PROFESSIONAL INFORMATION – PLEGRIDY®

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

PLEGRIDY 63 µg (Solution for Injection)

PLEGRIDY 94 µg (Solution for Injection)

PLEGRIDY 125 µg (Solution for Injection)

COMPOSITION:

PLEGRIDY 63 µg: Each pre-filled syringe or pen contains 63 micrograms of peginterferon beta-1a.

PLEGRIDY 94 µg: Each pre-filled syringe or pen contains 94 micrograms of peginterferon beta-1a.

PLEGRIDY 125 µg: Each pre-filled syringe or pen contains 125 micrograms of peginterferon beta-1a.

Peginterferon beta-1a is a recombinant interferon beta-1a conjugated to 20 kDa methoxy poly(ethyleneglycol) using an -O-2-methylpropionaldehyde linker.

Excipients

Sodium acetate trihydrate, glacial acetic acid, L-arginine hydrochloride, and polysorbate 20 in Water for Injection.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 32.16 Others

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties

Peginterferon beta-1a is interferon beta-1a conjugated to a single, linear 20 kDA methoxy poly (ethyleneglycol) molecule to the alpha-amino group of the N-terminal 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 peginterferon beta-1a 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 peginterferon beta-1a in multiple sclerosis is not known. However, as the biological effects of peginterferon beta-1a are consistent with those of non-pegylated interferon beta-1a, the mechanism of action of peginterferon beta-1a is likely to be similar. Peginterferon beta-1a 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 peginterferon beta-1a in multiple sclerosis.

While the pathogenesis of the disease is complex and multifaceted, peginterferon beta-1a 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-2, IFN-γ, TNF-α) and inhibiting the migration of activated T cells across the blood brain barrier; however additional mechanisms have been proposed.

Pharmacokinetic Properties

Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 to 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 to 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.

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

Renal elimination is postulated to be a major excretory pathway for peginterferon beta-1a. 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. 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.

Specific Patient Populations

Renal impairment

A single-dose study in healthy subjects and subjects with various degree of renal impairment showed a fractional increase in AUC (30-53 %) and C_{max} (26-42 %) 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, compared to subjects with normal renal function (creatinine clearance > 80 ml/minute). Subjects with end stage renal disease requiring 2-3 times haemodialysis weekly showed similar AUC 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 function

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

Elderly patients

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.

INDICATIONS

PLEGRIDY is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the progression of disability.

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.

Pregnancy and lactation (see *Pregnancy and Lactation*).

WARNINGS and SPECIAL PRECAUTIONS

Hepatic injury

Hepatic injury, including elevated serum hepatic transaminase levels, hepatitis, and autoimmune hepatitis, and cases of severe hepatic failure, have been reported with PLEGRIDY. Elevations in hepatic enzymes and hepatic injury have been observed with the use of PLEGRIDY. Patients should be monitored for signs of hepatic injury (see Side Effects).

Depression and suicidal ideation

Depression and suicidal ideation have been reported to occur with increased frequency in patients receiving interferon beta. If a patient develops depression or other severe psychiatric symptoms, PLEGRIDY therapy should be stopped (see Side Effects).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a complication of treatment with interferon beta, including PLEGRIDY. Discontinue PLEGRIDY if serious hypersensitivity reactions occur (see Side Effects).

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta, including PLEGRIDY. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see Side Effects).

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta medicines such as PLEGRIDY. Cytopenias, and 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 Side Effects).

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons, including PLEGRIDY. 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.

Seizure

Seizures have been associated with the use of PLEGRIDY. Caution should be exercised when administering PLEGRIDY to patients with pre-existing seizure disorder (see Side Effects).

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving PLEGRIDY. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or dysrhythmia should be monitored for worsening of their cardiac condition, particularly during initiation of treatment (see Side Effects).

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alpha and interferon beta products. Patients developing suspicious symptoms (e.g. dyspnoea, fatigue) should be assessed for PAH.

General

Immunogenicity

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

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

Special Populations

Paediatric patients

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

Elderly patients

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

Patients with 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 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).

Patients with Hepatic Impairment

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 PLEGRIDY is used concomitantly with other medicines associated with hepatic injury (see Side Effects and Pharmacokinetics).

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should determine their individual responses to PLEGRIDY for effects on driving and machine use.

INTERACTIONS

No formal medicine interaction studies have been conducted with PLEGRIDY. Patients who experienced a relapse in the study could receive standard therapy with corticosteroids.

PREGNANCY AND LACTATION

PLEGRIDY is contraindicated in pregnancy and lactation.

Pregnancy

Safety and efficacy of PLEGRIDY in pregnant women have not been established.

Women who can become pregnant should use contraception while receiving PLEGRIDY.

Lactation

It is not known whether PLEGRIDY is secreted in human milk. Mothers should not breastfeed their infants while on PLEGRIDY.

DOSAGE AND DIRECTIONS FOR USE

PLEGRIDY is administered subcutaneously using a single-use pre-filled pen or 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, increasing to 94 micrograms at dose 2, reaching the full dose of 125 micrograms by dose 3 and continuing with the full dose (125 micrograms) every 2 weeks thereafter (see table 1).

Table 1: Titration Schedule at Initiation

Dose	Time*	Amount (micrograms)	Pen/Syringe label
Dose 1	Day 1	63	Orange
Dose 2	Week 2	94	Blue
Dose 3	Week 4 (and thereafter)	125 (full dose)	Grey

*Dosed every 2 weeks

A Starter Pack is available containing the 63 micrograms (dose 1) and 94 micrograms (dose 2) syringes/pens.

Special Dosage Instructions

It is recommended that a healthcare 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.

The recommended dosage of PLEGRIDY is 125 micrograms injected subcutaneously every 2 weeks. If a dose of PLEGRIDY is missed, it should be taken as soon as the patient remembers. However, the patient should not take 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.

Paediatric patients

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

Elderly patients

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.

Patients with 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 Warnings and Special Precautions and Pharmacokinetics).

Patients with Hepatic Impairment

PLEGRIDY has not been studied in patients with hepatic impairment (see Warnings and Special Precautions).

SIDE EFFECTS

The most common side effects 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 side effect leading to discontinuation in patients treated with PLEGRIDY 125 micrograms subcutaneously every 2 weeks was influenza-like illness (< 1 %).

In clinical studies, a total of 1 468 patients with relapsing multiple sclerosis received PLEGRIDY for up to 177 weeks (41 months). A total of 1 093 patients received at least 1 year, and 415 patients have received at least 2 years of treatment with PLEGRIDY.

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

Table 2: Side effects reported for PLEGRIDY 125 micrograms subcutaneously every 2 weeks at ≥ 2 % higher incidence than placebo.

*Side effect 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)

System Organ Class	**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 haematoma	3	1		Common
	Injection site rash	2	0		Common
Investigations	Increased body temperature	6	3		Common
	Increased alanine aminotransferase	6	3		Common
	Increased aspartate aminotransferase	4	2		Common
	Increased gamma-glutamyl-transferase	3	1		Common
Skin and Subcutaneous Tissue Disorder	Pruritus	4	1		Common

Flu-Like Symptoms

Influenza-like illness was experienced by 47 % of patients receiving PLEGRIDY 125 micrograms every 2 weeks. 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. Less than 1 % of patients who received PLEGRIDY during the placebo controlled phase of the 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 96 % reported them as mild or moderate in severity. One patient out of 1 468 patients who received PLEGRIDY in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic Transaminase Abnormalities

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 2 % of patients treated with PLEGRIDY respectively. Two patients treated with PLEGRIDY experienced asymptomatic elevations of serum hepatic transaminases combined with elevated bilirubin which resolved following discontinuation of PLEGRIDY.

Haematological Disorders

Decreases in white blood cell counts of < 3,0 x $10^9/\ell$ were observed in 7 % of patients receiving PLEGRIDY. Mean white blood cell counts remained within normal limits in patients treated with PLEGRIDY. The incidence of potentially clinically significant decreases in the lymphocyte count (< 0,5 x $10^9/\ell$) was < 1 %, neutrophil count (≤ 1,0 x $10^9/\ell$) was < 1 %, platelet count (≤ 100 x $10^9/\ell$) was < 1 %. Two serious cases were reported in patients treated with PLEGRIDY: one patient (< 1 %) experienced severe thrombocytopenia (platelet count < 10 x $10^9/\ell$), another patient (< 1 %) experienced severe neutropenia (neutrophil count < 0,5 x $10^9/\ell$). 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 PLEGRIDY treated patients.

Hypersensitivity reactions

Hypersensitivity events were reported in 16 % of patients treated with PLEGRIDY 125 micrograms every 2 weeks. 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 side effects related to depression and suicidal ideation was 8 % for both PLEGRIDY and placebo groups.

Seizure

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

Cardiovascular disorders

The incidence of cardiovascular events was similar between PLEGRIDY and placebo treatment groups (7 % in each group). No serious cardiovascular events were reported in patients who received PLEGRIDY in the study.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In case of overdosage, appropriate supportive treatment should be given.

No evidence or experience suggests that abuse or dependence occurs with PLEGRIDY therapy.

IDENTIFICATION

Sterile, clear, colourless liquid essentially free of visible particles.

PRESENTATION

PLEGRIDY Pre-filled syringe

Each unit of PLEGRIDY is stored in a 1 ml Type I clear colourless glass syringe with a latex free grey bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield. A 29 gauge, 1,27 cm staked needle is pre-affixed to the syringe. A single pre-filled syringe contains 0,5 ml of solution of PLEGRIDY containing either 63 micrograms, 94 micrograms, or 125 micrograms of peginterferon beta-1a.

PLEGRIDY Pre-Filled pen

Each unit of PLEGRIDY is stored in a 1 ml Type I clear colourless glass syringe with a latex free grey bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield. A 29 gauge, 1,27 cm staked needle is pre-affixed to the syringe. A single pre-filled syringe contains 0,5 ml of solution of PLEGRIDY containing either 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).

Pack sizes:

Pack size 1: Starter pack of 1 x PLEGRIDY 63 µg and 1 x PLEGRIDY 94 µg

Pack size 2: 2 x PLEGRIDY 125 µg

Pack size 3: 6 x PLEGRIDY 125 µg

STORAGE INSTRUCTIONS

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

Store in a refrigerator between 2 °C 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.

If PLEGRIDY is at room temperature (not to exceed 25 °C) for a total of 30 days, it should be used or discarded. If it is not clear if PLEGRIDY has been stored at room temperature for 30 days or more, it should be discarded.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS

PLEGRIDY 63 µg: 48/32.16/0426

PLEGRIDY 94 µg: 48/32.16/0427

PLEGRIDY 125 µg: 48/32.16/0428

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of registration: 23 November 2017