

## PLEGRIDY™ (peginterferon beta-1a) Summary Medicaid Pharmacy & Therapeutics Committee

- Multiple sclerosis (MS) is a progressive, debilitating disease that affects the CNS. It typically strikes young adults in their 30s, primarily women. PLEGRIDY was approved in August 2014, as the first pegylated beta-1a interferon with a prolonged half-life for the treatment of patients with relapsing forms of MS<sup>1</sup>. It currently has an overall exposure equivalent to 1932 person-years, and a total of 1093 patients have received at least 1 year of treatment (125 µg every 14 days and 125 µg every 28 days during the placebo controlled portion of study) and 415 patients have received at least 2 years of treatment with PLEGRIDY (only 125 µg every 14 days)<sup>1</sup>.
- PLEGRIDY is provided as both a single-use prefilled syringe and as a single-use autoinjector, (PLEGRIDY PEN); both have pre-attached, 0.5 inch, 29 gauge needles<sup>1</sup>.
  - PLEGRIDY is dosed subcutaneously (SQ), every 14 days<sup>1</sup>.
  - Patients should be advised to rotate sites for SQ injections: abdomen, back of upper arm, and thighs<sup>1</sup>.
  - Each titration dose and maintenance dose is color coded to assist patients in administering the correct dose on the correct day, (63 µg Orange, 94 µg Blue; 125 µg Grey).<sup>1</sup>
  - The starting dose is 63 µg on day 1; Dose 2 is 94 µg on day 15; Dose 3 is 125 µg on day 29 and every 14 days thereafter as maintenance. Each dose consists of 0.5 mL of solution<sup>1</sup>.
  - PLEGRIDY should be stored in refrigerator between 2°C to 8°C. Do not freeze. Prior to injection, PLEGRIDY should be allowed to warm to room temperature (30 minutes) naturally. Protect from light until ready to inject.<sup>1</sup>
  - If refrigeration is unavailable, PLEGRIDY, may be stored between 2°C to 25°C for a period up to 30 days, protected from light.
  - Once PLEGRIDY is administered, the empty prefilled syringe or PLEGRIDY PEN should be disposed of in a sharps-bin container or other hard plastic or metal container, and disposed of by following local regulations.<sup>1</sup>
- The mechanism by which PLEGRIDY exerts its therapeutic effect in multiple sclerosis is unknown<sup>1</sup>.
- The efficacy of PLEGRIDY was established in a Phase III, 2 year, multicenter, randomized, double-blind, placebo controlled (for the first year), trial with over 1500 relapsing remitting multiple sclerosis subjects<sup>2</sup>. The study was designed to evaluate the safety and efficacy of peginterferon beta-1a (125 µg given subcutaneously once every 2 or every 4 weeks) compared to placebo<sup>2</sup>. Study 1 (ADVANCE, Year 1 placebo controlled data) was published in Lancet Neurology May 2014; and Study 2 (ATTAIN), a long term safety study, is on-going. The approved dose is 125 µg administered once every 14 days.
  - Treatment with PLEGRIDY significantly decreased the annualized relapse rate (ARR), (total relapses/total time on trial) with a relative reduction of 36% vs. placebo in ADVANCE (primary endpoint; p=0.0007, at one year)<sup>1,2</sup>.
  - A significant reduction in proportion of patients relapsed (patients relapsed/total patient in trial) was observed with PLEGRIDY vs. placebo with a relative risk reduction of 39% (secondary endpoint; p=0.0003)<sup>1,2</sup>.
- Improvement was also demonstrated on measures of disability and neuroradiologic outcomes relative to placebo.
  - In ADVANCE (Study 1), the time to 12-week confirmed disability progression for PLEGRIDY had a statistically significant 38% relative risk reduction (p=0.0383) vs. placebo<sup>1,2</sup>.
  - PLEGRIDY significantly reduced MRI lesions vs. placebo including Gd+ by a relative reduction of 86% (p<0.0001), new or newly enlarging T2 lesions by a relative reduction of 67% (p<0.0001)<sup>1,2</sup>.
- PLEGRIDY (every 2 weeks vs. placebo) demonstrated reductions in annualized MS-related hospitalization rate by 44% (p=0.0148) and a reduction in the annualized rate of MS relapses requiring IV corticosteroid use by 34% (p=0.049)<sup>3</sup>.
- 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.<sup>1</sup>
- PLEGRIDY's safety profile is similar to other currently available interferons for the treatment of MS:
  - Hepatic injury: incidence of increases in ALT and AST greater with PLEGRIDY than placebo. Incidence of elevations of ALT above 5 times ULN was 1% in placebo vs. 2% in PLEGRIDY; incidence of elevations of AST above 5 times ULN was less than 1% for both placebo and PLEGRIDY treated patients<sup>1</sup>.
  - Depression/suicide: 8% for both placebo and PLEGRIDY treated patients. The incidence of serious events related to depression and suicidal ideation was less than 1% in both groups.<sup>1</sup>
  - Seizures: Less than 1% for both placebo and PLEGRIDY treated patients<sup>1</sup>.
  - Anaphylaxis/allergic reactions: Less than 1% of PLEGRIDY treated patients experienced serious allergic reaction such as angioedema or urticaria and recovered after treatment with antihistamines or corticosteroids<sup>1</sup>.

- Injection site reactions (ISR) (erythema, pain, pruritus, edema): 66% of PLEGRIDY group vs. 11% of placebo treated patients. Severe ISRs was 3% in PLEGRIDY and 0% in placebo treated patients<sup>1</sup>.
- Congestive heart failure: 7% for both placebo and PLEGRIDY treated patients, no serious cardiovascular events reported in PLEGRIDY treated group<sup>1</sup>.
- Decreased peripheral blood counts: decreases in WBC below  $3.0 \times 10^9/L$  occurred in 7% patients receiving PLEGRIDY and 1% receiving placebo; no apparent association of increased risk of infections or serious infections. Decreases in lymphocytes, neutrophils and platelet counts were all less than 1% and similar between PLEGRIDY and placebo.<sup>1</sup>
- Autoimmune disorders: incidence less than 1% in both placebo and PLEGRIDY treated patients<sup>1</sup>.

9. The most common adverse reactions (incidence  $\geq 10\%$  overall and  $\geq 2\%$  vs. placebo) were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus and arthralgia<sup>1</sup>.

- 47% of patients receiving PLEGRIDY experienced flu-like symptoms vs. 13% of placebo treated patients. Fewer than 1% of PLEGRIDY treated patients discontinued due to flu-like symptoms. Flu-like symptoms were the most common reason for discontinuation.<sup>1</sup>
- Prophylactic and concurrent use of analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms.<sup>1</sup>
- For therapeutic proteins there is a potential for immunogenicity. Fewer than 1% of patients treated during the first year with PLEGRIDY developed neutralizing antibodies. Approximately 7% of PLEGRIDY treated patients developed antibodies to polyethylene glycol (PEG).<sup>1</sup>
- PLEGRIDY is classified as Pregnancy Category C.<sup>1</sup>

10. In summary PLEGRIDY offers:

- Once every 14 day subcutaneous administration.
- Demonstrated clinical efficacy with statistically significant reductions in annualized relapse rate and proportion of patients relapsing, a statistically significant reduction in the risk of sustained disability progression, and statistically significant effects on MRI endpoints.

References:

1. PLEGRIDY Package Insert 2014.
2. Calabresi P, et al. Lancet Neurol 2014;13:657-665.
3. O'Day K, et al. Presented at 66<sup>th</sup> Annual Meeting of the American Academy of Neurology, April 26-May 3 2014; Philadelphia, PA. P4.146.