon beta by subcutaneous injection every other day during early pregnancy, no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses.

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/>.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Safety and effectiveness in geriatric patients have not been established.

8.6 Renal Impairment

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

11 DESCRIPTION

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

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

PLEGRIDY 125 micrograms contains 125 micrograms of interferon beta-1a plus 125 micrograms of poly(ethylene glycol). Using the World Health Organization International Standard for interferon beta, PLEGRIDY has a specific antiviral activity of approximately 100 million International Units (MIU) per mg of protein as determined using an *in vitro* cytopathic effect assay. PLEGRIDY 125 micrograms contains approximately 12 MIU of antiviral activity. PLEGRIDY contains no preservative.

11.1 PLEGRIDY PEN Single-Dose Prefilled Pen

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

11.2 PLEGRIDY Single-Dose Prefilled Syringe

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

Absorption

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

Distribution

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

Metabolism and Elimination

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

Specific Populations

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

PLEGRIDY was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in an *in vitro* assay in human lymphocytes.

Impairment of Fertility

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

14 CLINICAL STUDIES

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

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

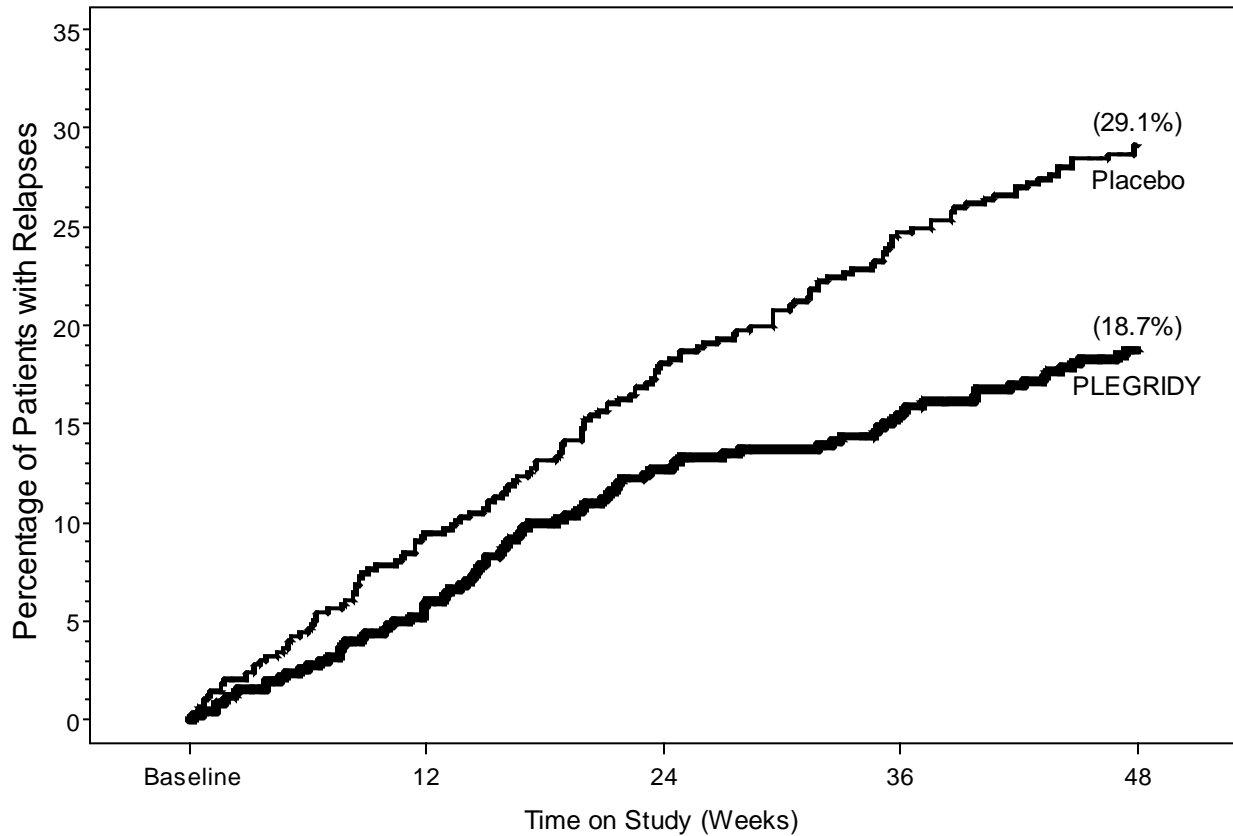
The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48.

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

Table 3: Clinical and MRI Results of Study 1

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

Figure 1: Time to first relapse



Number of Subjects at Risk

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

16.1 PLEGRIDY PEN Single-Dose Prefilled Pen

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

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

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

16.2 PLEGRIDY Single-Dose Prefilled Syringe

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

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

16.3 Storage and Handling

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

Store in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Discard if frozen. Once removed from the refrigerator, PLEGRIDY should be allowed to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm PLEGRIDY.

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

16.4 Instructions for Disposal

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

17 PATIENT COUNSELING INFORMATION

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

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

Instructions for Self-Injection Technique and Procedures

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

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

Advise patients:

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

Pregnancy and Pregnancy Registry

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

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.

Depression and Suicide

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

Seizure

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

Anaphylaxis and Other Allergic Reactions

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

Injection Site Reactions

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

Cardiac Disease

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

Flu-like Symptoms

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

Manufactured by:

Biogen Inc.

Cambridge, MA 02142

U.S. License # 1697

PLEGRIDY is a trademark of Biogen.

©2013-2016 Biogen