PEG-INTRON* Pen

Pre-filled Pen

Brand of peginterferon alfa-2b

FOR SUBCUTANEOUS ADMINISTRATION

Schering-Plough

DESCRIPTION: PEG-INTRON Pre-filled Pen is a single dose presentation available in strengths of 50 mcg, 80 mcg, 100 mcg, 120 mcg, and 150 mcg powder and solvent for solution for injection in pre-filled pens.
Peginterferon alfa-2b is a conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. When reconstituted with solvent as recommended, each PEG-INTRON Pre-filled Pen provides 0.5 ml of solution containing either 50 mcg, 80 mcg, 100 mcg, 120 mcg or 150 mcg.
PEG-INTRON Pre-filled Pen also contains as excipients anhydrous disodium phosphate, dihydrate sodium dihydrogen phosphate, sucrose and polysorbate 80. The solvent provided for parenteral use is sterile water for injection.
The deliverable volume from each PEG-INTRON Pre-filled Pen is 0.5 ml. An overfill is included for proper dispensing from the pen delivery system.

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 actiities (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 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 peginterferon alfa-2b 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 hybrid encompassing 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 monopegylated species. The plasma half-life of peginterferon alfa-2b is prolonged compared with non-pegylated interferon alfa-2b. Peginterferon alfa-2b C_{max} 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 neutralizing factors: Interferon neutralizing factor assays were performed on serum samples of patients who received peginterferon alfa-2b in the clinical trial. Interferon neutralizing factors are antibodies that neutralize the antiviral activity of interferon. The clinical incidence of neutralizing factors in patients who received 0.5 mcg/kg of peginterferon alfa-2b was 1.1%, and 2% to 3%. In those who received a dose of 1.5 mcg/kg
Special Populations:
Renal function: Renal clearance appears to account for 30 % of total clearance of peginterferon alfa-2b. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, 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 has not been evaluated in patients with severe hepatic dysfunction. Therefore, PEG-INTRON Pre-filled Pen should 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 peginterferon alfa-2b. However, as in younger patients, renal function should be determined prior to the administration of PEG-INTRON Pre-filled Pen.
Patients under the age of 18 years: Specific pharmacokinetic evaluations in patients under 18 years of age were not performed. PEG-INTRON Pre-filled Pen 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 ≥40 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: **Peginterferon alfa-2b:** The results of a large multi-center randomized, Phase III clinical trial demonstrated efficacy and safety of peginterferon alfa-2b 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 peginterferon alfa-2b (0.5, 1.0, 1.5 mcg/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 normalization of ALT (biochemical) 6 months after completing 1 year of treatment. Using the virologic assessment, all doses of peginterferon alfa-2b in the clinical trial were statistically superior to Intron A (Table 1).

Table 1 Proportion of Patients with Sustained Loss HCV # (%) of Patients

	A	*B*	*C*	*D*	*p Values***
*Response**	*PEG-INTRON 0.5 mcg/kg*	*PEG-INTRON 1 mcg/kg*	*PEG-INTRON 1.5 mcg/kg*	*Intron A 3 MIU*	*A vs D B vs D C vs D*
Sustained Response 6 Months Post Treatment	*57 (18%)*	*73 (25%)*	*71 (23%)*	*37(12%)*	*0.042 < 0.001 < 0.001*

* *Serum HCV RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA)*
** *Chi-square Test*

The Quality of Life was less affected by the 0.5 mcg/kg dose of peginterferon alfa-2b than by either the 1.0 microgram/kg dose once weekly or the 3 million IU of Intron A three times a week.

Peginterferon alfa-2b with ribavirin: A single pivotal randomized clinical trial has been conducted with peginterferon alfa-2b 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 histological diagnosis of chronic hepatitis with no other cause for 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:
– Peginterferon alfa-2b (1.5 mcg/kg/week) + ribavirin†† capsules (800 mg/day), (n = 511).
– Peginterferon alfa-2b (1.5 mcg/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin†† capsules (1,000/1,200 mg/day), (n = 514).
– Interferon alfa-2b† (3 MIU TIW) + ribavirin†† capsules (1,000/1,200 mg/day) (n = 505).
Peginterferon alfa-2b 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 viral 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 2**). Response rates in patients who received > 13.2 mg/kg ribavirin were even higher.
The benefit of the combination regimen of peginterferon alfa-2b 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 peginterferon alfa-2b 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 received < 80 % of their treatment regimen (72 % vs. 46 %).
In a non-comparative trial, 235 patients with genotype 1 and low viral load (≤ 2,000,000 copies/ml) received PegIntron, 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])

HCV Genotype	**Ribavirin dose (mg/kg)**	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 2 million copies/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 2 million copies/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R Combination of peginterferon alfa-2b 1.5 mcg/kg + ribavirin 800 mg
P 0.5/R Combination of 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 Pre-filled Pen 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 Pre-filled Pen is to be used in combination with ribavirin, please also refer to the ribavirin product information.***

DOSAGE AND ADMINISTRATION

MONOTHERAPY:
PEG-INTRON Pre-filled Pen monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 mcg/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety. Treatment with PEG-INTRON Pre-filled Pen should be initiated and monitored only by a physician experienced in the treatment of patients with hepatitis C. In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, (i.e., 1 year of treatment).
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 Pre-filled Pen should be discontinued.

COMBINATION THERAPY:
PEG-INTRON REDIPEN Pre-filled Pre-filled Pen 1.5 mcg/kg/week subcutaneously in combination with ribavirin capsules.
The dose of ribavirin to be used in combination with PEG-INTRON Pre-filled Pen 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

Patient weight (kg)	**Daily ribavirin dose**	**Number of 200 mg capsules**
< 65	800 mg	4[a]
65 – 85	1,000 mg	5[b]
> 85	1,200 mg	6[c]

[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 pen 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

Weight (kg)	**PegIntron**		**Ribavirin Capsules**	
	Pen Strength (µg/0.5 ml)	**Administer once weekly (ml)**	**Total Daily Dose (mg)**	**Number of Capsules (200 mg)**
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

[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 and 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 Pre-filled Pen or PEG-INTRON Pre-filled Pen with ribavirin, modify the dosage of each product if appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, **Table 4a** for PEG-INTRON REDIPEN and **Table 4b** for PEG-INTRON REDIPEN with ribavirin).

Table 4a Dose modification guidelines for PEG-INTRON Pre-filled Pen

Laboratory values	**ReducePEG-INTRON REDIPEN to one-half dose if:**	**Discontinue PEG-INTRON REDIPEN if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Table 4b	Dose modification guidelines for PEG-INTRON Combination Therapy		
Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PEG-INTRON REDIPEN Injection dose to one-half dose if:**	**Discontinue PEG-INTRON Combination Therapy if:**
Hemoglobin	< 10 g/dl	–	< 8.5 g/dl
Hemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in hemoglobin during any four-week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	–	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	–	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	–	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	–	–	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	–	> 4 mg/dl (for > 4 weeks)
Creatinine	–	–	> 2.0 mg/dl
ALT/AST	–	–	2 x baseline and > 10 x ULN**

* 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 pen 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 REDIPEN Pre–filled Pen. Patients with moderate renal impairment should be closely monitored, and should have their dose of PEG-INTRON treatment reduced if medically appropriate. If serum creatinine rises to > 2 mg/dl (see **Table 4b**), PEG-INTRON treatment should 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, it should 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 should be determined prior to its administration.
Use in patients under the age of 18 years: Safety and effectiveness of PEG-INTRON treatment in these patients have not been evaluated. The use of PEG-INTRON is not recommended for children and adolescents under the age of 18 (see **Indications and Usage**).
Preparation and Administration: PEG-INTRON Pre-filled Pen contains peginterferon alfa-2b powder at strengths of 50, 80, 100, 120, and 150 mcg and the solvent (sterile water for injection) for single disposable use. The powder and solvent are contained in a dual-chamber cartridge. When the cartridge is activated, the powder will be reconstituted with the solvent and up to 0.5 ml of the reconstituted solution will be administered. A small volume is lost during preparation of the reconstituted solution when the dose is measured and injected. Thus, each unit contains an excess amount of solvent and peginterferon alfa-2b powder to ensure delivery of the labeled dose in 0.5 ml in the PEG-INTRON Pre-filled Pen. The reconstituted solution for each of the above strengths has a concentration of 50, 80, 100, 120 and 150 mcg/0.5 ml. The labeled strength will be contained in 0.5 ml of the reconstituted solution.
PEG-INTRON Pre-filled Pen is used for subcutaneous administration after the powder is reconstituted as instructed, the injection needle is attached, and the Pre-filled Pen is set for the administration of the prescribed dose. A complete and illustrated set of instructions is provided at the end of this insert [see attached ANNEX TO THE PI/PB].
Remove PEG-INTRON Pre-filled Pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25° C).
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. The PEG-INTRON REDIPEN product must not be mixed with other injectable products.
Stability of the reconstituted solution: Stability for the reconstituted solution has been demonstrated for 24 hours at 2° - 8° C. If not used immediately, PEG-INTRON Pre-filled Pen should be stored in the refrigerator (2 ° - 8° C) and used within 24 hours.

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

DRUG INTERACTIONS: No pharmacokinetic interactions were noted between peginterferon alfa-2b 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 (1.5 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 Human Immunodeficient Virus (HIV) and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PEG-INTRON Injection and ribavirin to HAART .

ADVERSE EFFECTS:
PEG-INTRON Pre-filled Pen 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, hypertonia, 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 10^9/l) occurred in 4% and 7%, and thrombocytopenia (< 70 x 10^9/l) in 1% and 3%, respectively, in patients receiving 0.5 or 1.0 mcg/kg of PEG-INTRON Injection.

PEG-INTRON Pre-filled Pen 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 5% and 10%: tachycardia, rhinitis and taste perversion.
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 PegIntron, 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 monotherapy or 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 Prefilled Pen, rhabdomyolysis, myositis, renal insufficiency and renal failure have been reported rarely. Cardiac ischemia, myocardial infarction, cerebrovascular ischemia, 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 Pre-filled Pen 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 REDIPEN Prefilled Pen 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 Pre-filled Pen 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 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 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 therapy with PEG-INTRON Pre-filled Pen be discontinued, and the patient followed with psychiatric intervention as appropriate.

Cardiovascular system: As with interferon alpha, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders receiving PEG-INTRON therapy 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 treatment.
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 PEG-INTRON treatment, 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 PEG-INTRON treatment in patients who develop prolongation of coagulation markers, which might indicate liver decompensation.
Renal function: Patients with impairment of renal function should be closely monitored for signs and symptoms of toxicity. PEG-INTRON treatment should not be used in patients with chronic renal failure or creatinine clearance < 50 ml/min (see CONTRAINDICATIONS).
Liver/kidney graft rejection: The safety and efficacy of PEG-INTRON REDIPEN Prefilled Pen 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 alpha 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 alpha 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 should be ruled out.
Hydration: Adequate hydration must be maintained in patients undergoing PEG-INTRON therapy 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, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha 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 treatment. Prompt discontinuation of therapy and treatment with corticosteroids appear to 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 should be considered in patients who develop new or worsening ophthalmologic disorders.
Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha 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, treatment with PEG-INTRON Pre-filled Pen 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 alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PEG-INTRON treatment 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 treatment are:
- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- 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 PEG-INTRON treatment 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 Pre-filled Pen is likely also to cause this effect. Because there are no data on its use in pregnant women, PEG-INTRON treatment is not recommended for use during pregnancy.
PEG-INTRON treatment 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 with ribavirin must not be used during pregnancy.
Significant teratogenic and/or embryocidal potential have 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 fertilization 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 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 Pre-filled Pen is available as a single dose presentation in strengths of 50 mcg, 80 mcg, 100 mcg, 120 mcg, and 150 mcg powder and solvent for solution for injection in pre-filled pens. Each pack contains 1 injection needle and 2 cleansing swabs.

STORAGE: Store at 2° to 8° C. (in refrigerator). Do not freeze

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THIS IS A MEDICAMENT
- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament. The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers & Union of Arab Pharmacist