

Powder and Solvent for Solution for Injection

Brand of peginterferon alfa-2b

FOR SUBCUTANEOUS ADMINISTRATION



Schering-Plough

DESCRIPTION: PEG-INTRON Powder for Solution for Injection (hereafter referred to as PEG-INTRON Injection) is available in vials to deliver either 50, 80, 100, 120 or 150 micrograms of peginterferon alfa-2b, which is a conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol.

PEG-INTRON Injection also contains dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80 as excipients. The solvent provided for parenteral use is sterile water for injection.

ACTIONS: In vitro and in vivo studies suggest that the biological activity of peginterferon alfa-2b is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon.

These responses include inhibition of virus replication in virus-infected cells, suppression of cell proliferation and immunomodulating activities (e.g. enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells).

Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication in vitro and in vivo. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PRECLINICAL TOXICOLOGY: Peginterferon alfa-2b - Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. Significant effects in monkeys included leukopenia. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies with peginterferon alfa-2b have not been performed. Since interferon alfa-2b has been shown to be an abortifacient in primates, peginterferon alfa-2b is likely to cause this effect as well. Effects on fertility have not been determined. Peginterferon alfa-2b showed no genotoxic potential.

The non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is a part of the peginterferon alfa-2b molecule, has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-fetal development studies and in vitro mutagenicity assays.

Peginterferon with ribavirin: Preclinical safety - Peginterferon alfa-2b when used in combination with ribavirin did not cause any effects not previously seen with either active substance alone. The major treatment-related effect was reversible, mild to moderate anemia, the severity of which was greater than that produced by either active substance alone.

CLINICAL PHARMACOLOGY: Peginterferon alfa-2b is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

In vitro and in vivo studies suggest that the biological activity of peginterferon alfa-2b is derived from its interferon alfa-2b moiety. Recombinant interferon alfa-2b is obtained from a clone of E. coli, which harbors a genetically engineered plasmid moiety encoding an interferon alfa-2b gene from human leukocytes.

Pharmacodynamics: The pharmacodynamics of peginterferon alfa-2b were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin as well as white cell and neutrophil counts. Subjects treated with peginterferon alfa-2b showed mild dose-related elevations in body temperature and neopterin levels and reductions in white cell and neutrophil counts.

Pharmacokinetics: Peginterferon alfa-2b is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and it is predominantly composed of monopeglylated species. The plasma half-life of peginterferon alfa-2b is prolonged compared with non-pegylated interferon alfa-2b. Peginterferon alfa-2b Cmax and AUC measurements increase in a dose-related manner. Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose. Mean apparent volume of distribution is 0.99 l/kg. Upon multiple dosing, there is an accumulation of immunoreactive interferons.

Mean (SD) peginterferon alfa-2b elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of peginterferon alfa-2b apparent clearance.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received peginterferon alfa-2b in the clinical trial. Interferon neutralising factors are antibodies that neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received peginterferon alfa-2b 0.5 was 1.1% and 1.5 micrograms/kg was 2 to 3%.

Special Populations: Renal function: Renal clearance appears to account for 30 % of total clearance of peginterferon alfa-2b. In a single dose study (10 microgram/kg) in patients with impaired renal function, Cmax, AUC, and half-life increased in relation to the degree of renal impairment (see Contraindication and Precautions).

Following multiple dosing of PEG-INTRON Solution for Injection (1 mcg/kg subcutaneously administered every week for four weeks) the clearance of PEG-INTRON is reduced by a mean of 17% in patients with moderate renal impairment (creatinine clearance 30-49 ml/min) and by a mean of 44% in patients with severe renal impairment (creatinine clearance 10-29 ml/min) compared to subjects with normal renal function.

Clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PEG-INTRON for monotherapy should be reduced in patients with moderate or severe renal impairment (See DOSAGE AND ADMINISTRATION: DOSE REDUCTION). Hepatic function: The pharmacokinetics of peginterferon alfa-2b have not been evaluated in patients with severe hepatic dysfunction. Therefore, PEG-INTRON Injection must not be used in these patients.

Elderly patients ≥ 65 years of age: There does not appear to be a significant age-related effect on the pharmacokinetics of PEG-INTRON Injection. However, as in younger patients, renal function must be determined prior to the administration of PEG-INTRON Injection.

Patients under the age of 18 years: Specific pharmacokinetic evaluations in patients under 18 years of age were not performed. PEG-INTRON Injection is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Methadone Drug Interaction Study: The pharmacokinetics of concomitant administration of methadone and PEG-INTRON Solution for Injection were evaluated in 18 patients with chronic hepatitis C, who were naïve to peginterferon alfa-2b, and were receiving 1.5 mcg/kg/week of PEG-INTRON subcutaneously. All patients were on stable methadone maintenance therapy receiving 240 mg/day prior to initiating therapy with PEG-INTRON. Mean methadone AUC was approximately 16% higher after 4 weeks of PEG-INTRON treatment as compared to baseline.

CLINICAL TRIALS: PEG-INTRON Injection: The results of a large multi-center randomized, Phase III clinical trial demonstrated efficacy and safety of PEG-INTRON Injection for the treatment of chronic hepatitis C. The objectives of this trial in 1,219 patients were to assess the safety and efficacy of 48 weeks of treatment with 3 doses of PEG-INTRON (0.5, 1.0, 1.5 micrograms/kg administered once weekly subcutaneously) vs Intron A (3 MIU administered subcutaneously three times a week). Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (>100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, as well as abnormal serum ALT.

The primary measures of efficacy in the clinical trial were loss of HCV-RNA (< 100 copies/ml) (virologic) and normalisation of ALT (biochemical) 6 months after completing 1 year of treatment. Using the virologic assessment, all doses of PEG-INTRON in the clinical trial were statistically superior to Intron A (Table 1).

Table 1: Proportion of Patients with Sustained Loss of HCV # (% of Patients). Columns: Response\*, Sustained Response 6 Months Post Treatment. Rows: PEG-INTRON 0.5, 1.0, 1.5 micrograms/kg, Intron A 3 MIU.

The Quality of Life was less affected by the 0.5 microgram/kg dose of PEG-INTRON Injection than by either the 1.0 microgram/kg dose once weekly or the 3 million IU of Intron A three times a week.

PEG-INTRON Injection with ribavirin: A single pivotal randomized clinical trial (C/198-590) has been conducted with PEG-INTRON Injection in combination with ribavirin. In this trial, two combination regimens were compared with the combination of interferon alfa-2b + ribavirin. Eligible patients for this trial had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 100 copies/ml), a liver biopsy consistent with a histologic diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In this trial, 1,530 naïve patients were treated for one year with one of the following combination regimens: - PEG-INTRON Injection (1.5 micrograms/kg/week) + PEG-INTRON Capsules (800 mg/day), (n = 511).

- PEG-INTRON Injection (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + PEG-INTRON Capsules (1,000/1,200 mg/day), (n = 514).

- Interferon alfa-2b (3 MIU TIW) + ribavirin (1,000/1,200 mg/day) (n = 505).

PEG-INTRON Injection with ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin, particularly in patients infected with Genotype 1 (Table 2). Sustained response was assessed by the response rate six months after the cessation of treatment.

Hepatitis C virus (HCV) genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in the combination.

Response rates in those patients who received > 10.6 mg/kg ribavirin capsules (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, were significantly higher than in those patients who received ≤ 10.6 mg/kg ribavirin (Table 1). Response rates in patients who received > 13.2 mg/kg ribavirin were even higher. The benefit of the combination regimen of PEG-INTRON Injection with ribavirin was evident for both patients with developing cirrhosis/cirrhosis or fibrosis (55 %) and for those with minimal fibrosis (61 %).

In patients with developing cirrhosis/cirrhosis or fibrosis, the sustained virological response rate was higher for patients treated with the combination of PEG-INTRON Injection with ribavirin than for those given the combination of interferon alfa-2b with ribavirin (55 % vs 43 %).

Response rates in this trial were increased if patients were able to maintain compliance. Regardless of genotype, patients who received the recommended combination regimen and received ≥ 80 % of their treatment with peginterferon alfa-2b and ribavirin had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (72 % vs 46 %).

In a non-comparative trial, 235 patients with genotype 1 and low viral load (≤ 2,000,000 copies/ml) received PEG-INTRON, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at Week 4 and Week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n = 49) and prospectively confirmed (n = 48).

Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

Table 2: Sustained response rates with combination treatment by ribavirin dose (mg/kg). Columns: Ribavirin dose (mg/kg), P 1.5/R, P 0.5/R, I/R. Rows: All Genotypes, Genotype 1, Genotype 1 ≤ 2 million copies/ml, Genotype 1 > 2 million copies/ml, Genotype 2/3.

P 1.5/R PEG-INTRON Injection in combination with ribavirin (peginterferon alfa-2b 1.5 micrograms/kg + ribavirin 800 mg)

P 0.5/R PEG-INTRON Injection in combination with ribavirin (peginterferon alfa-2b 1.5 to 0.5 microgram/kg + ribavirin 1,000/1,200 mg)

I/R Interferon alfa-2b 3 MIU + ribavirin 1,000/1,200 mg

INDICATIONS AND USAGE: PEG-INTRON Injection is indicated for the treatment of chronic hepatitis C. Patients must be 18 years of age or older and have compensated liver disease.

The optimal treatment for chronic hepatitis C is considered to be the administration of the combination of peginterferon alfa-2b with ribavirin. When PEG-INTRON Injection is to be used in combination with ribavirin, please refer also to the ribavirin product information.

MONOTHERAPY: The recommended dose is 0.5 microgram/kg administered subcutaneously once weekly for one year. Treatment with PEG-INTRON Injection should be initiated and monitored only by a physician experienced in the treatment of patients with hepatitis C. Treatment is to be continued for one year; the dose is to be administered subcutaneously on the same day of each week. The patient may self-administer the dose at the discretion of the physician. When self-administration is recommended, the patient should be advised to vary the injection site each time the injection is administered.

In patients who fail to show loss of HCV-RNA at 6 months, treatment with PEG-INTRON Injection should be discontinued.

COMBINATION THERAPY: PEG-INTRON Injection 1.5 micrograms/kg/week subcutaneously in combination with ribavirin capsules. The dose of ribavirin to be used in combination with PEG-INTRON Injection is based on patient body weight (Table 3). Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 3: Ribavirin dose based on body weight. Columns: Patient weight (kg), Daily ribavirin dose, Number of 200 mg capsules. Rows: < 65, 65-85, > 85.

a: 2 morning, 2 evening

b: 2 morning, 3 evening

c: 3 morning, 3 evening

As an alternative to exact calculation of dose, a simplified PEG-INTRON Powder for Solution for Injection dosage was developed based on experience in clinical trials (see Table 4). This table coordinates the PEG-INTRON simplified dose by weight-based groups and relates that dose to the most appropriate vial presentation. The corresponding ribavirin capsule dose is also integrated.

PEG-INTRON Powder for Solution for Injection is administered subcutaneously once weekly. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 4: Dosing for Combination Therapy. Columns: Weight (kg), Vial/Strength (µg/0.5 ml), Administer once weekly (mg), Total Daily Dose (mg), Number of Capsules (200 mg). Rows: <40, 40-50, 51-64, 65-75, 76-85, >85.

a: 2 morning, 2 evening

b: 2 morning, 3 evening

c: 3 morning, 3 evening

Duration of treatment Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders.

- Genotype 1: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks). In the subset of patients with genotype 1 infection at low viral load (<2,000,000 copies/ml) who became HCV RNA negative at treatment week 4 and remain HCV RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration).

However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration.

- Genotypes 2 or 3: It is recommended that all patients be treated for 24 weeks.

- Genotype 4: In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

Dose modification: If severe adverse reactions or laboratory abnormalities develop during treatment with PEG-INTRON Injection or PEG-INTRON Injection with ribavirin, modify the dosages of each product if appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, Table 5a for PEG-INTRON Injection and Table 5b for PEG-INTRON Injection with ribavirin).

Table 5a: Dose modification guidelines for PEG-INTRON Injection. Columns: Laboratory values, Reduce PEG-INTRON Injection to one-half dose if, Discontinue PEG-INTRON Injection if. Rows: Neutrophils, Platelets.

Table 5b: Dose modification guidelines for PEG-INTRON Combination Therapy. Columns: Laboratory values, Reduce only ribavirin dose to 600 mg/day\* if, Reduce only PEG-INTRON Injection dose to one-half dose if, Discontinue PEG-INTRON Combination Therapy if. Rows: Haemoglobin, Haemoglobin in: Patients with history of stable cardiac disease, White blood cells, Neutrophils, Platelets, Bilirubin - direct, Bilirubin - indirect, Creatinine, ALT/AST.

\* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

\*\* Upper limit of normal

Simplified dosing schedule reduction: Dose modification by 50% in patients using the simplified dosing schedule may be achieved by use of a different vial presentation

**Special populations**

**Use in renal impairment: Monotherapy:** In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/min), the starting dose of PEG-INTRON should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 10-29 ml/min), including those on hemodialysis, should have the starting dose of PEG-INTRON reduced by 50%. If renal function decreases during treatment, PEG-INTRON therapy should be discontinued. **Combination therapy:** Patients with creatinine clearance < 50 ml/min must not be treated with PEG-INTRON Injection in combination with ribavirin (see CONTRAINDICATIONS). When administered in combination with REBETOL, subjects with impaired renal function should be more carefully monitored with respect to the development of anemia. It is recommended that renal function be evaluated in all patients prior to initiation of PEG-INTRON Injection. Patients with moderate renal impairment should be closely monitored and, should have their dose of PEG-INTRON Injection reduced if medically appropriate. If serum creatinine rises to > 2 mg/dl (see Table 5b), PEG-INTRON Injection must be discontinued (see PRECAUTIONS).

**Use in hepatic impairment:** The safety and efficacy of peginterferon alfa-2b has not been evaluated in patients with severe hepatic dysfunction. Therefore, PEG-INTRON Injection must not be used in these patients. Use in the elderly (≥ 65 years of age): There does not appear to be a significant age-related effect on the pharmacokinetics of peginterferon alfa-2b. However, as in younger patients, renal function must be determined prior to the administration of PEG-INTRON Injection. Use in patients under the age of 18 years: Safety and effectiveness of PEG-INTRON Injection in these patients have not been evaluated. PEG-INTRON Injection is not recommended for use in children and adolescents under the age of 18 (see Indications and Usage).

**Information for health professionals and patients:**

- Preparation and Administration:  
PEG-INTRON Injection is supplied as a powder of peginterferon alfa-2b at strengths of 50, 80, 100, 120, and 150 micrograms for single use  
Before reconstitution, PEG-INTRON Powder for Injection may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder. Each vial must be reconstituted with 0.7 ml of diluent (sterile water for injection) and up to 0.5 ml of solution will be administered.  
To reconstitute the PEG-INTRON Powder for Injection: Use a sterilized syringe and injection needle, inject 0.7 ml of solvent SLOWLY into the vial of PEG-INTRON Powder for Injection aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. Swirl the vial gently to complete dissolution of powder. Do not shake, but gently turn the vial upside down. The contents should now be completely dissolved. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. The appropriate dose can now be withdrawn with a sterilized injection syringe and injected. A small volume is lost during preparation of PEG-INTRON Powder when the dose is measured and injected. Thus, each unit contains an excess amount of diluent and PEG-INTRON Powder to ensure delivery of the labeled dose in 0.5 ml of PEG-INTRON Injection. The labeled strength will be contained in 0.5 ml of the reconstituted solution. The reconstituted solution for each of the available strengths will have a concentration of 50 mcg/0.5 ml, 80 mcg/0.5 ml, 100 mcg/0.5 ml, 120 mcg/0.5 ml or 150 mcg/0.5 ml. As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discoloration is present. Discard any unused solution. PEG-INTRON Injection must not be mixed with other injectable products.
- Stability of the reconstituted solution:  
The chemical and physical in-use stability for the reconstituted solution has been demonstrated for 24 hours at 2° - 8° C. From a microbiological point of view, the reconstituted product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° - 8° C.
- Measuring the dose of PEG-INTRON from the reconstituted powder for injection:  
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PEG-INTRON reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger slowly to draw just more than the dose prescribed by your doctor into the syringe. Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.  
Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discoloration or particulate matter is present. You are now ready to inject the dose.
- Injecting the solution  
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.  
Change your injection site each time. Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently. Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage. The vial, ampoule and injection materials, are intended for single use and must be discarded. Dispose of the syringe and needles safely in a closed container.

**INCOMPATIBILITIES:** PEG-INTRON Injection should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also Preparation and Administration).

**DRUG INTERACTIONS:** No pharmacokinetic interactions were noted between PEG-INTRON Injection and ribavirin in a multiple-dose pharmacokinetic study.

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly peginterferon alfa-2b (15 mcg/kg) for 4 weeks demonstrated no change in activity of CYP1A2, CYP3A4, or N-acetyltransferase. There was an increase in activity of CYP2C8/9 and CYP2D6. Caution should be used when administering peginterferon alfa-2b with medications metabolized by CYP2C8/9 and CYP2D6, especially those with narrow therapeutic indices. Patients co-infected with the Human Immunodeficiency Virus (HIV) and are receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding treatment with PEG-INTRON and ribavirin to HAART.

Cimetidine may augment the anti-tumor effect of interferon in melanoma; vinblastine plus interferon may increase toxicity and paresthesia, and zidovudine plus interferon may increase myelosuppression.

**ADVERSE EFFECTS:**

**PEG-INTRON Injection monotherapy:**

Most undesirable effects were mild or moderate in severity and not treatment limiting. The majority of patients reported headache and myalgia. Very commonly reported effects (≥ 10% of patients) were pain/inflammation at injection site, fatigue, rigors, fever, depression, arthralgia, nausea, alopecia, musculoskeletal pain, irritability, influenza-like symptoms, insomnia, diarrhea, abdominal pain, asthenia, pharyngitis, weight decrease, anorexia, anxiety, impaired concentration, dizziness, and injection site reaction.

Commonly reported effects (≥ 2% of patients) were pruritus, dry skin, malaise, increased sweating, right upper quadrant pain, neutropenia, leukopenia, anemia, rash, vomiting, dry mouth, emotional lability, nervousness, dyspnea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthesia, coughing, agitation, sinusitis, hypertension, hyperesthesia, blurred vision, confusion, flatulence, decreased libido, erythema, eye pain, apathy, hypoesthesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder. In patients treated with PEG-INTRON in clinical trials, severe psychiatric events were uncommon; life-threatening psychiatric events occurred infrequently. These events included suicide, attempted suicide, suicidal ideation, aggressive behavior, sometimes directed towards others, and psychosis including hallucinations.

Granulocytopenia (< 0.75 x 10<sup>9</sup>/l) occurred in 4% and 7%, and thrombocytopenia (< 70 x 10<sup>9</sup>/l) in 1% and 3%, respectively, in patients receiving 0.5 or 1.0 micrograms/kg of PEG-INTRON Injection.

The use of alpha interferons, has rarely or very rarely been associated with nephrotoxicity, hepatotoxicity, hyperglycemia, coma and seizures

**PEG-INTRON Injection in combination with ribavirin:**

In addition to the adverse effects reported with PEG-INTRON Injection Monotherapy, the following adverse effects have been reported with PEG-INTRON Injection in combination with ribavirin:  
Adverse effects reported between 2% and 5%: hypotension, syncope, hypertension, lacrimal gland disorder, tremor, gingival bleeding, glossitis, stomatitis, ulcerative stomatitis, hearing impairment/loss, tinnitus, palpitation, thirst, aggressive behavior, fungal infection, prostatitis, otitis media, bronchitis, respiratory disorder, rhinorrhea, eczema, abnormal hair texture, photosensitivity reaction, and lymphadenopathy.

Rarely reported events with interferon alfa-2b include seizures, pancreatitis, hypertriglyceridemia, arrhythmia, diabetes and peripheral neuropathy.

Very rarely, alfa interferons, including PEG-INTRON, used alone or in combination with ribavirin may be associated with aplastic anemia or pure red cell aplasia.

Other reported adverse effects that may occur in association with PEG-INTRON Injection Monotherapy or PEG-INTRON Injection in combination with ribavirin:  
Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular edema), retinal hemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilledema (see PRECAUTIONS).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents. Cardiomyopathy that may be reversible upon discontinuation of interferon alfa, has been reported rarely in patients without prior evidence of cardiac disease.

Following the marketing of PEG-INTRON Injection, rhabdomyolysis, myositis, renal insufficiency and renal failure have been reported rarely. Cardiac ischemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy (see PRECAUTIONS) ulcerative and ischemic colitis, sarcoidosis or exacerbation of sarcoidosis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and injection site necrosis also have been reported very rarely.

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura

**CONTRAINDICATIONS:**

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women. PEG-INTRON Injection in combination with ribavirin must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy;
- Men whose female partners are pregnant must not be treated with PEG-INTRON Injection when used in combination with ribavirin.
- Autoimmune hepatitis or a history of autoimmune disease
- Decompensated liver disease.
- When used in combination with ribavirin, patients with creatinine clearance < 50 ml/min.

**PRECAUTIONS: Psychiatric and Central Nervous System (CNS):** *Patients with existence of or history of severe psychiatric conditions:* If treatment with PEG-INTRON Combination Therapy is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition.

If severe neuropsychiatric effects, particularly depression, are observed, PEG-INTRON Combination Therapy should be discontinued. Severe central nervous system (CNS) effects particularly depression, suicidal ideation, suicide or attempted suicide have been observed in some patients during PEG-INTRON Combination Therapy. Other CNS effects including aggressive behavior, sometimes directed towards others, psychosis including hallucinations, confusion and alterations of mental status have been observed. These adverse effects have occurred in adult patients treated with recommended doses as well as in patients treated with higher doses of alfa interferon. More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses of interferon alfa. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of alfa interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored by the prescribing physician during treatment and in the 6-month-follow-up period. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior towards others is identified, it is recommended that PEG-INTRON Combination Therapy be discontinued, and the patient followed with psychiatric intervention as appropriate.

**Cardiovascular system:** As with interferon alfa, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders receiving therapy with PEG-INTRON Injection require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PEG-INTRON Injection.

**Acute hypersensitivity:** Acute hypersensitivity reactions, (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis), have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PEG-INTRON Injection, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

**Liver function:** As with treatment with any interferon, discontinue treatment with PEG-INTRON Injection in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

**Liver/kidney graft rejection:** The safety and efficacy of PEG-INTRON Injection alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alfa therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection also has been reported but a causal association with interferon alfa therapy has not been established.

**Fever:** While fever may be associated with the flu-like syndrome reported commonly during any interferon therapy, other causes of persistent fever must be ruled out.

**Hydration:** Adequate hydration must be maintained in patients undergoing therapy with PEG-INTRON Injection since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

**Pulmonary changes:** Pulmonary infiltrates, pneumonia, pleural effusions, and pneumonitis, occasionally resulting in fatality, have been observed rarely in interferon alfa treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely. If appropriate, discontinue PEG-INTRON Injection. Prompt discontinuation of therapy and treatment with corticosteroids should be associated with resolution of pulmonary adverse events.

**Autoimmune disease:** The development of autoantibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

**Ocular changes:** Ophthalmologic disorders, including retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see ADVERSE EFFECTS). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Because these ocular events may occur in conjunction with other disease states, periodic visual examinations during PEG-INTRON therapy are recommended in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PEG-INTRON Injection should be considered in patients who develop new or worsening ophthalmological disorders.

**Thyroid changes:** Infrequently, patients treated for chronic hepatitis C with interferon alfa have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PEG-INTRON Injection may be continued if TSH levels can be maintained in the normal range by medication.

**Dental and periodontal disorders:** Dental and periodontal disorders have been reported in patients receiving ribavirin peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of Rebetol and peg-interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

**Metabolic disturbances:** Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

**Other:** Due to reports of interferon alfa exacerbating pre-existing psoriatic disease and sarcoidosis, use of PEG-INTRON Injection in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

**Laboratory tests:** Standard hematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PEG-INTRON Injection are:

- Platelets ≥ 100,000/mm<sup>3</sup>
- Neutrophil count ≥ 1,500/mm<sup>3</sup>
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

**Effects on ability to drive and use machines:** Patients who develop fatigue, somnolence or confusion during treatment with PEG-INTRON Injection are cautioned to avoid driving or operating machinery.

**USAGE DURING PREGNANCY AND LACTATION**

**MONOTHERAPY:**

Interferon alfa-2b has been shown to be abortifacient in primates. PEG-INTRON is likely to also cause this effect. Because there are no data on the use of PEG-INTRON Injection in pregnant women, PEG-INTRON Injection is not recommended for use during pregnancy.

PEG-INTRON Injection is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue the treatment or discontinue nursing, taking into account the importance of the medicinal product to the mother.

**COMBINATION THERAPY:**

PEG-INTRON Injection with ribavirin must not be used during pregnancy.

Significant teratogenic and/or embryocidal potential has been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses as low as one twentieth of the recommended human dose. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of fetuses and offspring was reduced.

*Female patients:* Ribavirin capsules must not be used by women who are pregnant (see CONTRAINDICATIONS). Extreme care must be taken to avoid pregnancy in female patients. Therapy with ribavirin capsules must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and their partners must each use an effective contraceptive during treatment and for six months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within six months from stopping treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the fetus.

*Male patients and their female partners:* Extreme care must be taken to avoid pregnancy in partners of male patients taking ribavirin. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Male patients and their female partners of childbearing age must, therefore, be counseled to each use an effective contraceptive during treatment with ribavirin and for six months after treatment has been concluded. PEG-INTRON Injection in combination with ribavirin is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether pegylated interferon alfa-2b in combination with ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

**OVERDOSAGE INFORMATION:**

There is limited experience with overdosage. In the clinical studies, a few patients accidentally received a dose two times greater than that prescribed. There were no serious reactions attributed to these overdosages.

**HOW SUPPLIED:** PEG-Intron is available in vials of 50, 80, 100, 120, and 150 micrograms of peginterferon alfa-2b powder and solvent for solution for injection. The powder is contained in a 2 ml vial, Type I flint glass, with a grey butyl rubber stopper in an aluminum flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass.

**STORAGE:** Store at 2° to 8° C.

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Manufactured by Schering-Plough (Brinny) Co.

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