PLEGRIDY™ (peginterferon beta-1a)

OVERVIEW

PLEGRIDY™ (peginterferon beta-1a) is a new treatment for relapsing forms of multiple sclerosis (RMS), which includes remitting multiple sclerosis (RRMS), the most common form of MS.[1] PLEGRIDY, the only pegylated beta interferon approved for use in RMS, allows for once every two week dosing and is administered subcutaneously via PLEGRIDY PEN (a new, ready-to-use autoinjector) or prefilled syringe.

BACKGROUND ON MS AND BETA INTERFERONS

MS is a chronic, often disabling disease that attacks the central nervous system (CNS),[2] which is made up of the brain, spinal cord and optic nerves. Symptoms result when a person's immune system attacks the myelin sheath and interferes with the transmission of nerve signals between the brain, spinal cord and other parts of the body.[3]

Beta interferons are a commonly used class of RMS treatments.[4] Beta interferons are thought to stimulate the natural defenses of the immune system and help regulate the body's immune response.[5] The exact mechanism by which PLEGRIDY exerts its effects in patients with multiple sclerosis is unknown.

ABOUT PEGYLATION

Pegylation—the attachment of polyethylene glycol (PEG) molecules—is a well-established scientific process which:

- Prolongs circulation time by increasing molecular size, resulting in a longer half-life
- Stabilizes the molecule by improving chemical stability and solubility for a longer shelf life
- Shields from degradation[6]

The process of pegylation allows patients to receive the benefits of an interferon treatment with less frequent dosing, which may be an attractive option for appropriate patients with RMS seeking treatment with a less frequent dosing schedule.

PHASE 3 ADVANCE STUDY

ADVANCE was a multi-center, randomized, double-blind, parallel-group, placebo-controlled (for the first year) Phase 3 study that evaluated the efficacy, safety and tolerability of PLEGRIDY 125 mcg compared to placebo in people with RMS. After the first year, patients on placebo received PLEGRIDY for the duration of the study. With more than 1,500 patients in over 180 sites in 26 countries, ADVANCE was one of the largest pivotal studies with interferons conducted in people living with RRMS.

The primary endpoint of ADVANCE was to determine the efficacy of PLEGRIDY in reducing annualized relapse rate (ARR) at year one. Secondary endpoints included determining the efficacy of PLEGRIDY in reducing the risk of 12-week confirmed disability progression, the proportion of patients who relapsed and MRI assessments. The analysis for all primary and secondary efficacy endpoints occurred at the end of year one.

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After completing two years in the ADVANCE study, patients had the option of enrolling in an open-label extension study called ATTAIN and may be followed for up to four years.

ADVANCE EFFICACY & SAFETY RESULTS

Results from year one of ADVANCE showed that PLEGRIDY dosed every two weeks reduced ARR by 36 percent (p=0.0007) compared to placebo (primary endpoint). PLEGRIDY also met additional study endpoints at one year (see below).

Additional efficacy results:

- PLEGRIDY reduced the risk of 12-week confirmed disability progression, as measured by the Expanded Disability Status Scale, by 38 percent (p=0.0383) compared to placebo.
- PLEGRIDY significantly reduced the number of gadolinium-enhancing (Gd+) lesions by 86 percent (p<0.0001) compared to placebo.
- PLEGRIDY reduced the number of new or newly enlarging T2-hyperintense lesions on brain MRI scans by 67 percent (p<0.001) compared to placebo.

Safety and tolerability results:

The most common adverse reactions associated with PLEGRIDY treatment are injection site reaction, flu-like illness, fever, headache, muscle pain, chills, injection site pain, weakness, injection site itching, and joint pain.

The ADVANCE two-year data were consistent with the safety results observed in year one.[7]

REGULATORY STATUS

PLEGRIDY was approved by the U.S. Food and Drug Administration in August 2014.

The European Commission (EC) granted marketing authorization for PLEGRIDY in the European Union in July 2014, following the positive opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in May 2014.

Indication

PLEGRIDY is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Important Safety Information

- *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.*

- *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. Monitor patients for signs and symptoms of hepatic injury.*

- *Depression, suicidal ideation, and suicide occur more frequently in patients receiving interferon beta than in patients receiving placebo. 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.

- *Seizures are associated with the use of interferon beta. Exercise caution when administering PLEGRIDY to patients with a seizure disorder.*

- *Anaphylaxis and other serious allergic reactions are rare complications of treatment with interferon beta. Discontinue PLEGRIDY if a serious allergic reaction occurs.*

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

- *Congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure occur in patients receiving interferon beta. Monitor patients with significant cardiac disease for worsening of their cardiac condition during initiation and continuation of treatment with PLEGRIDY.*

- *Interferon beta can cause decreased peripheral blood counts in all cell lines, including rare instances of pancytopenia and severe thrombocytopenia. 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.*

- *Autoimmune disorders of multiple target organs including idiopathic thrombocytopenia, hyper and hypothyroidism, and autoimmune hepatitis have been reported with interferon beta. If patients develop a new autoimmune disorder, consider stopping PLEGRIDY.*

- *The most common adverse reactions associated with PLEGRIDY treatment are injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia.*

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

Please see PLEGRIDY.com for full Prescribing Information for additional important safety information.

References

[1] National Multiple Sclerosis Society (NMSS). Relapsing-Remitting MS. Available at http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS. Accessed March 2014.

[2] NMSS. Frequently Asked Questions about Multiple Sclerosis. 2012. Accessed March 2014. Available at http://www.nationalmssociety.org/What-is-MS/MS-FAQ-s

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[4] NMSS. Disease Modification in Multiple Sclerosis. 2013. Accessed July 2014. Available at http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Paper-Cavallo-Treatment-Update.pdf

[5] NMSS. Beta interferon and glatiramer acetate. Accessed May 2014. Available at http://www.mssociety.org.uk/what-is-ms/treatments-and-therapies/licensed-disease-modifying-drugs/beta-interferon-and-glatiramer-acetate

[6] Fishburn CS. The Pharmacology of PEGylation: Balancing PD with PK to Generate Novel Therapeutics. Journal of Pharmaceutical Sciences. DOI 10.1002/jps.21278, 2008.

[7] Deykin A et al. Analysis of 2-year Clinical Efficacy and Safety of Peginterferon Beta-1a in Patients with Relapsing-Remitting Multiple Sclerosis: Data from the Pivotal Phase 3 ADVANCE Study. Platform presentation at 66th American Academy of Neurology (AAN) annual meeting, 2014.