



# PEGIN

Peginterferon alfa-2a

## COMPOSITION

**Pegin Injection** : Each pre-filled syringe contains Peginterferon alfa-2a INN 180 mcg.  
**Pegin 135 Injection** : Each pre-filled syringe contains Peginterferon alfa-2a INN 135 mcg.

## PHARMACOLOGICAL INFORMATION

Therapeutic Class: Antiviral Agent

## PHARMACOLOGICAL ACTION

### Description

Pegylated interferon alfa-2a is an antiviral drug, has a dual mode of action - both antiviral and on the immune system. The addition of polyethylene glycol to the interferon, through a process known as pegylation, enhances the half-life of the interferon when compared to its native form.

### Mechanism of Action

When interferon alfa-2a undergoes the process of pegylation in which one or more chains of polyethylene glycol (also known as PEG) are attached to another molecule. A large, branched, mobile PEG is attached to the interferon alfa-2a molecule, providing a selectively protective barrier against rapid absorption, metabolism and elimination. At the same time, the PEG maintains the ability of the interferon alfa-2a to attack the virus.

## PHARMACOLOGY

### Pharmacokinetic Properties

Chronic hepatitis B or C patients, Peginterferon alfa-2a serum concentrations accumulate 2-3 fold after 6 -8 weeks of once weekly dosing compared to single dose values. There is no further accumulation after 8 weeks.

*Plasma half life*: Approx 60-80 hours (IV administration); mean of 160 hours (84 to 353) (subcutaneous administration)

*Cmax*: 14.2 ng/ml (180 mcg subcutaneous dose, with 1000-1200 mg Ribavirin)

*Cmin*: 9 ng/ml (range 0-15) single dose 16 ng/ml (range 4-28) weekly dosing, week 48

*AUC*: 1141.54 µg.h/ml (180mcg dose, with oral ribavirin 100-1200mg OD)

*Bioavailability*: 84%

*Protein Binding*: Data not available

*Volume of Distribution*: 6-14 L, at steady-state, intravenous administration

*Renal Clearance*: Major route

*Renal Impairment*: In patients with creatinine clearance 20-40 ml/min, clearance is reduced by 25%. In end stage renal disease, there is 25%-45% reduction in clearance, and the manufacturer recommends a reduced starting dose in these patients. Monitoring is required, and appropriate dose reductions should be made in the event of adverse reactions.

*Hepatic Impairment*: HCV: If alanine aminotransferase (ALT) increase is progressive/persistent, the manufacturer recommends dose reduction. If increase in ALT is progressive despite dose reduction, or is accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be discontinued HBV: Although transient flares of ALT levels to >10 times the upper limit of normal are not uncommon, the manufacturer recommends treatment should not normally be initiated in such cases. Consideration should be given to continuing treatment with frequent monitoring of liver function during ALT flares. General: In patients with compensated cirrhosis (Child-Pugh A), PEG Interferon alfa-2a has been shown to be effective and safe. Data is not available for decompensated cirrhosis (Child-Pugh B, C or bleeding oesophageal varices).

*Metabolism and Distribution*

*Metabolised by*: Not fully characterised; Metabolized by both the kidneys and the liver; <10% renal elimination.

*Inducer of*: No effect in vivo on CYP450 3A4, 2C9, 2C19 and 2D6

*Inhibitor of*: CYP1A2. No effect in vivo on CYP450 3A4, 2C9, 2C19 and 2D6

*Transported by*: Data not available

## CLINICAL INFORMATION

### Therapeutic Indications

Peginterferon alfa-2a, alone or in combination with RIBAVIRIN, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and patients with HIV disease that is clinically stable (e.g., antiretroviral therapy not required or receiving stable antiretroviral therapy).

Peginterferon alfa-2a is indicated for the treatment of adult patients with HBe Ag positive and HBe Ag negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation.

### Dosage

There is no safety and efficacy data on treatment of chronic hepatitis C or hepatitis B for longer than 48 weeks. For patients with hepatitis C, consideration should be given to discontinuing therapy after 12 to 24 weeks of therapy if the patient has failed to demonstrate an early virologic response defined as undetectable HCV RNA or at least a 2log<sub>10</sub> reduction from baseline in HCV RNA titer by 12 weeks of therapy.

A patient should self-inject PEGINTERFERON ALFA-2A only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and training in proper injection technique has been provided to him/her.

Peginterferon alfa-2a should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Vials and prefilled syringes with particulate matter or discoloration should be returned to the pharmacist.

### General

When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 µg (which is 0.75 mL for the vials or adjustment to the corresponding graduation mark for the syringes) is generally adequate. However, in some cases, dose reduction to 90 µg (which is 0.5 mL for the vials or adjustment to the corresponding graduation mark for the syringes) may be needed. Following improvement of the adverse reaction, re-escalation of the dose may be considered.

### Hematological

| Laboratory Values   | Reduce PEGINTERFERON ALFA-2A Dose to: | Discontinue PEGINTERFERON ALFA-2A if:   |
|---|---------------------------------------|---|
| ANC 750/mm <sup>3</sup><br>ANC <750/mm <sup>3</sup>                 | Maintain 180 µg<br>Reduce to 135 µg   | ANC <500/mm <sup>3</sup> , treatment should be suspended until ANC values return to more than 1000/mm <sup>3</sup> Reinstitute at 90 µg and monitor ANC |
| Platelet 50,000/mm <sup>3</sup><br>Platelet <50,000/mm <sup>3</sup> | Maintain 180 µg Reduce to 90 µg       | Platelet count <25,000/mm <sup>3</sup>  |

### Psychiatric: Depression

Guidelines for Modification or Discontinuation of PEGINTERFERON ALFA-2A and for Scheduling Visits for Patients with Depression

| Depression Severity | Initial Management (4-8 weeks)  |   | Depression   |  |                                     |
|---------------------|---|---|--|--|-------------------------------------|
|                     | Dose modification   | Visit schedule  | Remains stable   | Improves   | Worsens                             |
| Mild                | No change   | Evaluate once weekly by visit and/or phone;                   | Continue weekly visit schedule                             | Resume normal visit schedule   | (See moderate or severe depression) |
| Moderate            | Decrease PEGINTERFERON ALFA-2A dose to 135 µg (in some cases dose reduction to 90 µg may be needed) | Evaluate once weekly (office visit at least every other week) | Consider psychiatric consultation. Continue reduced dosing | If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose | (See severe depression)             |
| Severe              | Discontinue PEGINTERFERON ALFA-2A permanently   | Obtain immediate psychiatric consultation                     | Psychiatric therapy necessary                              |  |                                     |

In patients with persistent, severe (ALT > 10 times above the upper limit of normal) hepatitis B flares, consideration should be given to discontinuation of treatment.

## Ribavirin

### Ribavirin Dosage Modification Guidelines

| Laboratory Values   | Reduce Only RIBAVIRIN Dose to 600 mg/day* if:                    | Discontinue RIBAVIRIN if:                |
|---|--|--|
| Hemoglobin in patients with no cardiac disease                | <10 g/dL   | <8.5 g/dL                                |
| Hemoglobin in patients with history of stable cardiac disease | 2 g/dL decrease in hemoglobin during any 4 week period treatment | <12 g/dL despite 4 weeks at reduced dose |

\*One 200 mg tablet in the morning and two 200 mg tablets in the evening.

Once RIBAVIRIN has been withheld due to a laboratory abnormality or clinical manifestation, an attempt may be made to restart RIBAVIRIN at 600 mg daily and further increase the dose to 800 mg daily depending upon the physician's judgment. However, it is not recommended that RIBAVIRIN be increased to the original dose (1000 mg or 1200 mg).

### Peginterferon alfa-2a and ribavirin combination therapy

The recommended dose of PEGINTERFERON ALFA-2A when used in combination with ribavirin for chronic hepatitis C is 180 µg (1.0 mL vial or 0.5 mL prefilled syringe) once weekly. The recommended dose of RIBAVIRIN and duration for PEGINTERFERON ALFA-2A/RIBAVIRIN therapy is based on viral genotype (see the table below).

The daily dose of RIBAVIRIN is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen. Since RIBAVIRIN absorption increases when administered with a meal, patients are advised to take RIBAVIRIN with food.

### Peginterferon alfa-2a and RIBAVIRIN Dosing Recommendations

| Genotype       | Pegin Dose      | Pegin 135 Dose (for CKD patients) | Ribavirin Dose                      | Duration             |
|----------------|-----------------|-----------------------------------|-------------------------------------|----------------------|
| Genotypes 1, 4 | 180 µg (weekly) | 135 µg (weekly)                   | <75 kg = 1000 mg<br>75 kg = 1200 mg | 48 weeks<br>48 weeks |
| Genotypes 2, 3 | 180 µg (weekly) | 135 µg (weekly)                   | 800 mg                              | 24 weeks             |

Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks. Data on genotypes 5 and 6 are insufficient for dosing recommendations.

### Contraindications

- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before or during treatment
- Neonates and infants due to the benzyl alcohol content

### Precaution

Before taking Peginterferon alfa-2a, tell your doctor or pharmacist if you are allergic to it; or to polyethylene glycol (PEG); or if you have any other allergies. This medication should not be used if you have certain medical conditions. Before using this medicine, consult your doctor or pharmacist if you have: other severe liver disease (e.g., autoimmune hepatitis, hepatic decompensation). Before taking this medication, tell your doctor or pharmacist your medical history, especially of: psychiatric conditions (e.g., depression), low blood counts (e.g., red cells, white cells, or platelets), heart disease, thyroid problems, autoimmune disease (e.g., rheumatoid arthritis, lupus, psoriasis), eye problems, kidney disease, lung disease (e.g., COPD, asthma, pneumonia), history of cancer, intestinal disease (e.g., colitis), pancreatitis, history of drug/alcohol abuse, diabetes, other infections (e.g., HIV, hepatitis B, chickenpox), history of organ transplant, liver problems (other than hepatitis C). Do not have immunizations/vaccinations without the consent of your doctor. Use caution with sharp objects like safety razors or nail cutters and avoid activities such as contact sports to lower the chance of getting cut, bruised, or injured. This drug may make you drowsy or dizzy; use caution engaging in activities requiring alertness such as driving or using machinery. This medicine may cause stomach bleeding. Daily use of alcohol and this medicine may increase your risk for stomach bleeding. A preservative (benzyl alcohol) which may be found in this product can infrequently cause serious problems (sometimes death) if given in large amounts (more than 100 milligrams per kilogram daily) to an infant during the first months of life (neonatal period). The risk is also greater with low birth weight infants. Symptoms include sudden gasping, low blood pressure, or a very slow heartbeat. Report these symptoms to the doctor immediately should they occur. If possible, a preservative-free product should be used when treating neonates. Caution is advised when using this drug in the elderly because they may be more sensitive to its effects. This medication is not recommended for use during pregnancy because of possible serious harm to the fetus. Consult your doctor for more details and to discuss reliable forms of birth control. It is recommended that men and women use birth control measures while being treated with this medication and for the 6 months after treatment has stopped. If you become pregnant or think you may be pregnant, inform your doctor immediately. It is not known whether this drug passes into breast milk. Because of the potential risk to the infant, breast-feeding while using this drug is not recommended. Consult your doctor before breast-feeding.

### Overdosage

If overdose is suspected, contact your local poison control center or emergency room immediately. US residents can call the US national poison hotline at 1-800-222-1222. Canadian residents should call their local poison control center directly.

*NOTES*: Do not share this medication with others. Laboratory and/or medical tests (e.g., blood tests, thyroid tests, virus levels, and kidney function tests) should be performed periodically to monitor your progress. Consult your doctor for more details. You may need an eye exam before using this medication. If you have an eye disease or are at risk for eye disease (e.g., diabetes), you should then have periodic eye exams while using this drug. Do not change brands of interferon without checking with your doctor or pharmacist. Other interferons may not have the same effects on your disease.

### Missed Dose

If you miss a dose and you remember within 2 days of when you should have taken the medication, give the injection as soon as remembered. Take your next dose on the day you usually would take it. If it is more than 2 days past your missed dose, contact your doctor or pharmacist to establish a new dosing schedule.

### Drug Interactions

Your healthcare professionals (e.g., doctor or pharmacist) may already be aware of any possible drug interactions and may be monitoring you for it. Do not start, stop or change the dosage of any medicine before checking with them first. Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of: theophylline.

### Side Effects

- Confusion, severe depression, thoughts of hurting yourself or others;
- Unusual anxiety, aggression, or unusual thoughts or behaviors;
- Sudden numbness, weakness, or loss of balance or coordination;
- Fever, chills, body aches, flu symptoms;
- Easy bruising or bleeding;
- Worsening of psoriasis;
- Chest pain, uneven heartbeats, pain spreading to the arm or shoulder, nausea, sweating, general ill feeling;
- Cough, stabbing chest pain, feeling short of breath;
- Severe pain in your upper stomach spreading to your back, fast heart rate;
- Blurred vision, headache or pain behind your eyes; or
- Fever with severe stomach pain and bloody diarrhea.
- Less serious side effects may include:
- Increased hunger, thirst, or urination;
- Feeling mildly anxious or irritable;
- Headache, muscle or joint pain;
- Nausea, vomiting, dry mouth, loss of appetite;
- Hair loss, weight loss;
- Sleep problems (insomnia);
- Skin itching; or
- Pain, redness, swelling, or irritation where the medicine was injected.

## PHARMACEUTICAL INFORMATION

### Storage Conditions

Store between 2° C to 8° C (59° to 77° F). Do not freeze or shake. Keep out of the reach of children.

### Presentation & Packaging

**Pegin Injection** : Each commercial box contains one pre-filled syringe containing Peginterferon alfa-2a INN 180 mcg and one alcohol pad.

**Pegin 135 Injection** : Each commercial box contains one pre-filled syringe containing Peginterferon alfa-2a INN 135 mcg and one alcohol pad.

Manufactured By  
  
 Mymensingh, Bangladesh