What is the medication?

**Generic**: Peginterferon Beta-1a  
**Brand name**: Plegridy

Has the medication received US Food and Drug Administration (FDA) approval?

**Yes** – approved August 2014.

If so, what are the indications and uses (e.g., in which types of MS)?

Plegridy was approved by the FDA for treatment of relapsing forms of multiple sclerosis (MS).

What were the findings in the pivotal and supportive trials of this medication?

In the pivotal trial of peginterferon (ADVANCE), 1,512 people with relapsing-remitting MS were each randomly assigned to receive placebo injections, or injections of peginterferon 125 micrograms every 2 weeks, or placebo injections or injections of peginterferon 125 micrograms every 4 weeks. After one year, the subjects treated every 2 weeks had a 35.6% reduction in clinical relapses as compared with those who received placebo injections, and those who received treatment every 4 weeks had a 27.5% reduction as compared with those receiving placebo. New lesions on brain MRI were reduced in the treated groups by 67% and 28%, respectively; gadolinium (Gd)-enhancing lesions were reduced by 86% in the group treated every 2 weeks, whereas the reduction of Gd-enhancing lesions in the group treated every 4 weeks was not statistically significant. The risk of disability progression was reduced by 38% in both treated groups.

What is the mechanism of action and the rationale for the use in MS?

Interferons are thought to modulate the immune system, and peginterferon is thought to act similarly to the other beta-interferon medications already approved to treat MS. The difference between peginterferon and the already approved interferons is that pegylation of interferon leads to a longer effective half-life, allowing less frequent dosing. Pegylation of other medications has been shown to reduce formation of neutralizing antibodies, and its use in this trial had the same result, with less than 1% of treated patients developing neutralizing antibodies.
What is the delivery route and recommended dosing?

Peginterferon dosing is 125 micrograms subcutaneously every 14 days. The dose should be titrated such that 63 micrograms are delivered on day 1, followed by 94 micrograms on day 15 and 125 micrograms (full dose) on day 29. For details of initial dose titration and Starter Pack, see below.

Can this medication be used with other medications?

- **Disease-modifying Therapies (DMT):**
  
  No published studies have evaluated the use of peginterferon in combination with other MS DMTs.

- **Other Medications:**
  
  No specific concerns were identified in the pivotal trial regarding concurrent or prior use of other medications with peginterferon. The major pathway of peginterferon elimination is renal, and peginterferon is not extensively metabolized in the liver.

How does the expected treatment effect compare with the treatment effect provided by other available medications?

The available data are insufficient for drawing firm conclusions about the relative effectiveness of peginterferon as compared with the other FDA-approved MS DMTs. In the pivotal ADVANCE trial, peginterferon was not compared with other interferon medications or with other MS therapies. Head-to-head comparative studies would be needed to determine relative effectiveness.

What are the possible short-term adverse effects (AEs)? What is the range of severity of AEs, and what are the recommended management strategies?

- Safety and AEs appear to be similar to those for other approved forms of interferon-beta. The most common AEs were injection site reactions, flu-like symptoms, fever, headache, muscle pain, chills, injection site pain, weakness, and joint pain. Most AEs were of mild or moderate severity.

  - Injection site reactions can be reduced through use of proper injection techniques and appropriate site rotation, as well as allowing the medication to come to room temperature prior to injection.

- On the basis of clinician preference, patients may be instructed on premedication to reduce the flu-like AEs of interferon treatment.

What are the known long-range (morbidity and mortality) health risks?

- Hepatic AEs: 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. Elevations in hepatic enzymes and hepatic injury have been observed with peginterferon in clinical studies. A greater proportion of participants taking peginterferon had increased liver enzymes as compared with those in the placebo group, but this AE did not result in discontinuation of treatment in the ADVANCE trial.

- **Psychological AEs:** Depression, suicidal ideation, and suicide occur more frequently in patients receiving interferon beta than in patients receiving placebo. In MS clinical studies, the overall incidence of AEs related to depression and suicidal ideation was 8% in both the peginterferon and placebo groups.

- **Seizures:** Seizures are associated with the use of interferon beta. The incidence of seizures in MS clinical studies was less than 1% in patients receiving peginterferon or placebo.

- **Anaphylaxis and other allergic reactions:** Less than 1% of peginterferon-treated patients experienced a serious allergic reaction such as angioedema or urticaria.

- **Injection site reactions:** injection site reactions, including injection site necrosis, can occur with the use of subcutaneous interferon beta. One patient of 1,468 patients who received peginterferon in clinical studies experienced injection site necrosis.

- **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 peginterferon and placebo groups.

- **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 x 10^9/L occurred in 7% of patients receiving peginterferon and 1% receiving placebo. Two serious cases (less than 1%) were reported in patients treated with peginterferon: one patient experienced severe thrombocytopenia, and another experienced severe neutropenia; cell counts recovered after discontinuation of peginterferon.

- **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 peginterferon and placebo groups.

Has the FDA included any black box warnings about this medication?

The FDA has not included any black box warnings about this medication.
What training is recommended or required for clinicians or patients before initiating this treatment?

Plegridy is administered subcutaneously every 14 days. Treatment initiation begins with a dose titration Starter Pack that is provided with either two prefilled pens or two prefilled syringes, depending on clinician or patient preference.

- On day one (1), using Dose 1 (Orange color), patients self-inject with 63 micrograms. The patient should be instructed on skin preparation, site rotation (abdomen, back of the upper arm, thigh), method of subcutaneous injection, and disposal of the needle and syringe.
- On day 15, the patient must be instructed to use Dose 2 (Blue color) which is 94 micrograms.
- On day 29, the patient should be instructed on using Dose 3 (Grey color), which is 125 micrograms.
- Subsequently, each dose of 125 micrograms should be injected subcutaneously every 14 days.

The Plegridy pen and syringe are provided with the needle attached and are for single use only. They must be discarded appropriately and safely after each use.

What is the pregnancy rating for this medication?

The pregnancy rating for Plegridy is 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. This medication 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 AEs on fetal development were observed. Abortifacient activity was evident following three to five doses.

With regard to 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.

What is known about possible carcinogenesis, mutagenesis, and impairment of fertility?

The carcinogenic potential of Plegridy has not been tested in animals. Plegridy was not mutagenic when tested in an in vitro bacterial reverse mutation (Ames) test and was not clastogenic (capable of causing breakage in chromosomes) in an in vitro assay in human lymphocytes. 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 the drug.
Does this medication interact or interfere with oral contraceptives?

Plegridy is not known to interact with or interfere with oral contraceptives.

Has the FDA recommended or required a safety-monitoring program?

A safety monitoring program is not required by the FDA.

What kind of safety monitoring is recommended (including prescreening, routine checkups, and laboratory tests)?

- It is important to obtain baseline blood work prior to initiation of therapy with peginterferon. Complete blood count with differential and platelets and liver function testing is advisable as well as regular monitoring during therapy.
- Clinicians should monitor patients for infections, bleeding, and symptoms of anemia. Patients with myelosuppression may require more intensive monitoring of blood counts.
- Clinicians should monitor patients for signs and symptoms of hepatic injury.
- Many clinicians monitor thyroid function annually in patients on interferon beta preparations.
- If patients develop a new autoimmune disorder, clinicians should consider stopping peginterferon.
- Clinicians should advise patients to report immediately any symptoms of depression or suicidal ideation.
- Clinicians should monitor patients with significant cardiac disease for worsening of their cardiac conditions during initiation and continuation of treatment.
- For patients with severe renal impairment, clinicians should monitor for AEs to peginterferon.

Are there any recommended limits on treatment duration with this medication?

There are no limitations on the duration of treatment.

What happens following termination of treatment with this medication?

As is the case when any DMT is discontinued, MS activity may return following the discontinuation of peginterferon.

What treatment options are available for patients who have been treated with peginterferon?

There are a number of other FDA-approved DMTs for patients with relapsing forms of MS.
What is the washout period??

There is no published information about a washout period.

How can the provider identify a suboptimal treatment response?

Suboptimal treatment response may be identified through clinical assessment, neuroimaging (MRI), and patient self-report indicative of continued MS disease activity in a patient adherent to treatment.

Is the manufacturer/distributor offering any financial assistance program for patients?

Patients can receive information about financial assistance by visiting www.MSActiveSource.com or calling 1-800-456-2255. A 24-hour nurse educator is available to answer questions.

Are there any special considerations with this medication?

- Plegridy is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulations. These patients are advised to seek immediate medical attention if an allergic reaction or anaphylaxis occurs. Discontinue peginterferon if a serious allergic reaction occurs.
- Clinicians should exercise caution when administering peginterferon to patients with seizure disorders. Patients are advised to report the advent of seizures immediately to their clinicians.

COMMENTARY BY TEMPLATE AUTHORS

- In the absence of head-to-head comparison trials, there is insufficient evidence to draw conclusions about the relative efficacy of peginterferon as compared with other interferon products or other DMTs.
- There have been reports of worsening significant cardiac disease in patients with a prior history during interferon beta use. Patients should be advised to report any changes immediately to their clinicians.
- Injection site reactions should be reported.
- Flu-like symptoms, particularly in the early stages of treatment, can be managed through a variety of pharmacologic and nonpharmacologic strategies. Education and training of patients and families is highly recommended prior to initial injection.
- In clinical studies, less than 1% of patients treated with peginterferon every 14 days for one year developed neutralizing antibodies.
- The safety and effectiveness of this medication have not been established in pediatric or geriatric populations.
WEB LINKS PROVIDED IN THIS DOCUMENT

- Biogen Idec website: www.BiogenIdec.com
- Plegridy website: www.Plegridy.com
- Support program: www.MSActiveSource.com

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DISCLOSURES:
Dr. Bever has no disclosures related to peginterferon or Biogen Idec. Dr. Whitham has no disclosures related to peginterferon or Biogen Idec. Ms. Halper has served as a consultant to Biogen Idec related to side-effect management.

DISCLAIMER:
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FOR COMPLETE DISCLOSURES AND OTHER INFORMATION:
Please visit our website at http://www.ms-coalition.org/emergingtherapies or email us at emergingtherapies@ms-coalition.org.

For additional information, healthcare professionals are invited to email the National MS Society’s Professional Resource Center at healthprof_info@nmss.org.