PRODUCT INFORMATION

PLEGRIDY® (peginterferon beta-1a (rch))

NAME OF THE MEDICINE

Peginterferon beta-1a (rch) is recombinant interferon beta-1a conjugated to 20 kDa methoxy poly(ethylene glycol) using an -O-2-methylpropionaldehyde linker. It is expressed in mammalian cells and has the same sequence as naturally-occurring human interferon beta. The 20 kDa mPEG-O-2-methylpropionaldehyde is attached to the a-amino group of the N-terminal amino acid residue using reductive amination chemistry.

The CAS Registry Number is 1211327-92-2.

DESCRIPTION

PLEGRIDY is produced by recombinant DNA technology and is manufactured in three strengths, 63 micrograms, 94 micrograms, and 125 micrograms. PLEGRIDY is supplied as pre-filled pen and pre-filled syringe.

PLEGRIDY also contains sodium acetate trihydrate, glacial acetic acid, L-arginine hydrochloride, and polysorbate 20 in water for injections.

PHARMACOLOGY

Pharmacodynamics

PLEGRIDY is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule to the alpha-amino group of the N-terminal amino acid residue.

Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature.

The pharmacological properties of PLEGRIDY are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule.

A definitive mechanism of action of PLEGRIDY in multiple sclerosis is not known. However, as the biological effects of PLEGRIDY are consistent with those of non-pegylated interferon beta-1a, the mechanism of action of PLEGRIDY is likely to be similar. PLEGRIDY binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. These genes, and their gene products, are believed to mediate the efficacy of PLEGRIDY in multiple sclerosis.

As an interferon beta, PLEGRIDY modulates immune responses that are believed to play a role in the pathogenesis of multiple sclerosis. While the pathogenesis of the disease is complex and multifaceted, PLEGRIDY may act at several levels including up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ, TNF-α) and inhibiting the migration of activated T cells across the blood brain barrier; however additional mechanisms have been proposed.

Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2′,5′-oligoadenylate synthetase (2′,5′-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as the gene product neopterin (D-erythro-1, 2, 3,-trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for PLEGRIDY compared to non-pegylated interferon beta-1a (IM) when both were given at equivalent doses as measured by in vitro activity in a cytopathic effect assay (6 MIU). The duration of this response was sustained and prolonged for PLEGRIDY, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with PLEGRIDY, with a sustained and prolonged elevation over 10 days compared to 5 days observed for non-pegylated interferon beta-1a. Neopterin concentrations return to baseline within the two week dosing interval.

Pharmacokinetics

The serum half-life of PLEGRIDY peginterferon beta-1a is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 – 188 micrograms as observed in a single dose and a multiple dose study in healthy subjects. Pharmacokinetics observed in multiple sclerosis patients was consistent with those seen in healthy subjects.

Absorption

Following subcutaneous administration of peginterferon beta-1a in multiple sclerosis patients, the peak concentration was reached between 1 – 1.5 days post-dose. The observed C_{max} (mean±SE) was 280 ± 79 pg/mL following repeat dosing of 125 micrograms every two weeks.

Subcutaneous peginterferon beta-1a resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC168h) values and approximately 2, 3.5 and 5-fold higher C_{max}, following single doses of 63 (6MIU), 125 (12MIU), and 188 (18MIU) micrograms respectively, compared to intramuscular administration of 30 (6MIU) micrograms non-pegylated beta-1a.

Distribution

Following repeat dosing of 125 microgram doses every two weeks by subcutaneous administration in multiple sclerosis patients, peginterferon beta-1a was widely distributed with a volume of distribution of 481 ± 105 L (mean±SE).

Biotransformation and Elimination

Clearance mechanisms for PLEGRIDY include catabolism and excretion. The major pathway of elimination of peginterferon beta-1a is renal. Renal elimination is postulated to be a major excretory pathway for the PEG moiety. Other potential minor routes of elimination for the PEG moiety include hepatic metabolism and biliary excretion.

The process of covalently conjugating a PEG moiety to a protein can alter the *in vivo* properties of the unmodified protein, including decreased renal clearance and decreased proteolysis thus extending the circulating half-life. Accordingly, the half-life ($t_{1/2}$) of peginterferon beta-1a is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean±SE) of peginterferon beta-1a was 78 ± 15 hours at steady state. The mean steady state clearance of peginterferon beta-1a was 4.1 ± 0.4 L/hr.

Special Populations

Elderly (>65 years)

Clinical experience in patients aged above 65 years is limited. However, results from a population pharmacokinetic analysis suggest that age does not impact peginterferon beta-1a clearance.

Gender

No gender effect on the pharmacokinetics of peginterferon beta-1a was found in a population pharmacokinetic analysis.

Race

Race had no effect on the pharmacokinetics of peginterferon beta-1a in a population pharmacokinetic analysis.

Renal Impairment

A single-dose study in healthy subjects (creatinine clearance >80 mL/minute) and subjects with various degree of renal impairment showed a fractional increase in AUC336h (30%, 40% and 53%) and C_{max} (27%, 26% and 42%) in subjects with mild (creatinine clearance 50 to ≤ 80 mL/minute), moderate (creatinine clearance 30 to <50 mL/minute), and severe (creatinine clearance <30 mL/minute) renal impairment respectively, compared to subjects with normal renal function (creatinine clearance >80 mL/minute). Subjects with end stage renal disease requiring haemodialysis 2-3 times weekly showed similar AUC336h and C_{max} as compared to subjects with normal renal function. Each haemodialysis reduced peginterferon beta-1a concentration by approximately 24%, suggesting that haemodialysis partially removes peginterferon beta-1a from systemic circulation.

Hepatic Impairment

The pharmacokinetics of peginterferon beta-1a have not been evaluated in patients with hepatic insufficiency.

CLINICAL TRIALS

The efficacy and safety of PLEGRIDY was assessed from the first year of a 2-year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). Efficacy results were derived from the placebo-controlled first year of the study. At study entry 1512 patients were randomised and dosed to 125 micrograms PLEGRIDY injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500). At the end of the first year, patients who received placebo were randomised to PLEGRIDY every 2 or every 4 weeks while the patients randomised to PLEGRIDY in the first year remained on their original dose assignment.

The study enrolled patients who had experienced at least two relapses within the prior three years including at least one in the year prior to randomisation and had an Expanded Disability Status Scale (EDSS) score ranging from 0 to 5. Neurological evaluations were performed at baseline, every 12 weeks and at time of suspected relapse. Brain MRI evaluations were performed at baseline, weeks 24 and 48. The primary endpoint was the annualized relapse rate (ARR) over one year. Secondary endpoints included the proportion of subjects relapsing, new or newly enlarging T2 hyperintense lesions and time to confirmed disability progression, defined as at least a 1 point

increase from baseline EDSS ≥ 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 weeks.

The mean age of the study population was 37 years, the mean disease duration was 3.6 years and the mean EDSS at baseline was 2.46. The majority of the patients were female (71%).

PLEGRIDY had a statistically significant effect on the primary and all secondary endpoints.

PLEGRIDY every two weeks reduced the ARR by 36% compared to placebo (p=0.0007) at one year (Table 1). There was a consistent reduction of the ARR noted in subgroups defined by demographic and baseline disease characteristics. PLEGRIDY reduced the proportion of subjects who relapsed by 39% (p=0.0003), the proportion of subjects with sustained disability progression by 38% (p=0.0383), the number of new or newly enlarging T2 lesions by 67% (p<0.0001), the number of Gd-enhancing lesions by 86% (p<0.0001) and the number of T1 hypointense lesions by 53% (p<0.0001). A treatment effect was observed as early as six months, with the PLEGRIDY group demonstrating a 61% reduction (p<0.0001) in new or newly enlarging T2 lesions as compared with placebo.

Across relapse and MRI endpoints PLEGRIDY 125 micrograms every two weeks showed a numerically greater treatment effect over the PLEGRIDY every four weeks dosing regimen.

Results for this study are shown in Table 1 and Figure 1

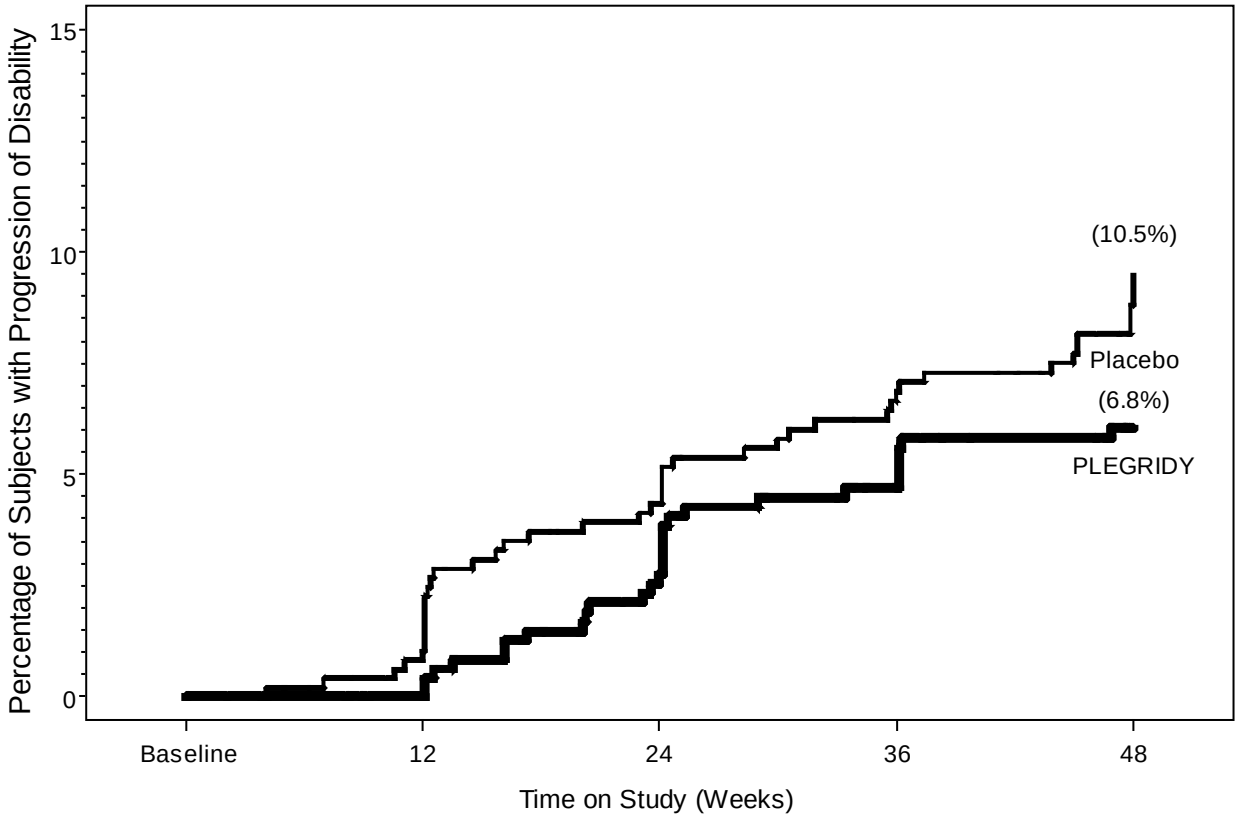
Table 1: Clinical and MRI Results of Study 1*

Endpoint		**Placebo**	**PLEGRIDY 125 micrograms every 2 weeks**
Clinical endpoints		**n=500**	**n=512**
Annualized relapse rate (primary endpoint)	Adjusted rate (95% CI)	0.397 (0.328, 0.481)	0.256 (0.206, 0.318)
	% reduction vs placebo	—	36 (p=0.0007)
Proportion of subjects relapsed	Estimated proportion	0.291	0.187
	% risk reduction vs placebo	—	39 (p=0.0003)
Disability progression	Estimated proportion of subjects progressed	0.105	0.068
	% risk reduction vs placebo	—	38 (p=0.0383)
MRI endpoints		**n=476**	**n=457**

New or newly enlarging T2 hyperintense lesions	Adjusted mean	10.9	3.6
	% reduction vs placebo	—	67 (p<0.0001)
Gd enhancing lesions	Mean	1.4^	0.2
	% reduction vs placebo	—	86 (p<0.0001)
New T1 hypointense lesions	Mean	3.8	1.8
	% reduction vs placebo	—	53 (p<0.0001)

^n=477. * represents intent to treat analysis

Figure 1. Progression of Disability



Number of Subjects at Risk

Placebo	500	483	458	439	352
PLEGRIDY	512	482	453	430	355

PLEGRIDY 125 mcg every 14 days (n=512) versus placebo (n=500) Hazard Ratio (95% CI)=0.62(0.40, 0.97), p=0.0383

INDICATIONS

PLEGRIDY is indicated for the treatment of relapsing forms of Multiple Sclerosis (MS) (see CLINICAL TRIALS).

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.

The initiation of treatment is contraindicated during pregnancy, and in patients with current severe depression and/or suicidal ideation.

PRECAUTIONS

Hepatic injury

Hepatic injury, including elevated serum hepatic transaminase levels, hepatitis, and autoimmune hepatitis, and rare cases of severe hepatic failure, has been reported with interferon beta. Elevations in hepatic enzymes and hepatic injury have been observed with the use of PLEGRIDY. Patients should be monitored for signs of hepatic injury. Withdrawal of treatment with PLEGRIDY should be considered if hepatic transaminase levels significantly increase or if they are associated with clinical symptoms such as jaundice. (See ADVERSE EFFECTS)

Depression and suicidal ideation

Depression and suicidal ideation have been reported to occur with increased frequency in patients receiving interferon beta. Patients treated with PLEGRIDY should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with PLEGRIDY and treated appropriately. If a patient develops depression or other severe psychiatric symptoms, cessation of PLEGRIDY therapy should be considered. (See CONTRAINDICATIONS and ADVERSE EFFECTS)

Hypersensitivity reactions

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

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. One patient treated with PLEGRIDY in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. (See ADVERSE EFFECTS)

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with PLEGRIDY. Patients should be monitored for symptoms or signs of decreased peripheral blood counts. (See ADVERSE EFFECTS)

Seizure

Seizures have been associated with the use of interferon beta. Caution should be exercised when administering PLEGRIDY to patients with pre-existing seizure disorder. (See ADVERSE EFFECTS)

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving interferon beta. The incidence of cardiovascular events was similar between PLEGRIDY (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia should be monitored for worsening of their cardiac condition, particularly during initiation of treatment. PLEGRIDY does not have any known direct acting cardiac toxicity; however, symptoms of the flu-like syndrome seen with PLEGRIDY therapy may prove stressful to patients with cardiac conditions.

Endocrine disorders

Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

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.

Effects on Fertility

The weekly subcutaneous administration of peginterferon beta-1a at 170 times the clinical exposure (based on serum AUC) to sexually mature female rhesus monkeys over the course of one menstrual cycle (up to 5 weeks), resulted in menstrual irregularities, anovulation, and decreased serum progesterone. This is consistent with the effects observed with non-pegylated interferon beta. These effects were reversible after discontinuation of drug. The significance of these nonclinical effects to humans is unknown.

Use in Pregnancy (Category D)

Initiation of treatment is contraindicated during pregnancy (see CONTRAINDICATIONS).

Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Non-pegylated interferon beta-1a has shown no evidence of teratogenicity in pregnant animals. Similar results have been obtained with other interferons.

Non-pegylated interferon beta-1a was not teratogenic in rhesus monkeys at doses up to 50 micrograms (10 million IU)/kg SC. Abortifacient activity was evident at this dose but not at 1.25 micrograms (0.25 million IU)/kg. Patients should be advised of the abortifacient potential of interferon beta observed in animal studies.

There are no adequate and well-controlled studies in pregnant women. Women of child-bearing potential should take appropriate contraceptive measures during treatment. If a patient becomes or

plans to become pregnant whilst on therapy they should be informed of the potential hazards to the fetus. PLEGRIDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

It is not known whether PLEGRIDY is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants, a decision should be made either to discontinue breast-feeding or PLEGRIDY therapy.

Paediatric Use

The safety and effectiveness of PLEGRIDY in patients below the age of 18 have not been studied.

Use in the Elderly

The safety and effectiveness of PLEGRIDY in patients aged 65 and over have not been established.

Use in Renal Impairment

No dose adjustment is necessary for PLEGRIDY in patients with mild to severe renal impairment, or end stage renal disease.

The pharmacokinetics of PLEGRIDY were assessed in a single-dose study in healthy volunteers and subjects with mild, moderate, and severe renal impairment as well as patients with end state renal disease. No clinically important differences in pharmacokinetic profiles were identified based on renal function. (See Pharmacokinetics)

Use in Hepatic Impairment

It is recommended that liver function tests be undertaken prior to initiation of treatment with PLEGRIDY and monitored periodically thereafter. Caution should be used and close monitoring considered when administering PLEGRIDY to patients with severe hepatic impairment. Patients should be monitored for signs of hepatic injury and caution exercised when interferons are used concomitantly with other drugs or hepatotoxic agents (eg alcohol) associated with hepatic injury. (See ADVERSE EFFECTS and Pharmacokinetics)

Genotoxicity

Peginterferon beta-1a was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in an *in vitro* assay in human lymphocytes.

Carcinogenicity

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

Toxicology

Human interferon beta-1a is pharmacologically active in rhesus monkeys. Due to the immunogenicity of human interferons in rhesus monkeys, the studies were limited to five weeks duration. Exposure to peginterferon beta-1a by subcutaneous administration up to 325 times the clinical exposure, based on serum AUC, produced no signs of toxicity.

Effects on Ability to Drive and Use of Machines

No studies on the effects on the ability to drive and use machines have been performed.

Effects on Laboratory Tests

Laboratory abnormalities are associated with the use of interferons. Complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests, are recommended during PLEGRIDY therapy. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts

Immunogenicity

Immunogenicity to PLEGRIDY was evaluated in relapsing multiple sclerosis patients for a minimum of one year and up to two years. Less than 1% of patients (4/489) developed persistent treatment-emergent neutralizing antibodies to interferon beta-1a. Persistent treatment-emergent antibodies to the PEG moiety were also seen in 2% of patients.

In the ADVANCE study, the development of antibodies against the interferon or PEG moiety of PLEGRIDY had no discernible impact on the pharmacodynamic response, safety, or clinical efficacy.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been conducted with PLEGRIDY. Patients who experienced a relapse in the study could receive standard therapy with corticosteroids. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. antiepileptic's and some classes of antidepressants.

ADVERSE EFFECTS

The most common adverse drug reactions (incidence ≥10%, and ≥ 2% compared to placebo) for PLEGRIDY 125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.

The most commonly reported adverse events leading to discontinuation in patients treated with PLEGRIDY 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Clinical Trials

In clinical studies (ADVANCE, ATTAIN) , 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 have received at least 2 years of treatment with PLEGRIDY. A total of 512 and 500 patients, respectively, received PLEGRIDY 125 micrograms every 2 weeks or every 4 weeks during the placebo-controlled phase of ADVANCE (Year 1). The experience in Year 2 of the ADVANCE study and in the 2 year safety extension study ATTAIN (all patients received PLEGRIDY) was consistent with the experience in the 1-year placebo-controlled phase of the ADVANCE study.

Table 2 summarizes ADRs from 512 patients treated with PLEGRIDY 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 48 weeks.

The adverse reactions are presented as MedDRA preferred terms under the MedDRA system organ class (SOC).

Table 2 Adverse Reactions reported for PLEGRIDY 125 micrograms subcutaneously every 2 weeks at ≥ 2% higher incidence than placebo.

MedDRA System Organ Class	MedDRA preferred term	PLEGRIDY (N=512) %	Placebo (N=500) %	PLEGRIDY Frequency category*	
				Very Common (≥1/10)	Common (≥1/100 - <1/10)
Nervous System Disorders	Headache	44	33	Very Common	
Gastrointestinal disorders	Nausea	9	6		Common
	Vomiting	5	2		Common
Musculoskeletal and Connective Tissue Disorders	Myalgia	19	6	Very Common	
	Arthralgia	11	7	Very Common	
General Disorders and Administration Site Conditions	Injection site erythema	62	7	Very Common	
	Influenza like illness	47	13	Very Common	
	Pyrexia	45	15	Very Common	
	Chills	17	5	Very Common	
	Injection site pain	15	3	Very Common	
	Asthenia	13	8	Very Common	
	Injection site pruritus	13	1	Very Common	
	Hyperthermia	4	1		Common
	Pain	5	3		Common
	Injection site oedema	3	0		Common
	Injection site warmth	3	0		Common
	Injection site hematoma	3	1		Common
	Injection site rash	2	0		Common
Investigations	Body temperature increased	6	3		Common
	Alanine aminotransferase increased	6	3		Common
	Aspartate aminotransferase increased	4	2		Common

	Gamma-glutamyl-transferase increased	3	1		Common
Skin and Subcutaneous Tissue Disorder	Pruritus	4	1		Common

*ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10); Uncommon (≥1/1,000 - <1/100); Rare (≥1/10,000 - <1/1,000); Very Rare (<1/10,000)

Description of selected adverse events

Flu Like Symptoms

Influenza-like illness was experienced by 47% of patients receiving PLEGRIDY 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest during the initiation of treatment and generally decreased over the first 6 months.

Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received PLEGRIDY during the placebo controlled phase of the ADVANCE study discontinued treatment due to flu-like symptoms.

Injection Site Reactions

Injection site reactions (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received PLEGRIDY 125 micrograms every 2 weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported injection site reaction. Of the patients who experienced injection site reactions 95% reported them as mild or moderate in severity. One patient out of 1468 patients who received PLEGRIDY in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic Transaminase Abnormalities

The incidence of hepatic transaminase increases was greater in patients receiving PLEGRIDY compared to placebo. The majority of enzyme elevations were <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase (>5 times ULN), were reported in 1% and <1% of placebo-treated patients and 2% and <1% of patients treated with PLEGRIDY respectively. Elevations of serum hepatic transaminases combined with elevated bilirubin were observed in two patients who had pre-existing liver test abnormalities prior to receiving PLEGRIDY in the clinical trials. Both cases resolved following discontinuation of PLEGRIDY.

Haematological Disorders

Decreases in white blood cell counts of $<3.0 \times 10^9$/L were observed in 7% of patients receiving PLEGRIDY and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with PLEGRIDY. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts ($<0.5 \times 10^9$/L) (<1%), neutrophil ($\leq 1.0 \times 10^9$/L) (<1%) counts, platelet counts ($\leq 100 \times 10^9$/L) (≤1%) was similar in PLEGRIDY-treated patients compared to placebo-treated patients. Two serious cases were reported in patients treated with PLEGRIDY: one patient (<1%) experienced severe thrombocytopenia (platelet count <10 x

10^9/L), another patient (<1%) experienced severe neutropenia (neutrophil count <0.5 x 10^9/L). In both patients, cell counts recovered after discontinuation of PLEGRIDY. Compared to placebo, there were no significant differences observed in red blood cell counts in patients treated with PLEGRIDY.

Hypersensitivity reactions

Hypersensitivity events were reported in 16% of patients treated with PLEGRIDY 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of PLEGRIDY-treated patients experienced a serious hypersensitivity event (e.g. angioedema, urticaria) and they recovered promptly after treatment with anti-histamines and/or corticosteroids.

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both PLEGRIDY 125 micrograms every 2 weeks and placebo groups. The incidence of serious events related to depression and suicidal ideation were similar and low (<1%) in both PLEGRIDY 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

The incidence of seizure events was low and comparable in patients receiving PLEGRIDY (125 micrograms every 2 weeks) and placebo (<1% in each group).

Post-Marketing Experience

Not applicable

DOSAGE AND ADMINISTRATION

PLEGRIDY is administered subcutaneously using a single-use pre-filled pen or single-use pre-filled syringe.

The recommended dosage of PLEGRIDY is 125 micrograms injected subcutaneously every 2 weeks.

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (day 0), increasing to 94 micrograms at dose 2 (day 14), reaching the full dose of 125 micrograms by dose 3 (day 28) and continuing with the full dose (125 micrograms) every 14 days (2 weeks) thereafter (see Table 3).

Table 3: Titration Schedule at Initiation

Dose	Time*	Amount (micrograms)	Pen/Syringe label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

*Dosed every 14 days (2 weeks)

A Titration Pack is available containing the 63 micrograms (dose 1, orange label) and 94 micrograms (dose 2, blue label) syringes/pens.

It is recommended that a health care professional trains patients in the proper technique for self-administering subcutaneous injections using the pre-filled pen/syringe. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections include abdomen, arm, and thigh.

If a dose of PLEGRIDY is missed, it should be administered as soon as possible.

• If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.

• If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Plegridy within 7 days of each other.

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

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

Children and Adolescents

The safety and efficacy of PLEGRIDY in patients below 18 years of age has not been studied.

Dosage Adjustment in Renal Impairment

No dosage adjustments are necessary in patients with renal impairment based on study data in mild, moderate, and severe renal impairment and end stage renal disease. (See PRECAUTIONS and Pharmacokinetics)

Dosage Adjustment in Hepatic Impairment

PLEGRIDY has not been studied in patients with hepatic impairment. (See PRECAUTIONS and Pharmacokinetics)

Dosage Adjustment in the Elderly

The safety and efficacy of PLEGRIDY in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials.

OVERDOSAGE

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

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS†

Pre-filled pen

PLEGRIDY is formulated as a sterile clear liquid for subcutaneous injection. Each unit of PLEGRIDY is stored in a 1 mL Type I glass syringe with a latex free bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single pre-filled syringe contains 0.5 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-use, disposable, injection device (pre-filled pen).

The PLEGRIDY pre-filled pen Titration Pack holds 2 ready to use pens. Each Titration Pack for PLEGRIDY pen contains a clear, colorless liquid (0.5ml) containing either 63 or 94 micrograms of peginterferon- beta-1a.

The PLEGRIDY pre-filled pen Administration Dose Pack holds 2 or 6 ready to use pens. Each Administration Dose Pack pen contains a clear, colorless liquid (0.5ml) containing 125 micrograms of peginterferon beta-1a.

Pre-filled syringe

PLEGRIDY is formulated as a sterile clear liquid for subcutaneous injection. Each unit of PLEGRIDY is stored in a 1 mL Type I glass syringe with a latex free bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single pre-filled syringe contains 0.5 mL of solution of PLEGRIDY containing 63 micrograms, 94, micrograms or 125 micrograms of peginterferon beta-1a.

The PLEGRIDY pre-filled syringe Titration Pack holds 2 ready to use syringes. Each Titration Pack for PLEGRIDY syringe contains a clear, colorless liquid (0.5ml) containing either 63 or 94 micrograms of peginterferon- beta-1a.

The PLEGRIDY prefilled syringe Administration Dose Pack holds 2 or 6 ready to use syringes. Each Administration Dose Pack syringe contains a clear, colorless liquid (0.5ml) containing 125 micrograms of peginterferon beta-1a.

†Not all pack sizes are being distributed in Australia.

Storage Conditions

Store in the closed original carton to protect from light until ready for injection. Store in a refrigerator between 2 to 8°C. Do not freeze. Discard if frozen. The formulation is preservative-free.

When no refrigerator is available, PLEGRIDY may be stored protected from light between 2°C to 25°C for a maximum of 30 days in total.

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

PLEGRIDY can be removed from and returned to the refrigerator if necessary. The total combined time out of refrigeration should not exceed 30 days, at a temperature that does not exceed 2°C to 25°C, protected from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

10 November 2014