PEG-Intron™
(Peginterferon alfa-2b)
Powder For Injection

WARNING

Alpha interferons, including PEG-Intron, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping PEG-Intron therapy. See **WARNINGS, ADVERSE REACTIONS.**

DESCRIPTION

PEG-Intron™, peginterferon alfa-2b Powder for Injection, is a covalent conjugate of recombinant alfa interferon with monomethoxy polyethylene glycol (PEG). The molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the PEG-Intron molecule is approximately 31,000 daltons. The specific activity of pegylated interferon alfa-2b is approximately 0.7×10^8 IU/mg protein.

Interferon alfa-2b, the starting material used to manufacture PEG-Intron, is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon gene from human leukocytes.

PEG-Intron is a white to off-white lyophilized powder supplied in 2-mL vials for subcutaneous use. Each vial contains either 74 μg, 118.4 μg, 177.6 μg or 222 μg of

PEG-Intron, and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose and 0.074 mg polysorbate 80. Following reconstitution with 0.7 mL of the supplied diluent (Sterile Water for Injection, USP), each vial contains PEG-Intron at strengths of either 100 μg/mL, 160 μg/mL, 240μg/mL or 300 μg/mL.

CLINICAL PHARMACOLOGY

General: The biological activity of PEG-Intron, is derived from its interferon alfa-2b moiety. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events. These include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells. Interferon alfa upregulates the Th1 T-helper cell subset in *in vitro* studies. The clinical relevance of these findings is not known.

Pharmacodynamics*:* PEG-Intron raises concentrations of effector proteins such as serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts. The correlation between the *in vitro* and *in vivo* pharmacologic and pharmacodynamic and clinical effects is unknown.

Pharmacokinetics: Following a single subcutaneous dose of PEG-Intron, the mean absorption half-life ($t_{½\,k_a}$) was 4.6 hours. Maximal serum concentrations (C_{max}) occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours. The C_{max} and AUC measurements of PEG-Intron increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PEG-Intron. Week 48 mean trough concentrations (320 pg/ml; range 0, 2960) are approximately 3-fold higher than Week 4 mean trough concentrations (94 pg/ml; range 0, 416). The

mean PEG-Intron elimination half-life is approximately 40 hours (range 22 to 60 hours) in patients with HCV infection. The apparent clearance of PEG-Intron is estimated to be approximately 22.0 mL/hr·kg. Renal elimination accounts for 30% of the clearance. Single dose peginterferon alfa-2b pharmacokinetics following a subcutaneous 1.0 μg/kg dose suggest the clearance of peginterferon alfa-2b is reduced by approximately half in patients with impaired renal function (creatinine clearance <50 mL/minute).

Pegylation of interferon alfa-2b produces a product (PEG-Intron) whose clearance is lower than that of non-pegylated interferon alfa-2b. When compared to INTRON A, PEG-Intron (1.0 μg/kg) has approximately a seven-fold lower mean apparent clearance and a five-fold greater mean half-life permitting a reduced dosing frequency. At effective therapeutic doses, PEG-Intron has approximately ten-fold greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

Pharmacokinetic data from geriatric patients (> 65 years of age) treated with a single subcutaneous dose of 1.0 μg/kg of PEG-Intron showed no remarkable differences in C_{max}, AUC, clearance, or elimination half-life from those obtained in younger patients.

During the 48 week treatment period with PEG-Intron no differences in the pharmacokinetic profiles were observed between male and female patients with chronic hepatitis C infection.

***Drug Interactions*:** It is not known if PEG-Intron therapy causes clinically significant drug-drug interactions with drugs metabolized by the liver in patients with hepatitis C. In 12 healthy subjects known to be CYP2D6 extensive metabolizers, a single subcutaneous dose of 1 μg/kg PEG-Intron did not inhibit CYP1A2, 2C8/9, 2D6, hepatic 3A4 or N-acetyltransferase; the effects of PEG-Intron on CYP2C19 were not assessed.

CLINICAL STUDIES

A randomized study compared treatment with PEG-Intron (0.5, 1.0, or 1.5 µg/kg once weekly SC) to treatment with INTRON A, (3 million units three times weekly SC) in 1219 adults with chronic hepatitis from HCV infection. The patients were not previously treated with interferon alfa, had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis. Patients were treated for 48 weeks and were followed for 24 weeks post-treatment. Seventy percent of all patients were infected with HCV genotype 1, and 74% of all patients had high baseline levels of HCV RNA (more than 2 million copies per mL of serum), two factors known to predict poor response to treatment.

Response to treatment was defined as undetectable HCV RNA and normalization of ALT at 24 weeks post-treatment. The response rates to the 1.0 and 1.5 µg/kg PEG-Intron doses were similar to each other and were both higher than response rates to INTRON A. (See **Table 1**)

Table 1. Rates of Response to Treatment

	A PEG-Intron 0.5 µg/kg (N=315)	B PEG-Intron 1.0 µg/kg (N=298)	C INTRON A 3 MIU TIW (N=307)	B - C (95% CI) Difference between PEG-Intron 1.0 µg/kg and INTRON A
Treatment Response (Combined Virologic Response and ALT Normalization)	17%	24%	12%	11 (5, 18)
Virologic Response[a]	18%	25%	12%	12 (6,19)
ALT Normalization	24%	29%	18%	11 (5,18)

[a]Serum HCV RNA is measured by a research-based quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml at the National Genetics Institute, Culver City, CA.

Patients with both viral genotype 1 and high serum levels of HCV RNA at baseline were less likely to respond to treatment with PEG-Intron. Among patients with the two unfavorable prognostic variables, 8% (12/157) responded to PEG-Intron treatment and 2% (4/169) responded to INTRON A. Doses of PEG-Intron higher than the recommended dose did not result in higher response rates in these patients.

Patients receiving PEG-Intron with viral genotype 1 had a response rate of 14% (28/199) while patients with other viral genotypes had a 45% (43/96) response rate.

Ninety-six percent of the responders in the PEG-Intron groups and 100% of responders in the INTRON A group first cleared their viral RNA by week-24 of treatment. See **DOSAGE AND ADMINISTRATION.**

The treatment response rates were similar in men and women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of

poor prognostic factors compared to Caucasians the number of non-Caucasians studied (9% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 60% of patients. A modest reduction in inflammation compared to baseline that was similar in all four treatment groups was observed.

INDICATIONS AND USAGE

PEG-Intron, peginterferon alfa-2b, monotherapy is indicated for the treatment of chronic hepatitis C in patients not previously treated with interferon alpha who have compensated liver disease and are at least 18 years of age. The safety and efficacy of peginterferon alfa-2b (PEG-Intron) in combination with ribavirin (REBETOL) for the treatment of chronic hepatitis C have not been established.

CONTRAINDICATIONS

PEG-Intron, is contraindicated in patients with:

- hypersensitivity to PEG-Intron or any component of the product
- autoimmune hepatitis
- decompensated liver disease

WARNINGS

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should be withdrawn from therapy.

Neuropsychiatric events

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive

behavior have occurred in patients with and without a previous psychiatric disorder during PEG-Intron treatment and follow-up. Psychoses and hallucinations have been observed in patients treated with alpha interferons. PEG-Intron should be used with extreme caution in patients with a history of psychiatric disorders. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. In severe cases, PEG-Intron should be stopped immediately and psychiatric intervention instituted.

Bone marrow toxicity

PEG-Intron suppresses bone marrow function, sometimes resulting in severe cytopenias. PEG-Intron should be discontinued in patients who develop severe decreases in neutrophil or platelet counts. Very rarely alpha interferons may be associated with aplastic anemia. (See **DOSAGE AND ADMINISTRATION**)

Endocrine disorders

PEG-Intron causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with PEG-Intron. Diabetes mellitus has been observed in patients treated with alpha interferons. Patients with these conditions who cannot be effectively treated by medication should not begin PEG-Intron therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PEG-Intron therapy.

Cardiovascular events

Cardiovascular events, which include hypotension, arrhythmia, tachycardia, cardiomyopathy and myocardial infarction have been observed in patients treated with PEG-Intron. PEG-Intron should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require PEG-Intron therapy should be closely monitored (see **Laboratory tests**).

Colitis

Fatal and nonfatal ulcerative and hemorrhagic colitis has been observed within 12 weeks of the start of alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations. PEG-Intron treatment should be discontinued immediately in patients who develop these symptoms and signs. The colitis usually resolves within 1-3 weeks of discontinuation of alpha interferons.

Pancreatitis

Fatal and nonfatal pancreatitis has been observed in patients treated with alpha interferon. PEG-Intron therapy should be suspended in patients with signs and symptoms suggestive of pancreatitis and discontinued in patients diagnosed with pancreatitis.

Autoimmune disorders

Development or exacerbation of autoimmune disorders (e.g. thyroiditis, thrombocytopenia, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, psoriasis) have been observed in patients receiving PEG-Intron. PEG-Intron should be used with caution in patients with autoimmune disorders.

Pulmonary disorders

Dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, some resulting in patient deaths, have been associated with PEG-Intron or alpha interferon therapy. Patients with pulmonary infiltrates or pulmonary function impairment should be closely monitored.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment with PEG-Intron, discontinue

treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

PRECAUTIONS

- PEG-Intron has not been studied in patients who have failed other alpha interferon treatments.

- The safety and efficacy of PEG-Intron for the treatment of hepatitis C in patients who have received liver or other organ transplant recipients have not been studied.

- The safety and efficacy of PEG-Intron for the treatment of patients with HCV coinfected with HIV or HBV have not been established.

Ophthalmologic disorders Retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction have been observed after treatment with PEG-Intron or alpha interferons. Patients who have diabetes mellitus or hypertension should have eye examinations before the start of PEG-Intron treatment.

Patients with renal failure: Patients with impairment of renal function should be closely monitored for signs and symptoms of interferon toxicity and doses of PEG-Intron should be adjusted accordingly. PEG-Intron should be used with caution in patients with creatinine clearance <50 mL/min. **See DOSAGE AND ADMINISTRATION.**

Immunogenicity: One percent of patients (7/734) receiving PEG-Intron developed low-titer (≤64) neutralizing antibodies to INTRON A. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The incidence of post-treatment binding antibody was approximately

10% for patients receiving PEG-Intron and approximately 15% for patients receiving INTRON A. The data reflect the percentage of patients whose test results were considered positive for antibodies to Peg-Intron in a Biacore assay that is used to measure binding antibodies, and in an antiviral neutralization assay which measures serum neutralizing antibodies. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays. Additionally the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEG-Intron with the incidence of antibodies to other products may be misleading.

Laboratory Tests: PEG-Intron may cause severe decreases in neutrophil and platelet counts, and abnormality of TSH. In 10% of patients treated with PEG-Intron ALT levels rose 2 to 5-fold above baseline. The elevations were transient and were not associated with deterioration of other liver functions.

Patients on PEG-Intron therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the clinical trial CBC (including neutrophil and platelet counts) and chemistries (including AST, ALT and bilirubin) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. TSH levels were measured every 12 weeks during the treatment period.

Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with PEG-Intron.

Information for Patients: Patients receiving PEG-Intron should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the **MEDICATION GUIDE**.

A puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient for at home use. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

Patients should be informed that there are no data evaluating whether PEG-Intron therapy will prevent transmission of HCV infection to others. Also, it is not known if treatment with PEG-Intron will cure hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C virus.

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter (see **Laboratory Tests**). It is advised that patients be well-hydrated, especially during the initial stages of treatment. "Flu-like" symptoms associated with administration of PEG-Intron may be minimized by bedtime administration of PEG-Intron or by use of antipyretics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: PEG-Intron has not been tested for its carcinogenic potential.

Mutagenesis: Neither PEG-Intron, nor its components interferon or methoxypolyethylene glycol caused damage to DNA when tested in the standard battery of mutagenesis assays, in the presence and absence of metabolic activation.

Impairment of Fertility: Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 $\mu g/m^2$ PEG-Intron every other day for one month, at approximately 345 times the recommended weekly human dose (based upon body surface area). These effects included transiently decreased serum levels of estradiol and progesterone, suggestive of anovulation. Normal menstrual cycles and serum hormone levels resumed in these

animals 2 to 3 months following cessation of PEG-Intron treatment. Every other day dosing with 262 μg/m^2 (approximately 21 times the weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of PEG-Intron on male fertility have not been studied.

Pregnancy Category C: Non-pegylated Interferon alfa-2b, has been shown to have abortifacient effects in Macaca mulatta (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60 kg adult). PEG-Intron should be assumed to also have abortifacient potential. There are no adequate and well-controlled studies in pregnant women. PEG-Intron therapy is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Therefore, PEG-Intron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Nursing Mothers: It is not known whether the components of PEG-Intron are excreted in human milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the treatment, taking into account the importance of the product to the mother.

Pediatric Use Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Patients

Clinical studies of PEG-Intron did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, treatment with alpha interferons, including PEG-Intron, is associated with CNS, cardiac, and systemic (flu-

like) adverse effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in use of PEG-Intron in this population. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

ADVERSE REACTIONS

Nearly all study patients experienced one or more adverse events. The incidence of serious adverse events was similar (about 12%) in all treatment groups. In many but not all cases, events resolved after stopping PEG-Intron therapy. Some patients continued to experience adverse events for several months after discontinuation of therapy. There was one patient death, a suicide, among patients receiving PEG-Intron and two patient deaths in the Intron A group (1 murder/suicide and 1 sudden death). Overall, 10% of patients in the PEG-Intron groups discontinued therapy due to adverse events compared to 6% in the INTRON A group. Fourteen percent of patients in the PEG-Intron groups required dose reduction compared to 6% in the INTRON A group.

The most common adverse events associated with PEG-Intron were “flu-like” symptoms which occurred in approximately 50% of patients, and may decrease in severity as treatment continues. Application site disorders occurred frequently (47%) and included injection site inflammation, and reaction (i.e. bruise, itchiness, irritation). Injection site pain was reported in 2% of patients receiving PEG-Intron. Alopecia (thinning of the hair) is also often associated with PEG-Intron.

Fifty-seven percent of patients treated with PEG-Intron experienced psychiatric adverse events, most commonly depression (29%). Suicidal behavior (ideation, attempts, and suicides) occurred in 1% of all patients during or shortly after treatment with PEG-Intron. (see **WARNINGS**).

Patients receiving PEG-Intron appeared to experience a greater number of adverse events (e.g. injection site reaction, fever, rigors, nausea) compared to patients receiving INTRON A. The number of adverse events in all body systems in general was higher in patients receiving the higher PEG-Intron dosages.

Adverse events that occurred in the Phase 3 clinical trial at ≥5% incidence are provided in **Table 2** by treatment group.

Table 2. Adverse Events Occurring in ≥ 5% of Patients

Adverse Events	PEG-Intron 1.0 µg/kg (N=297)	INTRON A 3 MIU (N=303)
	Percentage of Patients Reporting Adverse Events*	
Application Site Disorders		
Injection Site Inflammation/Reaction	47	20
Autonomic Nervous System Disorders		
Flushing	6	3
Sweating Increased	6	7
Body as a Whole – General Disorders		
Headache	56	52
Fatigue	52	54
Influenza-Like Symptoms	46	38
Rigors	23	19
Fever	22	12
Weight Decrease	11	13
RUQ Pain	8	8
Malaise	7	6
Central and Peripheral Nervous System Disorders		
Dizziness	12	10
Hypertonia	5	3
Endocrine Disorders		
Hypothyroidism	5	3
Gastro-intestinal System Disorders		
Nausea	26	20
Anorexia	20	17
Diarrhea	18	16
Abdominal pain	15	11
Vomiting	7	6
Dyspepsia	6	7
Hematologic Disorders		

Adverse Events	PEG-Intron 1.0 µg/kg (N=297)	INTRON A 3 MIU (N=303)
Neutropenia	6	2
Thrombocytopenia	7	< 1
Liver and Biliary System Disorders		
Hepatomegaly	6	5
Musculoskeletal System Disorders		
Musculoskeletal Pain	56	58
Psychiatric Disorders		
Depression	29	25
Insomnia	23	23
Anxiety/Emotional Lability/Irritability-	28	34
Infectious Disorders		
Infection Viral	11	10
Respiratory System Disorders		
Pharyngitis	10	7
Sinusitis	7	7
Coughing	6	5
Skin and Appendages Disorders		
Alopecia	22	22
Pruritus	12	8
Skin Dry	11	9
Rash	6	7

*Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

Numerous adverse events were observed at a frequency <5%. In the absence of a non-treatment control group the relationship to study drug could not be determined.

Individual serious adverse events occurred at a frequency ≤1% and included suicide attempt, suicidal ideation, severe depression; relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, retinal ischemia, retinal vein thrombosis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (pneumonia, abscess); autoimmune thrombocytopenia, hyperthyroidism, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, aggravated psoriasis; urticaria.

Laboratory Values

Neutrophils Neutrophil counts decreased in 70% of patients. Severe potentially life-threatening neutropenia (<0.5 x 10^9/L) occurred in 1% of patients.

Platelets Platelet counts decreased in 20% of patients. Treatment with Peg-Intron resulted in severe decreases in platelet counts (<50,000/mm^3) in 1% of patients.

The incidence and severity of thrombocytopenia and neutropenia were greater in the PEG-Intron groups compared to the interferon alfa group. Platelet and neutrophil counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

Thyroid Function TSH abnormalities developed in 16% of patients and were associated with clinically apparent hypothyroidism (5%) or hyper-thyroidism (1%). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period 7% of subjects still had abnormal TSH values.

OVERDOSAGE

There is limited experience with overdosage. In the clinical study, 13 patients accidentally received a dose greater than that prescribed. There were no instances in which a patient received more than 2.5 times the intended dose. The maximum dose received by any patient was 3.45 μg/kg weekly over a period of approximately 12 weeks. There were no serious reactions attributed to these overdosages.

DOSAGE AND ADMINISTRATION

A patient should self-inject 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 given to him/her. (See illustrated **MEDICATION GUIDE** for instructions.)

PEG-Intron is administered subcutaneously once weekly for one year. The dose should be administered on the same day of each week. Initial dosing should be based on weight as described in **Table 3.**

Table 3. Recommended Dosing

Vial Strength* to Use (µg/mL)	Weight (kg)	Amount of PEG-Intron to Administer (µg)	Volume of PEG-Intron* to Administer (mL)
100	37-45	40	0.4
	46-56	50	0.5
160	57-72	64	0.4
	73-88	80	0.5
240	89-106	96	0.4
	107-136	120	0.5
300	137-160	150	0.5

* When reconstituted as directed

Serum HCV RNA levels should be assessed after 24 weeks of treatment. Discontinuation of treatment should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay after 24 weeks of therapy with PEG-Intron. (See **CLINICAL STUDIES.**)

There are no safety and efficacy data for treatment longer than 48 weeks or for retreatment of patients who relapse following PEG-Intron therapy.

Dose Reduction

If a serious adverse reaction develops during the course of treatment **(**See **WARNINGS)** discontinue or modify the dosage of PEG-Intron to one-half the starting dosage until the adverse event abates or decreases in severity. If persistent or recurrent intolerance develops despite adequate dosage adjustment, discontinue treatment with PEG-Intron. For dose modification in the event of neutropenia and thrombocytopenia see Table 4.

Table 4. Guidelines for Dose Modifications for Neutropenia and Thrombocytopenia

	Dose Reduction	Permanent Discontinuation
Neutrophil Count	$<0.75 \times 10^9$/L	$<0.50 \times 10^9$/L
Platelet Count	$<80 \times 10^9$/L	$<50 \times 10^9$/L

Preparation and Administration

Two B-D Safety Lok™ syringes are provided in the package; one syringe is for the reconsitution steps and one for the patient injection. There is a plastic safety sleeve to be pulled over the needle after use. The syringe locks with an audible click when the green stripe on the safety sleeve covers the red stripe on the needle. Brief instructions for the preparation and administration of PEG-Intron Powder for Injection are provided below. Please refer to the Medication Guide for detailed, step by step instructions.

Reconstitute the PEG-Intron lyophilized product with only 0.7 mL of supplied diluent (Sterile Water for Injection, USP). **The diluent vial is for single use only. The remaining diluent should be discarded.** No other medications should be added to solutions containing PEG-Intron, and PEG-Intron should not be reconstituted with other diluents. Swirl gently to hasten complete dissolution of the powder. The reconstituted solution should be clear and colorless. Visually inspect the solution for particulate matter and discoloration prior to administration. The

solution should not be used if discolored or cloudy, or if particulates are present (see **Medication Guide** for detailed instructions).

The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2-8^0 C (See **Storage**). The appropriate PEG-Intron dose should be withdrawn and injected subcutaneously. (See **Medication Guide** for detailed instructions). The PEG-Intron vial is a single use vial and does not contain a preservative. **DO NOT REENTER VIAL. DISCARD UNUSED PORTION.** Once the dose from a single dose vial has been withdrawn, the sterility of any remaining product can no longer be guaranteed. Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

After preparation and administration of the PEG-Intron injection, it is essential to follow the procedure for proper disposal of syringes and needles. A puncture-resistant container should be used for disposal of syringes. Patients should be instructed in the technique and importance of proper syringe disposal and be cautioned against reuse of these items (See **Medication Guide** for detailed instructions.)

Storage

PEG-Intron, should be stored at 25°C (77°F): excursions permitted to 15-30 ^{o}C (59-86 ^{o}F) [see USP Controlled Room Temperature]. After reconstitution with supplied Diluent the solution should be used immediately, but may be stored up to 24 hours at 2° to 8°C (36° to 46°F). The reconstituted solution contains no preservative, is clear and colorless. **Do not freeze.**

HOW SUPPLIED

PEG-Intron is a white to off-white lyophilized powder supplied in 2-mL vials. The PEG-Intron Powder for Injection should be reconstituted with 0.7 mL of the supplied Diluent (Sterile Water for Injection, USP) prior to use.

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	Each PEG-Intron Package Contains	
For Patients 37-56 kg	A box containing one 100 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1368-01)
For Patients 57-88 kg	A box containing one 160 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1291-01)
For Patients 89-136 kg	A box containing one 240 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1304-01)
For Patients 137-160 kg	A box containing one 300 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1279-01)

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