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 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 plegridy. The primary outcome was the proportion of people who experienced a relapse within 4 weeks of the start of the trial. The difference between the two groups 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 its use in MS?

Interferons are thought to modulate the immune system, and peginterferon is thought to act similarly to the other interferons. The main advantage of pegylation of interferon 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 are the delivery route and recommended dosing?

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Peginterferon dosing is 125 micrograms subcutaneously every 14 days. The dose should be titrated such that 63 micrograms on day 1 and 63 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 (DMTs):**
  - 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.

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 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 these 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 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 and theoretical long-range (morbidity and mortality) health risks?

- **Hepatic AEs:** Severe hepatic injury, including hepatitis, autoimmune hepatitis, and rare cases of severe hepatic failure. The incidence of severe hepatic injury in the ADVANCE trial was not higher than 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. 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 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 have been reported with the use of 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. One patient experienced severe neutropenia; cell counts recovered after discontinuation of peginterferon.
- **Autoimmune disorders:** Autoimmune disorders of multiple target organs, including idiopathic thrombocytopenia, hyper- and hypothyroidism, myasthenia gravis, inflammatory bowel disease, and myelodysplastic syndrome 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 and 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 the 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. Studies in animals have not demonstrated teratogenicity. No human data are available. No teratogenic or abortifacient activity was 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 human lymphocyte chromosomal aberration test using human lymphocytes. An increase in serum creatinine, decreased serum cholesterol, 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 condition 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 a 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 interferon alfa. Patients are advised to discontinue peginterferon if a serious allergic reaction occurs. Discontinue peginterferon 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:**
PEGYLATED INTERFERON BETA-1A (PLEGRIDY) – PATIENT INFORMATION – Information for People Affected by MS

Click here for information for Healthcare Professionals

The Multiple Sclerosis Emerging Therapies Collaborative includes the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), the MS Coalition, the American Academy of Neurology, and the VA Multiple Sclerosis Centers of Excellence East and West.
**What is the medication?**

**Generic:** Peginterferon beta-1a  
**Brand name:** Plegridy™

**Has the FDA approved the medication?**

Yes, Plegridy was approved in August 2014.

**What are the indications and uses?**

Peginterferon 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 one of three options:

1. injections with a placebo (drug that is not active) every two weeks or every four weeks.
2. injections of peginterferon (125 micrograms) every two weeks
3. injections of peginterferon (125 micrograms) every four weeks

- After one year, the number of relapses in people given peginterferon every two weeks dropped by 35.6 percent when compared with the group who received placebo injections. The number of relapses in people given peginterferon every four weeks dropped by 27.5%.
- For people given peginterferon every two weeks, the formation of new brain lesions (scar tissue shown on MRI scans) dropped by 28 percent when compared with the growth rate in the placebo group.
- Gadolinium (Gd)-enhancing lesions (the new or newly-active lesions that show up on MRI when gadolinium is injected prior to scanning) were reduced by 22.7 percent among people given peginterferon every two weeks. The reduction of Gd-enhancing lesions in the group treated every four weeks was not statistically significant.
- The risk of disability progression was reduced by 38% in both treated groups compared with the placebo group.

**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 interferons. Pegylation offers the advantage of allowing the medication to stay active in the body for a longer period of time, which means that it can be taken less frequently.
Some people develop antibodies that neutralize beta-interferon drugs. This means the antibodies can weaken the drugs’ effectiveness.

**What is the delivery route and recommended dosing?**

A dose of 125 micrograms of peginterferon is given subcutaneously (under the skin) every 14 days. People use a “Starter Pack,” which contains 25-microgram doses for the first 3 injections (on day 1, day 8, and day 15), and 125-microgram (full dose) on day 29. The 125-microgram dose is injected every 14 days after that.

Doctors and their patients may choose between the peginterferon prefilled pen (autoinjector) or prefilled syringe. These prefilled pens are disposable. They come with the needle attached and are for single use only. They must be disposed of appropriately and safely after each use.

**Can this medication be used with other medications?**

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

- **Other Medications:**
  
  No specific concerns were identified in the ADVANCE trial with regard to the use of other medications at the same time as peginterferon or before starting peginterferon (such as the different drugs used for managing symptoms).

**How does the expected treatment effect compare with the treatment effect of other available medications?**

In the pivotal ADVANCE trial, peginterferon was not compared with other interferon medications or with other MS therapies. Head-to-head studies would need to be carried out to accurately determine how effective these medications are in comparison with one another.

**What are the possible short–term side effects? What is the range of severity of side effects, and what are the recommended management strategies?**

- Safety and side effects appear to be similar to those of other approved forms of interferon-beta (for example, Avonex®).
- Injection-site reactions can be reduced by proper injection techniques and appropriate site rotation (varying where the injection is given on the body). Allowing the medication to come to room temperature prior to injection can also reduce reactions.
- You health care provider may tell you to take acetaminophen, ibuprofen, naproxen, or other over-the-counter medication for fever prior to your injection to reduce peginterferon’s flu-like side effects.

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

- Severe hepatic (liver) injury, including hepatitis, autoimmune hepatitis, and rare cases of severe hepatitis, has been reported. Hepatic injury may be associated with elevated liver enzymes, jaundice, fever, and jaundice and swelling of the abdominal region. It is unknown whether hepatitis can occur before a person stops taking the medication.
- Depression, suicidal ideation (thoughts about suicide), and suicide occur more often in people receiving interferon beta. The incidence (occurrence) of seizures in people taking interferon beta is less than 1 percent. Seizures can occur even in people taking placebo.
- Seizures are associated with the use of interferon beta. The incidence (occurrence) of seizures in people taking interferon beta is less than 1 percent. Seizures can occur even in people taking placebo.
- Less than 1 percent of people treated with peginterferon experienced a serious allergic reaction such as angioedema (hives, which are swollen red bumps on the surface of the skin).
- Injection-site reactions, including injection-site necrosis (sores or skin breakdown at the injection site), can occur. Of 1,468 people who received peginterferon in clinical studies, one person experienced injection-site necrosis.
- Congestive heart failure, cardiomyopathy (diseases of the heart muscle), and cardiomyopathy with congestive heart failure have been reported among people receiving interferon beta. In clinical studies, the incidence of cardiovascular events was 7 percent in both the peginterferon and placebo groups.
- Interferon beta can lower blood counts in peripheral blood (flowing, circulating blood) in all cell lines. This results in a reduction of a certain type of white blood cell that fights infection); cell counts recovered after peginterferon was discontinued.
- Autoimmune disorders (including those affecting blood counts, the thyroid, and the liver) have been reported among people receiving interferon beta. Of 1,468 people who received peginterferon in clinical studies, less than 1 percent of people in both the peginterferon and placebo groups developed new autoimmune disorders.

**Has the FDA included any black box warnings about this medication?**
The FDA has not included any black box warnings about this medication. A black box warning is required by the FDA when a serious health risk may result from use of a certain medication.

**What is the pregnancy rating for this medication?**

Peginterferon is not approved for use during pregnancy. The pregnancy rating for peginterferon is Category C. This means that this medication during pregnancy may cause harm to the developing fetus but the benefits may outweigh the possible risks.

With regard to nursing mothers, it is not known whether this drug is excreted (leaves the body) in human milk. Because many drugs are excreted in human milk, clinicians should use caution when giving pegylated interferon to a nursing woman.

**What is known about possible cancers, genetic changes, and lowering of fertility?**

The potential for cancers resulting from peginterferon has not been tested in animals. In laboratory studies, peginterferon lowered levels of the hormone estrogen. This lowering of estrogen causes bleeding to stop, menstruation and the levels of the hormone progesterone. These effects were reversible after the drug was discontinued.

**Does this medication interact or interfere with oral contraceptives (birth control pills)?**

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

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

The FDA does not require a safety monitoring program.

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

- Baseline blood work should be done prior to initiation of therapy with peginterferon. During treatment, a complete blood count should be done on a regular basis, including liver function testing.
- People should be monitored for infections, bleeding, and symptoms of anemia. People taking peginterferon need to be monitored for signs and symptoms of liver injury.
- Many doctors monitor thyroid function yearly in people who take interferon beta preparations.
- People who develop new autoimmune disorders should talk with their physicians about whether to consider stopping peginterferon.
- People taking peginterferon need to report any symptoms of depression or suicidal thinking immediately.
- People with significant cardiac (heart) disease need to be monitored for worsening of their cardiac condition during initiation and continuation of treatment.
- People with severe renal (kidney) impairment should be monitored for adverse reactions to peginterferon.

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

There are no limitations on the duration of treatment.

**What happens after this medication is stopped?**

As is the case when any DMT is stopped, MS activity may return after peginterferon is stopped. **What treatment options are available for people who have been treated with**...
Information for Healthcare Professionals

Written by Jennifer Pichardo

**peginterferon?**

There are a number of other FDA-approved DMTs for people with relapsing forms of MS.

**What is the washout period?**

There is no published information about a washout period. A washout period is the time that is allowed for a medication to leave the body before a new medication is started.

**How can doctors identify a suboptimal (weak) treatment response?**

In people who have taken their medication on a consistent basis, clinicians can perform the following to identify a suboptimal (weak) treatment response:

- A neurologic examination
- An MRI scan to observe a potential increase in lesion activity
- The person's report of new or worsening symptoms that may indicate continued MS disease activity

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

Members of the MS community can receive information about financial assistance by visiting www.MSActiveSource.com or calling 1-800-456-2255. A 24-hour nurse educator is available for questions.

**Are there any special considerations for this medication?**

- Pegylated interferon is not recommended for patients with a history of hypersensitivity to natural or recombinant interferons. These patients require an adequate prescreening evaluation and should be observed closely for signs of a serious allergic reaction. Peginterferon should be discontinued if a serious allergic reaction occurs.
- People with a seizure disorder need to be closely monitored. They are advised to report seizure signs or symptoms immediately to their doctors.

**COMMENTARY BY TEMPLATE AUTHORS:**

- In the absence of head-to-head comparison trials, it is not possible to compare peginterferon with other interferon products or other DMTs.
- There have been reports of worsening significant cardiac disease in patients with a prior cardiac history while using interferon beta. People should report any changes immediately to their clinicians.
- Injection-site reactions should be reported as well.
- Flu-like symptoms, particularly in the early stages of treatment, can be managed through strategies that involve use of over-the-counter strategies. People starting peginterferon should expect to receive adequate training prior to the first injection.
- In clinical studies, less than 1 percent of people treated with peginterferon every 14 days for one year developed neutralizing antibodies.
- The safety and effectiveness of this medication have not been established in children or the elderly.

**WEB LINKS PROVIDED IN THIS DOCUMENT:**
Information for Healthcare Professionals

Written by Jennifer Pichardo

- Peginterferon website: www.Pegylated interferon.com
- Support program: www.MSActiveSource.com

EDITOR:
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DISCLAIMER:
The Emerging Therapies Collaborative is proud to be a source of information about multiple sclerosis. Our comments are general in nature and should not be construed as individual therapeutic recommendations or prescriptions. For specific information and advice, consult your physician.

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.

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