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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PegIntron safely and effectively. See full prescribing information for Intron.

PegIntron (peginterferon alfa-2b) Injection, Powder for Solution for Subcutaneous Use
Initial U.S. Approval: 2001

- Hepatic decompensation (Child-Pugh score >6 [class B and C]) in cirrhotic CHC patients before or during treatment (4)
- Additional contraindications for combination therapy with ribavirin:
 - Pregnant women and men whose female partners are pregnant (4, 8.1)
 - Hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) (4)
 - Creatinine clearance <50 mL/min (4)

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

- See full prescribing information for complete boxed warning.*
- May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders (5)
- Use with Ribavirin**
- Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients (5.1)
 - Ribavirin is a potential carcinogen (5.1, 13.1)

RECENT MAJOR CHANGES

Indications and Usage, Chronic Hepatitis C (1.1)	[3/2009]
Dosage and Administration, Combination Therapy (2.1)	[3/2009]
Dosage and Administration, PegIntron Monotherapy (2.2)	[3/2009]
Dosage and Administration, Dose Reduction (2.3)	[3/2009]
Dosage and Administration, Discontinuation of Dosing (2.4)	[3/2009]
Contraindications (4)	[12/2008]
Warnings and Precautions, Laboratory Tests (5.15)	[12/2008]
Warnings and Precautions, Impact on Growth-Pediatric Use (5.18)	[12/2008]

INDICATIONS AND USAGE

- PegIntron is an antiviral indicated for
- **Combination therapy** with REBETOL (ribavirin): Chronic Hepatitis C (CHC) in patients ≥3 years with compensated liver disease (1.1)
Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection (1.1)
 - **Monotherapy:** CHC in patients (≥18 years) with compensated liver disease previously untreated with interferon alpha (1.1)

DOSAGE AND ADMINISTRATION

- PegIntron is administered by subcutaneous injection

	PegIntron Dose (Adults) ^a	PegIntron Dose (Pediatric Patients)	REBETOL Dose ^a (Adults)	REBETOL Dose (Pediatric Patients)
PegIntron/REBETOL Combination Therapy (2.1)	1.5 mcg/kg/week	60 mcg/m ² /week	800-1400 mg orally daily with food	15 mg/kg/day orally with food in two divided doses

a-Refer to Tables 1 and 3 of the full Prescribing Information.

- Dose reduction is recommended in patients experiencing certain adverse reactions or renal dysfunction (2.3, 2.5)

DOSAGE FORMS AND STRENGTHS

- Single-use vial (with 1.25 mL diluent) and REDIPEN (3):
- 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL

CONTRAINDICATIONS

- Known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis to interferon alpha or any other product component (4)
- Autoimmune hepatitis (4)

WARNINGS AND PRECAUTIONS

- Birth defects and fetal death with ribavirin: Patients must have a negative pregnancy test prior to therapy; use at least 2 forms of contraception and undergo monthly pregnancy tests (5.1)

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia with ribavirin (5.1)
- Neuropsychiatric events (5.2)
- History of significant or unstable cardiac disease (5.3)
- Hypothyroidism, hyperthyroidism, hyperglycemia, diabetes mellitus that cannot be effectively treated by medication (5.4)
- New or worsening ophthalmologic disorders (5.5)
- Ischemic and hemorrhagic cerebrovascular events (5.6)
- Severe decreases in neutrophil or platelet counts (5.7)
- History of autoimmune disorders (5.8)
- Pancreatitis and ulcerative or hemorrhagic/ischemic colitis and pancreatitis (5.9, 5.10)
- Pulmonary infiltrates or pulmonary function impairment (5.11)
- Child-Pugh score >6 (class B and C) (4, 5.12)
- Increased creatinine levels in patients with renal insufficiency (5.13)
- Serious, acute hypersensitivity reactions and cutaneous eruptions (5.14)
- Dental/periodontal disorders reported with combination therapy (5.16)
- Hypertriglyceridemia may result in pancreatitis (e.g., triglycerides >1000 mg/dL) (5.17)
- Weight loss and growth inhibition reported with combination therapy in pediatric patients (5.18)

ADVERSE REACTIONS

Most common adverse reactions (>40%) in adult patients receiving either PegIntron or PegIntron/REBETOL are injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability (6.1). Most common adverse reactions (>25%) in pediatric patients receiving PegIntron/REBETOL are pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Schering Corporation at 1-800-526-4099 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drug Metabolized by CYP450: Caution with drugs metabolized by CYP2C8/9 (e.g., warfarin, phenytoin) or CYP2D6 (e.g., flecainide) (7.1)
- Methadone: Monitor for increased narcotic effect (7.2)
- Nucleoside Analogues: Closely monitor for toxicities. Discontinue Nucleoside Reverse Transcriptase Inhibitors or reduce dose or discontinue interferon, ribavirin, or both with worsening toxicities (7.3)
- Didanosine: Concurrent use with REBETOL is not recommended (7.3)

USE IN SPECIFIC POPULATIONS

- Ribavirin Pregnancy Registry: 1-800-593-2214 (8.1)
- Pediatrics: safety and efficacy in pediatrics <3 years old have not been established (8.4)
- Geriatrics: neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse reactions may be more severe (8.5)
- Organ transplant: safety and efficacy have not been studied (8.6)
- HIV or HBV co-infection: safety and efficacy have not been established (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [3/2009]

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

Alpha interferons, including PegIntron, may 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 PegIntron therapy. [See *Warnings and Precautions (5) and Adverse Reactions (6.1)*]

Use with Ribavirin

Ribavirin may cause birth defects and death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with REBETOL therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen. [See *REBETOL package insert*]

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C

Combination therapy:

PegIntron™ in combination with REBETOL® (ribavirin) is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease.

The following points should be considered when initiating therapy with PegIntron in combination with REBETOL:

- These indications are based on achieving undetectable HCV RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
- Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection [see *Clinical Studies (14)*].
- No safety and efficacy data are available for treatment of longer than one year.

Monotherapy (for patients who are intolerant to ribavirin):

PegIntron (peginterferon alfa-2b) is indicated for use alone for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with interferon alpha and who are at least 18 years of age.

The following points should be considered when initiating therapy with PegIntron alone:

- Combination therapy with REBETOL is preferred over PegIntron monotherapy unless there are contraindications to or significant intolerance of REBETOL. Combination therapy provides substantially better response rates than monotherapy [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 PegIntron/REBETOL Combination Therapy

REBETOL should be taken with food. REBETOL should not be used in patients with creatinine clearance <50 mL/min.

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The recommended dose of PegIntron is 1.5 mcg/kg/week subcutaneously in combination with 800-1400 mg of REBETOL orally based on patient body weight. The volume of PegIntron to be injected depends on the strength of PegIntron and patient's body weight [See *Table 1*].

Duration of Treatment – Interferon Alpha-naïve Patients

The treatment duration for patients with genotype 1 is 48 weeks. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 log₁₀ drop or loss of HCV-RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy. Patients with genotype 2 and 3 should be treated for 24 weeks.

Duration of Treatment – Retreatment with PegIntron/REBETOL of Prior Treatment Failures

The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Retreated patients who fail to achieve undetectable HCV-RNA at week 12 of therapy, or whose HCV-RNA remains detectable after 24 weeks of therapy, are highly unlikely to achieve SVR and discontinuation of therapy should be considered [see *Clinical Studies (14.1)*].

**Table 1
Recommended PegIntron Combination Therapy Dosing (Adults)**

Body weight kg (lbs)	PegIntron REDIPEN® or Vial Strength to Use	Amount of PegIntron (mcg) to Administer	Volume (mL)* of PegIntron to Administer	REBETOL Daily Dose	REBETOL Number of Capsules
<40 (<87)	50 mcg per 0.5 mL	50	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
40 – 50 (87 – 111)	80 mcg per 0.5 mL	64	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
51 – 60 (112 – 133)		80	0.5	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
61 – 65 (134 – 144)	120 mcg per 0.5 mL	96	0.4	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
66 – 75 (145 – 166)		96	0.4	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
76 – 85 (167 – 188)		120	0.5	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
86 – 105 (189 – 231)	150 mcg per 0.5 mL	150	0.5	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.

>105 (>231)	**	**	**	1400 mg/day	3 x 200 mg capsules A.M. 4 x 200 mg capsules P.M.
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* When reconstituted as directed.

** For patients weighing >105 kg (>231 pounds), the PegIntron dose of 1.5 mcg/kg/week should be calculated based on the individual patient weight. Two vials of PegIntron may be necessary to provide the dose.

Pediatric Patients

Dosing for pediatric patients is determined by body surface area for PegIntron and by body weight for REBETOL. The recommended dose of PegIntron is 60mcg/m²/week subcutaneously in combination with 15 mg/kg/day of REBETOL orally in two divided doses [see Table 2] for pediatric patients ages 3-17 years. Patients who reach their 18th birthday while receiving PegIntron/REBETOL, should remain on the pediatric dosing regimen. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

Table 2
Recommended REBETOL[†] Dosing in Combination Therapy (Pediatrics)

Body weight kg (lbs)	REBETOL Daily Dose	REBETOL Number of Capsules
<47 (<103)	15 mg/kg/day	Use REBETOL Oral Solution**
47 – 59 (103-131)	800 mg/day	2 x 200 mg capsules A.M. 2 x 200 mg capsules P.M.
60 – 73 (132-162)	1000 mg/day	2 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.
>73 (>162)	1200 mg/day	3 x 200 mg capsules A.M. 3 x 200 mg capsules P.M.

[†]REBETOL to be used in combination with PegIntron 60 mcg/m² weekly.

** REBETOL Oral Solution may be used for any patient regardless of body weight.

2.2 PegIntron Monotherapy

The recommended dose of PegIntron regimen is 1 mcg/kg/week subcutaneously for one year administered on the same day of the week. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 log₁₀ drop or loss of HCV-RNA at 12 weeks of therapy, or whose HCV-RNA levels remain detectable after 24 weeks of therapy. The volume of PegIntron to be injected depends on patient weight [see Table 3].

Table 3
Recommended PegIntron Monotherapy Dosing

Body weight kg (lbs)	PegIntron REDIPEN or Vial Strength to Use	Amount of PegIntron (mcg) to Administer	Volume (mL) [*] of PegIntron to Administer
≤45 (≤100)	50 mcg per 0.5 mL	40	0.4
46 – 56 (101 – 124)		50	0.5
57 – 72 (125 – 159)	80 mcg per 0.5 mL	64	0.4
73 – 88 (160 – 195)		80	0.5
89 – 106 (196 – 234)	120 mcg per 0.5 mL	96	0.4
107 – 136 (235 – 300)		120	0.5
137 – 160 (301 – 353)	150 mcg per 0.5 mL	150	0.5

* When reconstituted as directed.

2.3 Dose Reduction

If a serious adverse reaction develops during the course of treatment [see Warning and Precautions (5)] discontinue or modify the dosage of PegIntron and REBETOL until the adverse event abates or decreases in severity. If persistent or recurrent serious adverse events develop despite adequate dosage adjustment, discontinue treatment. For guidelines for dose modifications and discontinuation based on laboratory parameters, see Tables 4 and 5. Dose reduction of PegIntron in adults may be accomplished by utilizing a lower dose strength as shown in Table 6 or 7. For vials, 50% dose reduction may also be accomplished by reducing the volume administered by one-half without changing the dose strength.

In the adult combination therapy trial dose reductions occurred in 42% of subjects receiving PegIntron 1.5 mcg/kg plus REBETOL 800 mg daily including 57% of those subjects weighing 60 kg or less [see Adverse Reactions (6.1)].

Dose reduction in pediatric patients is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 mcg/m²/week, to 40 mcg/m²/week, then to 20 mcg/m²/week, if needed [see Tables 4 and 5]. In the pediatric combination therapy trial, dose reductions occurred in 25% of subjects receiving PegIntron 60 mcg/m² weekly plus REBETOL 15 mg/kg daily.

Table 4
Guidelines for Modification or Discontinuation of PegIntron or PegIntron/REBETOL and for Scheduling Visits for Patients with Depression

Depression Severity ¹	Initial Management (4-8 weeks)			Depression	
	Dose modification	Visit schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit or phone.	Continue weekly visit schedule.	Resume normal visit schedule.	See moderate or severe depression
Moderate	Adults: Decrease IFN dose 50% Pediatrics: Decrease dose to 40 mcg/m ² /week, then to 20 mcg/m ² /week, if needed	Evaluate once weekly (office visit at least every other week).	Consider psychiatric consultation. Continue reduced dosing.	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose.	See severe depression
Severe	Discontinue IFN/R permanently.	Obtain immediate psychiatric consultation.	Psychiatric therapy as necessary		

¹ See DSM-IV for definitions.

Table 5.
Guidelines for Dose Modification and Discontinuation of PegIntron or PegIntron/REBETOL Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Values	PegIntron		REBETOL	
	Adults	Pediatrics	Adults	Pediatrics
Hgb < 10g/dL	For patients with cardiac disease, reduce by 50%*	See footnote*	Decrease by 200mg/day	1 st reduction to 12mg/kg/day 2 nd reduction to 8mg/kg/day
WBC < 1.5 x 10 ⁹ /L Neutrophils < 0.75 x 10 ⁹ /L Platelets < 80 x 10 ⁹ /L (Adults) < 70 x 10 ⁹ /L (Pediatrics)	Reduce by 50%	1 st reduction to 40mcg/m ² /week 2 nd reduction to 20mcg/m ² /week	No Dose Change	No Dose Change
Hgb < 8.5g/dL WBC < 1 x 10 ⁹ /L Neutrophils < 0.5 x 10 ⁹ /L Platelets < 50 x 10 ⁹ /L Creatinine > 2 mg/dL (Pediatrics)	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue	Permanently Discontinue

* For adult patients with a history of stable cardiac disease receiving PegIntron in combination with ribavirin, the PegIntron dose should be reduced by half and the ribavirin dose by 200 mg/day if a >2 g/dL decrease in hemoglobin is observed during any 4-week period. Both PegIntron and ribavirin should be permanently discontinued if patients have hemoglobin levels <12 g/dL after this ribavirin dose reduction. Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease ≥2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

Table 6
Reduced PegIntron Dose (0.5 mcg/kg) for (1 mcg/kg) Monotherapy in Adults

Body weight kg(lbs)	PegIntron REDIPEN/Vial Strength to Use	Amount of PegIntron (mcg) to Administer	Volume (mL)** of PegIntron to Administer
≤45 (≤100)	50 mcg per 0.5 mL*	20	0.2
46 – 56 (101 – 124)		25	0.25
57 – 72 (125 – 159)	50 mcg per 0.5 mL	30	0.3
73 – 88 (160 – 195)		40	0.4
89 – 106 (196 – 234)	50 mcg per 0.5 mL	50	0.5
107 – 136 (235 – 300)	80 mcg per 0.5 mL	64	0.4
137 – 160 (301 – 353)		80	0.5

* Must use vial. Minimum delivery for REDIPEN 0.3 mL.

** When reconstituted as directed.

Table 7
Reduced PegIntron Dose (0.75 mcg/kg) for (1.5 mcg/kg) Combination Therapy in Adults

Body weight kg(lbs)	PegIntron REDIPEN/Vial Strength to Use	Amount of PegIntron (mcg) to Administer	Volume (mL)** of PegIntron to Administer
<40 (<87)	50 mcg per 0.5 mL*	25	0.25
40 – 50 (87 – 111)	50 mcg per 0.5 mL	30	0.3
51 – 60 (112 – 133)		40	0.4
61 – 75 (134 – 166)	50 mcg per 0.5 mL	50	0.5
76 – 85 (167 – 188)	80 mcg per 0.5 mL	64	0.4
86-106 (189-234)		80	0.5
107-136 (235-300)	120 mcg per 0.5 mL	96	0.4
137-160 (301-353)		108	0.45

* Must use vial. Minimum delivery for REDIPEN 0.3 mL

** When reconstituted as directed

2.4 Discontinuation of Dosing

Adults

It is recommended that HCV genotype 1 interferon-alfa-naïve patients receiving PegIntron, alone or in combination with ribavirin, be discontinued from therapy if there is not at least a 2 log₁₀ drop or loss of HCV-RNA at 12 weeks of therapy, or whose HCV-RNA levels remain detectable after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at week 12 or 24, are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

Pediatrics (3-17 years of age)

It is recommended that patients receiving PegIntron/REBETOL combination (excluding those with HCV Genotype 2 and 3) be discontinued from therapy at 12 weeks if their treatment week 12 HCV-RNA dropped <2 log₁₀ compared to pretreatment or at 24 weeks if they have detectable HCV-RNA at treatment week 24.

2.5 Renal Function

In patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the PegIntron dose should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 10-29 mL/min) including those on hemodialysis, should have the PegIntron dose reduced by 50%. If renal function decreases during treatment, PegIntron therapy should be discontinued. When PegIntron is administered in combination with REBETOL, subjects with impaired renal function or those over the age of 50 should be more carefully monitored with respect to the development of anemia. PegIntron/REBETOL should not be used in patients with creatinine clearance <50 mL/min.

2.6 Preparation and Administration

PegIntron REDIPEN

PegIntron REDIPEN consists of a dual-chamber glass cartridge with sterile, lyophilized peginterferon alfa-2b in the active chamber and Sterile Water for Injection, USP in the diluent chamber. The PegIntron in the glass cartridge should appear as a white to off-white tablet shaped solid that is whole or in pieces, or powder.

To reconstitute the lyophilized peginterferon alfa-2b in the REDIPEN:

- Hold the REDIPEN upright (dose button down) and press the two halves of the pen together until there is an audible click.

- Gently invert the pen to mix the solution. **DO NOT SHAKE.** The reconstituted solution has a concentration of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL or 150 mcg per 0.5 mL for a single subcutaneous injection.
- Visually inspect the solution for particulate matter and discoloration prior to administration. The reconstituted solution should be clear and colorless. Do not use the solution if it is discolored, or not clear, or if particulates are present.

Keeping the pen upright, attach the supplied needle and select the appropriate PegIntron dose by pulling back on the dosing button until the dark bands are visible and turning the button until the dark band is aligned with the correct dose. The prepared PegIntron solution is to be injected subcutaneously.

The PegIntron REDIPEN is a single-use pen and does not contain a preservative. The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2°-8° C [see *How Supplied/Storage and Handling (16)*]. **DO NOT REUSE THE REDIPEN.** The sterility of any remaining product can no longer be guaranteed. **DISCARD THE UNUSED PORTION.** Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

PegIntron Vials

Two B-D® Safety Lok™ syringes are provided in the package; one syringe is for the reconstitution 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. Instructions for the preparation and administration of PegIntron Powder for Injection are provided below.

- **Reconstitute the PegIntron lyophilized product with only 0.7 mL of the 1.25 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 PegIntron, and PegIntron 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.
- The appropriate PegIntron dose should be withdrawn and injected subcutaneously. PegIntron vials are for single use only and do not contain a preservative.

The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2°-8° C [see *How Supplied/Storage and Handling (16)*]. **DO NOT REUSE THE VIAL.** The sterility of any remaining product can no longer be guaranteed. **DISCARD THE UNUSED PORTION.** Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

3 DOSAGE FORMS AND STRENGTHS

- Single-use vial: 1.25 mL diluent vial: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL
- Single-use REDIPEN: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL

4 CONTRAINDICATIONS

PegIntron is contraindicated in patients with:

- Known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis to interferon alpha or any other component of the product
- autoimmune hepatitis
- hepatic decompensation (Child-Pugh score >6 [class B and C]) in cirrhotic CHC patients before or during treatment.

PegIntron/REBETOL combination therapy is additionally contraindicated in:

- women who are pregnant. REBETOL may cause fetal harm when administered to a pregnant woman. REBETOL is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug the patient should be apprised of the potential hazard to a fetus. [see *Use in Specific Populations (8.1)*]
- men whose female partners are pregnant
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance <50 mL/min

5 WARNINGS AND PRECAUTIONS

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.

5.1 Use with Ribavirin

Pregnancy

REBETOL may cause birth defects and death of the unborn child. REBETOL therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and have monthly pregnancy tests [see BOXED WARNING, Contraindications (4), Patient Counseling Information (17) and REBETOL package insert].

Anemia

Ribavirin caused hemolytic anemia in 10% of PegIntron/REBETOL- treated subjects within 1-4 weeks of initiation of therapy. Complete blood counts should be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Anemia associated with REBETOL therapy may result in a worsening of cardiac disease. Decrease in dosage or discontinuation of REBETOL may be necessary [see *Dosage and Administration (2.3)* and *REBETOL package insert*].

5.2 Neuropsychiatric Events

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior sometimes directed towards others have occurred in patients with and without a previous psychiatric disorder during PegIntron treatment and follow-up. Psychoses, hallucinations, bipolar disorders, and mania have been observed in patients treated with interferon alpha. PegIntron 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 or suicidal ideation to their prescribing physicians. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. If patients develop psychiatric problems, including clinical depression, it is recommended that the patients be carefully monitored during treatment and in the 6-month follow-up period. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior towards others is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate. In severe cases, PegIntron should be stopped immediately and psychiatric intervention instituted [see *Dosage and Administration (2.3)*]. Cases of encephalopathy have been observed in some patients, usually elderly, treated at higher doses of PegIntron.

5.3 Cardiovascular Events

Cardiovascular events, which include hypotension, arrhythmia, tachycardia, cardiomyopathy, angina pectoris, and myocardial infarction, have been observed in patients treated with PegIntron. PegIntron should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require PegIntron therapy should be closely monitored [see *Warning and Precautions (5.15)*]. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron /REBETOL combination therapy [see *REBETOL package insert*].

5.4 Endocrine Disorders

PegIntron causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with PegIntron. 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 PegIntron therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PegIntron therapy.

5.5 Ophthalmologic Disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema may be induced or aggravated by treatment with peginterferon alfa-2b or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peginterferon alfa-2b treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

5.6 Cerebrovascular disorders

Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alpha-based therapies, including PegIntron. Events occurred in patients with few or no reported risk factors for stroke, including patients less than 45 years of age. Because these are spontaneous reports, estimates of frequency cannot be made and a causal relationship between interferon alpha-based therapies and these events is difficult to establish.

5.7 Bone Marrow Toxicity

PegIntron suppresses bone marrow function, sometimes resulting in severe cytopenias. PegIntron should be discontinued in patients who develop severe decreases in neutrophil or platelet counts [see *Dosage and Administration (2.3)*]. Ribavirin may potentiate the neutropenia induced by interferon alpha. Very rarely alpha interferons may be associated with aplastic anemia.

5.8 Autoimmune Disorders

Development or exacerbation of autoimmune disorders (e.g., thyroiditis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, and psoriasis) have been observed in patients receiving PegIntron. PegIntron should be used with caution in patients with autoimmune disorders.

5.9 Pancreatitis

Fatal and nonfatal pancreatitis have been observed in patients treated with alpha interferon. PegIntron therapy should be suspended in patients with signs and symptoms suggestive of pancreatitis and discontinued in patients diagnosed with pancreatitis.

5.10 Colitis

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

5.11 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, and sarcoidosis, some resulting in respiratory failure or patient deaths, may be induced or aggravated by PegIntron or alpha interferon therapy. Recurrence of respiratory failure has been observed with interferon rechallenge. PegIntron combination treatment should be suspended in patients who develop pulmonary infiltrates or pulmonary function impairment. Patients who resume interferon treatment should be closely monitored.

5.12 Hepatic Failure

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including PegIntron. Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy (HAART) and alpha interferons with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. During treatment, patients' clinical status and hepatic function should be closely monitored, and PegIntron treatment should be immediately discontinued if decompensation (Child-Pugh score >6) is observed [see *Contraindications (4)*].

5.13 Patients with Renal Insufficiency

Increases in serum creatinine levels have been observed in patients with renal insufficiency receiving interferon alpha products, including PegIntron. Patients with impaired renal function should be closely monitored for signs and symptoms of interferon toxicity, including increases in serum creatinine, and PegIntron dosing should be adjusted accordingly or discontinued [see *Clinical Pharmacology (12.3)* and *Dosage and Administration (2.3)*]. PegIntron monotherapy should be used with caution in patients with creatinine clearance <50 mL/min; the potential risks should be weighed against the potential benefits in these patients. Combination therapy with REBETOL must not be used in patients with creatinine clearance <50 mL/min [see *REBETOL Package Insert*].

5.14 Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) and cutaneous eruptions (Stevens Johnson syndrome, toxic epidermal necrolysis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

5.15 Laboratory Tests

PegIntron alone or in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities. Transient elevations in ALT (2- to 5-fold above baseline) were observed in 10% of subjects treated with PegIntron, and was not associated with deterioration of other liver functions. Triglyceride levels are frequently elevated in patients receiving alpha interferon therapy including PegIntron and should be periodically monitored.

Patients on PegIntron or PegIntron/REBETOL combination therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the adult clinical trial CBC (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. In pediatric subjects the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment week 6. TSH levels were measured every 12 weeks during the treatment period. HCV RNA should be measured periodically during treatment [see *Dosage and Administration (2)*].

Patients who have pre-existing cardiac abnormalities should have electrocardiograms done before treatment with PegIntron/REBETOL.

5.16 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving PegIntron/REBETOL 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 PegIntron. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, patients should be advised to rinse out their mouth thoroughly afterwards.

5.17 Triglycerides

Elevated triglyceride levels have been observed in patients treated with interferon alpha including PegIntron therapy. Hypertriglyceridemia may result in pancreatitis [see *Warnings and Precautions (5.9)*]. Elevated triglyceride levels should be managed as clinically appropriate. Discontinuation of PegIntron therapy should be considered for patients with symptoms of potential pancreatitis, such as abdominal pain, nausea, or vomiting and persistently elevated triglycerides (e.g., triglycerides >1000 mg/dL).

5.18 Impact on Growth-Pediatric Use

Data on the effects of PegIntron plus REBETOL on growth come from an open-label study in subjects 3 through 17 years of age, and weight and height changes are compared to U.S. normative population data. In general, the weight and height gain of pediatric subjects treated with PegIntron plus REBETOL lags behind that predicted by normative population data for the entire length of treatment. After about 6 months post-treatment (Follow-Up Week 24), subjects had weight gain rebounds and regained their weight to 53rd percentile, above the average of the normative population and similar to that predicted by their average baseline weight (57th percentile). After about 6 months post-treatment, height gain stabilized and subjects treated with PegIntron plus REBETOL had an average height percentile of 44th percentile, which was less than the average of the normative population and less than their average baseline height (51st percentile). Severely inhibited growth velocity (< 3rd percentile) was observed in 70% of the subjects while on treatment. Of the subjects experiencing severely inhibited growth, 20% had continued inhibited growth velocity (< 3rd percentile) after 6 months of follow-up.

Among the boys studied, the age groups of 3-11 years old and 12-17 years old had similar height percentile decreases of approximately 5 percentiles after 6 months post-treatment; weight gain continued to be similar to their average baseline percentile. Girls who were 3-11 years old and treated for 48 weeks had the largest average drop in height and weight percentiles (13 percentiles and 7 percentiles, respectively), whereas girls 12-17 years old continued along their average baseline height and weight percentiles after 6 months post-treatment.

6 ADVERSE REACTIONS

Clinical trials with PegIntron alone or in combination with REBETOL have been conducted in over 6900 subjects from 3 to 75 years of age

Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials with PegIntron with or without REBETOL. [See **BOXED WARNING**, *Warnings and Precautions (5)*]. The most common serious events occurring in subjects treated with PegIntron and REBETOL were depression and suicidal ideation [see *Warnings and Precautions (5.2)*] each occurring at a frequency of less than 1%. The most common fatal events occurring in subjects treated with PegIntron and REBETOL were cardiac arrest, suicidal ideation and suicide attempt [see *Warnings and Precautions (5.2 and 5.5)*], all occurring in less than 1% of subjects.

Greater than 96% of all subjects in clinical trials experienced one or more adverse events. The most commonly reported adverse reactions in adult subjects receiving either PegIntron or PegIntron/REBETOL were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and emotional lability/irritability. The most common adverse events in pediatric subjects, ages 3 and older, were pyrexia, headache, vomiting, neutropenia, fatigue, anorexia, injection site erythema, and abdominal pain.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

Study 1 compared PegIntron monotherapy with INTRON A monotherapy. Study 2 compared combination therapy of PegIntron/REBETOL with combination therapy with INTRON A/REBETOL. In these studies, nearly all study subjects in clinical trials experienced one or more adverse reactions.

Adverse reactions that occurred in Studies 1 and 2 at >5% incidence are provided in Table 8 by treatment group. Due to potential differences in ascertainment procedures, adverse reaction rate comparisons across studies should not be made.

Table 8
Adverse Reactions Occurring in > 5% of Subjects

Adverse Reactions	Percentage of Subjects Reporting Adverse Reactions*			
	Study 1		Study 2	
	PegIntron 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Application Site				
Injection Site	47	20	75	49
Inflammation/Reaction				
Autonomic Nervous System				
Dry Mouth	6	7	12	8
Increased Sweating	6	7	11	7
Flushing	6	3	4	3
Body as a Whole				
Fatigue/Asthenia	52	54	66	63
Headache	56	52	62	58
Rigors	23	19	48	41
Fever	22	12	46	33
Weight Loss	11	13	29	20
Right Upper Quadrant Pain	8	8	12	6
Chest Pain	6	4	8	7
Malaise	7	6	4	6
Central/Peripheral Nervous System				
Dizziness	12	10	21	17
Endocrine				
Hypothyroidism	5	3	5	4
Gastrointestinal				
Nausea	26	20	43	33
Anorexia	20	17	32	27
Diarrhea	18	16	22	17
Vomiting	7	6	14	12
Abdominal Pain	15	11	13	13
Dyspepsia	6	7	9	8
Constipation	1	3	5	5
Hematologic Disorders				
Neutropenia	6	2	26	14
Anemia	0	0	12	17
Leukopenia	<1	0	6	5
Thrombocytopenia	7	<1	5	2
Liver and Biliary System				
Hepatomegaly	6	5	4	4
Musculoskeletal				
Myalgia	54	53	56	50
Arthralgia	23	27	34	28
Musculoskeletal Pain	28	22	21	19
Psychiatric				
Insomnia	23	23	40	41
Depression	29	25	31	34
Anxiety/Emotional Lability/Irritability	28	34	47	47
Concentration Impaired	10	8	17	21
Agitation	2	2	8	5
Nervousness	4	3	6	6
Reproductive, Female				
Menstrual Disorder	4	3	7	6
Resistance Mechanism				
Viral Infection	11	10	12	12
Fungal Infection	<1	3	6	1
Respiratory System				
Dyspnea	4	2	26	24
Coughing	8	5	23	16
Pharyngitis	10	7	12	13
Rhinitis	2	2	8	6
Sinusitis	7	7	6	5
Skin and Appendages				

Adverse Reactions	Percentage of Subjects Reporting Adverse Reactions*			
	Study 1		Study 2	
	PegIntron 1 mcg/kg (n=297)	INTRON A 3 MIU (n=303)	PegIntron 1.5 mcg/kg/ REBETOL (n=511)	INTRON A/ REBETOL (n=505)
Alopecia	22	22	36	32
Pruritus	12	8	29	28
Rash	6	7	24	23
Skin Dry	11	9	24	23
Special Senses, Other				
Taste Perversion	<1	2	9	4
Vision Disorders				
Vision Blurred	2	3	5	6
Conjunctivitis	4	2	4	5

*Subjects reporting one or more adverse reactions. A subject may have reported more than one adverse reaction within a body system/organ class category.

The adverse reaction profile in Study 3, which compared PegIntron/weight-based REBETOL combination to a PegIntron/flat dose REBETOL regimen, revealed an increased rate of anemia with weight-based dosing (29% vs. 19% for weight-based vs. flat dose regimens, respectively). However, the majority of cases of anemia were mild and responded to dose reductions.

The incidence of serious adverse reactions was comparable in all studies. In the PEG monotherapy trial (Study 1) the incidence of serious adverse reactions was similar (about 12%) in all treatment groups. In Study 2, the incidence of serious adverse reactions was 17% in the PegIntron/REBETOL groups compared to 14% in the INTRON A/REBETOL group. In Study 3, there was a similar incidence of serious adverse reactions reported for the weight-based REBETOL group (12%) and with the flat dose REBETOL regimen.

In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some subjects experienced ongoing or new serious adverse reactions during the 6-month follow-up period. There have been 19 subject deaths which occurred during treatment or during follow-up in these clinical trials. In Study 1, there was one suicide in a subject receiving PegIntron monotherapy and two deaths among subjects receiving INTRON A monotherapy (1 murder/suicide and 1 sudden death). In Study 2, there was one suicide in a subject receiving PegIntron/REBETOL combination therapy; and 1 subject death in the INTRON A/REBETOL group (motor vehicle accident). In Study 3, there were 14 deaths, 2 of which were probable suicides and one was an unexplained death in a person with a relevant medical history of depression.

In Studies 1 and 2, 10-14% of subjects receiving PegIntron, alone or in combination with REBETOL, discontinued therapy compared with 6% treated with INTRON A alone and 13% treated with INTRON A in combination with REBETOL. Similarly in Study 3, 15% of subjects receiving PegIntron in combination with weight-based REBETOL and 14% of subjects receiving PegIntron and flat dose REBETOL discontinued therapy due to an adverse reaction. The most common reasons for discontinuation of therapy were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions.

In Study 2, dose reductions due to adverse reactions occurred in 42% of subjects receiving PegIntron (1.5 mcg/kg)/REBETOL and in 34% of those receiving INTRON A/REBETOL. The majority of subjects (57%) weighing 60 kg or less receiving PegIntron (1.5 mcg/kg)/REBETOL required dose reduction. Reduction of interferon was dose related (PegIntron 1.5 mcg/kg > PegIntron 0.5 mcg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose reduction for REBETOL was similar across all three groups, 33-35%. The most common reasons for dose modifications were neutropenia (18%), or anemia (9%). Other common reasons included depression, fatigue, nausea, and thrombocytopenia. In Study 3, dose modifications due to adverse reactions occurred more frequently with WBD compared to flat dosing (29 and 23%, respectively).

In the PegIntron/REBETOL combination trials the most common adverse reactions were psychiatric which occurred among 77% of subjects in Study 2 and 68-69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all subjects during treatment or during follow-up after treatment cessation [see *Warnings and Precautions* (5.2)].

PegIntron induced fatigue or headache in approximately two-thirds of subjects, with fever or rigors in approximately half of the subjects. The severity of some of these systemic symptoms (e.g., fever and headache) tends to decrease as treatment continues. In Studies 1 and 2, application site inflammation and reaction (e.g., bruise, itchiness, and irritation) occurred at approximately twice the incidence with PegIntron therapies (in up to 75% of subjects) compared with INTRON A. However, injection site pain was infrequent (2-3%) in all groups. In Study 3 there was a 23-24% incidence overall for injection site reactions or inflammation.

In Study 2, many subjects continued to experience adverse reactions several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse reactions by body class in the PegIntron 1.5/REBETOL group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI). In approximately 10-15% of subjects weight loss, fatigue, and headache had not resolved.

Individual serious adverse reactions occurred at a frequency ≤1% and included suicide attempt, suicidal ideation, severe depression; psychosis, aggressive reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia, retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema, bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout, hyperglycemia, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis, vasculitis, and phototoxicity.

Subjects receiving PegIntron/REBETOL as retreatment after failing a previous interferon combination regimen reported adverse reactions similar to those previously associated with this regimen during clinical trials of treatment-naïve subjects.

Pediatric Subjects

In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. In the pediatric study, the most prevalent adverse reactions in all subjects were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%) and vomiting (27%). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection site pain (1%), pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important adverse reactions that occurred in this subject population were nervousness (7%; 7/107), aggression (3%; 3/107), anger (2%; 2/107), and depression (1%; 1/107). Five subjects received levothyroxine treatment, 3 with clinical hypothyroidism and 2 with asymptomatic TSH elevations.

Dose modifications were required in 25% of subjects, most commonly for anemia, neutropenia and weight loss. Two subjects (2%; 2/107) discontinued therapy as a result of an adverse reaction.

Adverse reactions that occurred with a ≥10% incidence in the pediatric trial subjects are provided in Table 9.

Table 9

Percentage of Pediatric Subjects With Treatment-Related Adverse Reactions (in at Least 10% of All Subjects)

System Organ Class Preferred Term	All subjects n=107
Blood and Lymphatic System Disorders	
Neutropenia	33%
Anemia	11%
Leukopenia	10%
Gastrointestinal Disorders	
Abdominal Pain	21%
Abdominal Pain Upper	12%
Vomiting	27%
Nausea	18%
General Disorders and Administration Site Conditions	
Pyrexia	80%
Fatigue	30%
Injection Site Erythema	29%
Chills	21%
Asthenia	15%
Irritability	14%
Investigations	
Weight Decreased	19%
Metabolism and Nutrition Disorders	
Anorexia	29%
Decreased Appetite	22%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	17%
Myalgia	17%
Nervous System Disorders	
Headache	62%
Dizziness	14%
Skin and Subcutaneous Tissue Disorders	
Alopecia	17%

Laboratory Values

Adults

Changes in selected laboratory values during treatment with PegIntron alone or in combination with REBETOL treatment are described below. **Decreases in hemoglobin, neutrophils, and platelets may require dose reduction or permanent discontinuation from therapy** [See *Dosage and Administration (2.3)* and *Warnings and Precautions (5.1 and 5.7)*].

Hemoglobin. Hemoglobin levels decreased to <11 g/dL in about 30% of subjects in Study 2. In Study 3, 47% of subjects receiving WBD REBETOL and 33% on flat dose REBETOL had decreases in hemoglobin levels <11 g/dl. Reductions in hemoglobin to <9 g/dL occurred more frequently in subjects receiving WBD compared to flat dosing (4% and 2%, respectively). In study 2, dose modification was required in 9% and 13% of subjects in the PegIntron/REBETOL and INTRON A/REBETOL groups. Hemoglobin levels become stable by treatment week 4-6 on average. The typical pattern observed was a decrease in hemoglobin levels by treatment week 4 followed by stabilization and a plateau, which was maintained to the end of treatment. In the PegIntron monotherapy trial, hemoglobin decreases were generally mild and dose modifications were rarely necessary [See *Dosage and Administration (2.3)*].

Neutrophils. Decreases in neutrophil counts were observed in a majority of subjects treated with PegIntron alone (70%) or as combination therapy with REBETOL in Study 2 (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (<0.5 x 10⁹/L) occurred in 1% of subjects treated with PegIntron monotherapy, 2% of subjects treated with INTRON A/REBETOL, and in approximately 4% of subjects treated with PegIntron/REBETOL in Study 2. Two percent of subjects receiving PegIntron monotherapy and 18% of subjects receiving PegIntron/REBETOL in Study 2 required modification of interferon dosage. Few subjects (<1%) required permanent discontinuation of treatment. Neutrophil counts generally return to pretreatment levels 4 weeks after cessation of therapy [See *Dosage and Administration (2.3)*].

Platelets. Platelet counts decreased to <100,000/mm³ in approximately 20% of subjects treated with PegIntron alone or with REBETOL and in 6% of subjects treated with INTRON A/REBETOL. Severe decreases in platelet counts (<50,000/mm³) occur in <4% of subjects. Patients may require discontinuation or dose modification as a result of platelet decreases [See *Dosage and Administration (2.3)*]. In Study 2, 1% or 3% of subjects required dose modification of INTRON A or PegIntron, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy.

Triglycerides. Elevated triglyceride levels have been observed in patients treated with interferon alphas including PegIntron [see *Warnings and Precautions (5.17)*].

Thyroid Function. Development of TSH abnormalities, with and without clinical manifestations, are associated with interferon therapies. In study 2, clinically apparent thyroid disorders occur among subjects treated with either INTRON A or PegIntron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). 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 [see *Warnings and Precautions (5.4)*].

Bilirubin and Uric Acid. In Study 2, 10-14% of subjects developed hyperbilirubinemia and 33-38% developed hyperuricemia in association with hemolysis. Six subjects developed mild to moderate gout.

Pediatric Subjects

Decreases in hemoglobin, white blood cells, platelets and neutrophils may require dose reduction or permanent discontinuation from therapy [See Dosage and Administration (2.3)]. Changes in selected laboratory values during treatment of 107 pediatric subjects with PegIntron/REBETOL combination therapy are described in Table 10. Most of the changes in laboratory values in this study were mild or moderate.

Table 10. Selected Hematological Abnormalities During Treatment Phase with PegIntron Plus REBETOL in Previously Untreated Pediatric Subjects

Laboratory Parameter ^a	All subjects n=107
Hemoglobin (g/dL)	
9.5 – <11.0	30%
8.0 – <9.5	2%
WBC (x10⁹/L)	
2.0 – 2.9	39%
1.5 – <2.0	3%
Platelets (x10⁹/L)	
70 – 100	1%
50 – <70	-
25 – <50	1%
Neutrophils (x10⁹/L)	
1.0 – 1.5	35%
0.75 – <1.0	26%
0.5 – <0.75	13%
<0.5	3%
Total Bilirubin	
1.26 - 2.59 xN ^b	7%
Evidence of Hepatic Failure	
-	
a: The table summarizes the worst category observed within the period per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included.	
b: N=Upper limit of normal	

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Approximately 2% of subjects receiving PegIntron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (≤160) neutralizing antibodies to PegIntron or INTRON A. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PegIntron with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of PegIntron therapy: thrombotic thrombocytopenic purpura, pure red cell aplasia, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, seizures, memory loss, migraine headache, peripheral neuropathy, hearing impairment, hearing loss, vertigo, aphthous stomatitis, rhabdomyolysis, myositis, renal insufficiency, and renal failure. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P-450

When administering PegIntron with medications metabolized by CYP2C8/9 (e.g., warfarin and phenytoin) or CYP2D6 (e.g., flecainide), the therapeutic effect of these substrates may be decreased. [See Clinical Pharmacology (12.3)].

7.2 Methadone

PegIntron may increase methadone concentrations [see Clinical Pharmacology (12.3)]. The clinical significance of this finding is unknown; however, patients should be monitored for the signs and symptoms of increased narcotic effect.

7.3 Use with Ribavirin (Nucleoside Analogues)

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient subset. Patients receiving interferon with ribavirin and Nucleoside Reverse Transcriptase Inhibitors (NRTIs) should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate [see Individual NRTI Product Information]. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6).

Stavudine, Lamivudine, and Zidovudine

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as stavudine, lamivudine and zidovudine. In a study with another pegylated interferon alpha, no evidence of a pharmacokinetic or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was seen when ribavirin was co-administered with zidovudine, lamivudine or stavudine in HIV/HCV coinfecting subjects [See *Clinical Pharmacology* (12.3)].

HIV/HCV co-infected subjects who were administered zidovudine in combination with pegylated interferon alpha and ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) more frequently than similar subjects not receiving zidovudine.

Didanosine

Co-administration of REBETOL Capsules or Oral Solution and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [See *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PegIntron Monotherapy

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). PegIntron should be assumed to also have abortifacient potential. There are no adequate and well-controlled studies in pregnant women. PegIntron therapy is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Therefore, PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Use with Ribavirin

Pregnancy Category X: Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. REBETOL therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant [See *Contraindications* (4) and the *REBETOL Package Insert*].

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether the components of PegIntron and/or REBETOL are excreted in human milk. Studies in mice have shown that mouse interferons are excreted in breast 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 PegIntron and REBETOL treatment, taking into account the importance of the therapy to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 3 years have not been established. Clinical trials in pediatric patients < 3 years of age are not considered feasible due to the small proportion of patients in this age group requiring treatment for CHC.

8.5 Geriatric Use

In general, younger patients tend to respond better than older patients to interferon-based therapies. Clinical studies of PegIntron alone or in combination with REBETOL did not include sufficient numbers of subjects aged 65 and over, however, to determine whether they respond differently than younger subjects. Treatment with alpha interferons, including PegIntron, is associated with neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in the use of PegIntron 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 [see *Clinical Pharmacology* (12.3)]. When using PegIntron/REBETOL therapy, refer also to the REBETOL Package Insert.

8.6 Organ Transplant Recipients

The safety and efficacy of PegIntron alone or in combination with REBETOL for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

8.7 HIV or HBV Coinfection

The safety and efficacy of PegIntron/REBETOL for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

10 OVERDOSAGE

There is limited experience with overdosage. In the clinical studies, a few subjects accidentally received a dose greater than that prescribed. There were no instances in which a participant in the monotherapy or combination therapy trials received more than 10.5 times the intended dose of PegIntron. The maximum dose received by any subject was 3.45 mcg/kg weekly over a period of approximately 12 weeks. The maximum known overdosage of REBETOL was an intentional ingestion of 10 g (fifty 200 mg capsules). There were no serious reactions attributed to these overdosages. In cases of overdosing, symptomatic treatment and close observation of the patient are recommended.

11 DESCRIPTION

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

Interferon alfa-2b, 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.

PegIntron is supplied in both vials and the REDIPEN for subcutaneous use.

Vials

Each vial contains either 74 mcg, 118.4 mcg, 177.6 mcg, or 222 mcg of PegIntron as a white to off-white tablet-like solid, that is whole/in pieces or as a loose powder, 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 constitution with 0.7 mL of the supplied Sterile Water for Injection, USP, each vial contains PegIntron at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 100 mcg per 0.5 mL, or 150 mcg per 0.5 mL.

REDIPEN

REDIPEN is a dual-chamber glass cartridge containing lyophilized PegIntron as a white to off-white tablet or powder that is whole or in pieces in the sterile active chamber and a second chamber containing Sterile Water for Injection, USP. Each PegIntron REDIPEN contains either 67.5 mcg, 108 mcg, 162 mcg, or 202.5 mcg of PegIntron, and 1.013 mg dibasic sodium phosphate anhydrous, 1.013 mg monobasic sodium phosphate dihydrate, 54 mg sucrose, and 0.0675 mg polysorbate 80. Each cartridge is reconstituted to allow for the administration of up to 0.5 mL of solution. Following reconstitution, each REDIPEN contains PegIntron at strengths of either 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL for a single use. Because a small volume of reconstituted solution is lost during preparation of PegIntron, each REDIPEN contains an excess amount of PegIntron powder and diluent to ensure delivery of the labeled dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegylated recombinant human interferon alfa-2b is an inducer of the innate antiviral immune response. [See *Clinical Pharmacology* (12.4)].

12.2 Pharmacodynamics

The pharmacodynamic effects of peginterferon alfa-2b include inhibition of viral replication in virus-infected cells, the suppression of cell cycle progression/cell proliferation, induction of apoptosis, anti-angiogenic activities, and numerous immunomodulating activities, such as enhancement of the phagocytic activity of macrophages, activation of NK cells, stimulation of cytotoxic T-lymphocytes, and the upregulation of the Th1 T-helper cell subset.

PegIntron 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.

12.3 Pharmacokinetics

Following a single subcutaneous dose of PegIntron, the mean absorption half-life ($t_{1/2 k_a}$) was 4.6 hours. Maximal serum concentrations (C_{max}) occur between 15-44 hours postdose, and are sustained for up to 48-72 hours. The C_{max} and AUC measurements of PegIntron increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PegIntron. 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 PegIntron elimination half-life is approximately 40 hours (range 22 to 60 hours) in patients with HCV infection. The apparent clearance of PegIntron is estimated to be approximately 22 mL/hr·kg. Renal elimination accounts for 30% of the clearance.

Pegylation of interferon alfa-2b produces a product (PegIntron) whose clearance is lower than that of non-pegylated interferon alfa-2b. When compared to INTRON A, PegIntron (1 mcg/kg) has approximately a 7-fold lower mean apparent clearance and a 5-fold greater mean half-life permitting a reduced dosing frequency. At effective therapeutic doses, PegIntron has approximately 10-fold greater C_{max} and 50-fold greater AUC than interferon alfa-2b.

Renal Dysfunction

Following multiple dosing of PegIntron (1 mcg/kg subcutaneously given every week for four weeks) the clearance of PegIntron is reduced by a mean of 17% in subjects with moderate renal impairment (creatinine clearance 30-49 mL/min) and by a mean of 44% in subjects with severe renal impairment (creatinine clearance 10-29 mL/min) compared to subjects with normal renal function. Clearance was similar in subjects with severe renal impairment not on dialysis and subjects who are receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment [see *Dosage and Administration* (2.3) and *REBETOL Package Insert*]. REBETOL should not be used in patients with creatinine clearance <50 mL/min [see *REBETOL Package Insert, WARNINGS*].

Gender

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

Geriatric Patients

The pharmacokinetics of geriatric subjects (>65 years of age) treated with a single subcutaneous dose of 1 mcg/kg of PegIntron were similar in C_{max} , AUC, clearance, or elimination half-life as compared to younger subjects (28 to 44 years of age).

Pediatric Patients

Population pharmacokinetics for PegIntron and REBETOL (Capsules and Oral Solution) were evaluated in pediatric subjects with chronic hepatitis C between 3 and 17 years of age. In pediatric patients receiving PegIntron 60 mcg/m²/week subcutaneously, exposure may be approximately 50% higher than observed in adults receiving 1.5 mcg/kg/week subcutaneously. The pharmacokinetics of REBETOL (dose-normalized) in this trial were similar to those reported in a prior study of REBETOL in combination with INTRON A in pediatric subjects and in adults subjects.

Effect of Food on Absorption of Ribavirin

Both AUC_{0-∞} and C_{max} increased by 70% when REBETOL Capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study [see *Dosage and Administration* (2.2)].

Drug Interactions

Drugs Metabolized by Cytochrome P-450

The pharmacokinetics of representative drugs metabolized by CYP1A2 (caffeine), CYP2C8/9 (tolbutamide), CYP2D6 (dextromethorphan), CYP3A4 (midazolam), and N-acetyltransferase (dapson) were studied in 22 subjects with chronic hepatitis C who received PegIntron (1.5 mcg/kg) once weekly for 4 weeks. PegIntron treatment resulted in a 28% (mean) increase in a measure of CYP2C8/9 activity. PegIntron treatment also resulted in a 66% (mean) increase in a measure of CYP2D6 activity; however, the effect was variable as 13 subjects had an increase, 5 subjects had a decrease, and 4 subjects had no significant change [see *Drug Interactions* (7.1)].

No significant effect was observed on the pharmacokinetics of representative drugs metabolized by CYP1A2, CYP3A4, or N-acetyltransferase. The effects of PegIntron on CYP2C19 activity were not assessed.

Methadone

The pharmacokinetics of concomitant administration of methadone and PegIntron were evaluated in 18 PegIntron naïve chronic hepatitis C subjects receiving 1.5 mcg/kg PegIntron subcutaneously weekly. All subjects were on stable methadone maintenance therapy receiving ≥40 mg/day prior to initiating PegIntron. Mean methadone AUC was approximately 16% higher after 4 weeks of PegIntron treatment as compared to baseline. In 2 subjects, methadone AUC was approximately double after 4 weeks of PegIntron treatment as compared to baseline [see *Drug Interactions* (7.2)].

Use with Ribavirin

zidovudine, Lamivudine, and Stavudine

Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine, lamivudine, and stavudine. However, in a study with another pegylated interferon in combination with ribavirin, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic

(e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HIV/HCV coinfecting subjects [see *Drug Interactions (7.3)*].

Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'- triphosphate) is increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities [see *Drug Interactions (7.3)*].

1 Microbiology

Mechanism of Action

The biological activity of PegIntron is derived from its interferon alfa-2b moiety. Peginterferon alfa-2b binds to and activates the human type I interferon receptor. Upon binding, the receptor subunits dimerize, and activate multiple intracellular signal transduction pathways. Signal transduction is initially mediated by the JAK/STAT activation, which may occur in a wide variety of cells. Interferon receptor activation also activates NFκB in many cell types. Given the diversity of cell types that respond to interferon alfa-2b, and the multiplicity of potential intracellular responses to interferon receptor activation, peginterferon alfa-2b is expected to have pleiotropic biological effects in the body.

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity

The anti-HCV activity of interferon was demonstrated in cell culture using self-replicating HCV RNA (HCV replicon cells) or HCV infection and resulted in an effective concentration (EC₅₀) value of 1-10 IU/mL.

The antiviral activity of ribavirin in the HCV-replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin.

Resistance

HCV genotypes show wide variability in their response to pegylated recombinant human interferon/ribavirin therapy. Genetic changes associated with the variable response have not been identified.

Cross-resistance

There is no reported cross-resistance between pegylated/non-pegylated interferons and ribavirin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

PegIntron has not been tested for its carcinogenic potential. Neither PegIntron 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.

Use with Ribavirin: Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen. See REBETOL package insert for additional warnings relevant to PegIntron therapy in combination with ribavirin.

Impairment of Fertility

PegIntron may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 mcg/m² PegIntron alone every other day for one month (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 PegIntron treatment. Every other day dosing with 262 mcg/m² (approximately 21 times the weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of PegIntron on male fertility have not been studied.

14 CLINICAL STUDIES

14.1 Chronic Hepatitis C in Adults

PegIntron Monotherapy-Study 1

A randomized study compared treatment with PegIntron (0.5, 1, or 1.5 mcg/kg once weekly subcutaneously) to treatment with INTRON A (3 million units three times weekly subcutaneously) in 1219 adults with chronic hepatitis from HCV infection. The subjects were not previously treated with interferon alpha, had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis. Subjects were treated for 48 weeks and were followed for 24 weeks posttreatment.

Seventy percent of all subjects were infected with HCV genotype 1, and 74 percent of all subjects 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 posttreatment. The response rates to the 1 and 1.5 mcg/kg PegIntron doses were similar (approximately 24%) to each other and were both higher than the response rate to INTRON A (12%). [See *Table 11*].

Table 11
Rates of Response to Treatment-Study 1

	A PegIntron 0.5 mcg/kg (N=315)	B PegIntron 1 mcg/kg (N=298)	C INTRON A 3 MIU three times weekly (N=307)	B - C (95% CI) Difference between PegIntron 1 mcg/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 is measured by a research-based quantitative polymerase chain reaction assay by a central laboratory.

Subjects with both viral genotype 1 and high serum levels of HCV RNA at baseline were less likely to treatment with PegIntron. Among subjects with the two unfavorable prognostic variables, 8% (12/157) responded to PegIntron treatment and 2% (4/169) responded to INTRON A. Doses of PegIntron higher than the recommended dose did not result in higher response rates in these subjects. Subjects receiving PegIntron with viral genotype 1 had a response rate of 14% (28/199) while subjects with other viral genotypes had a 45% (43/96) response rate.

Ninety-six percent of the responders in the PegIntron groups and 100% of responders in the INTRON A group first cleared their viral RNA by week 24 of treatment [see *Dosage and Administration (2)*].

The treatment response rates were similar in men and women. Response rates were lower in African American and Hispanic subjects 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 subjects. A modest reduction in inflammation compared to baseline that was similar in all four treatment groups was observed.

PegIntron/REBETOL Combination Therapy-Study 2

A randomized study compared treatment with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg subcutaneously once weekly/REBETOL 800 mg orally daily (in divided doses); PegIntron 1.5 mcg/kg subcutaneously once weekly for 4 weeks then 0.5 mcg/kg subcutaneously once weekly for 44 weeks/REBETOL 1000 or 1200 mg orally daily (in divided doses)] with INTRON A [3 MIU subcutaneously three weekly /REBETOL 1000/1200 mg orally daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon-naïve subjects were treated for 48 weeks and followed for 24 weeks posttreatment. Eligible subjects had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment. The response rate to the PegIntron 1.5 mcg/kg plus ribavirin 800 mg dose was higher than the response rate to INTRON A/REBETOL [see *Table 12*]. The response rate to PegIntron 1.5→0.5 mcg/kg/REBETOL was essentially the same as the response to INTRON A/REBETOL (data not shown).

Table 12
Rates of Response to Treatment – Study 2

	PegIntron 1.5 mcg/kg once weekly REBETOL 800 mg daily	INTRON A 3 MIU three times weekly REBETOL 1000/1200 mg daily
Overall response ^{1,2}	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

¹Serum HCV RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

²Difference in overall treatment response (PegIntron/REBETOL vs. INTRON A/REBETOL) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline. Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to PegIntron (1.5 mcg/kg)/REBETOL (800 mg) compared to subjects with other viral genotypes. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/REBETOL.

Subjects with lower body weight tended to have higher adverse reaction rates [see *Adverse Reactions (6.1)*] and higher response rates than subjects with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PegIntron/REBETOL were 49% in men and 56% in women. Response rates were lower in African American and Hispanic subjects 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 (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors in this study.

Liver biopsies were obtained before and after treatment in 68% of subjects. Compared to baseline, approximately 2/3 of subjects in all treatment groups were observed to have a modest reduction in inflammation.

PegIntron/REBETOL Combination Therapy-Study 3

In a large United States community-based study (Study 3), 4913 subjects with chronic hepatitis C were randomized to receive PegIntron 1.5 mcg/kg subcutaneously once weekly in combination with a REBETOL dose of 800-1400 mg (weight-based dosing- [WBD]) or 800 mg (Flat) orally daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable HCV RNA (based on an assay with a lower limit of detection of 125 IU/mL) at 24 weeks posttreatment.

Treatment with PegIntron 1.5 mcg/kg and REBETOL 800-1400 mg resulted in a higher sustained virologic response compared to PegIntron in combination with a flat 800 mg daily dose of REBETOL. Subjects weighing >105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing >85-105 kg [see *Table 13*]. The benefit of WBD in subjects weighing >85 kg was observed with HCV genotypes 1-3. Insufficient data were available to reach conclusions regarding other genotypes. Use of WBD resulted in an increased incidence of anemia [see *Adverse Reactions (6.1)*].

Table 13
SVR Rate by Treatment and Baseline Weight- Study 3

Treatment Group	Subject Baseline Weight			
	<65 kg (<143 lb)	65-85 kg (143-188 lb)	>85-105 kg (>188-231 lb)	>105 kg (>231 lb)
WBD*	50% (173/348)	45% (449/994)	42% (351/835)	47% (138/292)
Flat	51% (173/342)	44% (443/1011)	39% (318/819)	33% (91/272)

* p=0.01, primary efficacy comparison (based on data from subjects weighing 65 kg or higher at baseline and utilizing a logistic regression analysis that includes treatment [WBD or Flat], genotype and presence/absence of advanced fibrosis, in the model).

A total of 1552 subjects weighing >65 kg in Study 3 had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.

PegIntron/REBETOL Combination Therapy in Prior Treatment Failures-Study 4

In a noncomparative trial, 2293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible patients included prior nonresponders (patients who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (patients who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after posttreatment follow-up). Patients who were negative at week 12 were treated for 48 weeks and followed for 24 weeks posttreatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks posttreatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Patients with the following characteristics were less likely to benefit from retreatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The retreatment sustained virologic response rates by baseline characteristics are summarized in Table 14.

**Table 14
SVR Rates by Baseline Characteristics of Prior Treatment Failures.**

HCV Genotype/ Metavir Fibrosis Score	Overall SVR by Previous Response and Treatment			
	Nonresponder		Relapser	
	alfa interferon/ribavirin % (number of patients)	peginterferon (2a and 2b combined)/ribavirin % (number of patients)	alfa interferon /ribavirin % (number of patients)	peginterferon (2a and 2b combined)/ribavirin % (number of patients)
Overall	18 (158/903)	6 (30/476)	43 (130/300)	35 (113/344)
HCV 1	13 (98/761)	4 (19/431)	32 (67/208)	23 (56/243)
F2	18 (36/202)	6 (7/117)	42 (33/79)	32 (23/72)
F3	16 (38/233)	4 (4/112)	28 (16/58)	21 (14/67)
F4	7 (24/325)	4 (8/202)	26 (18/70)	18 (19/104)
HCV 2/3	49 (53/109)	36 (10/28)	67 (54/81)	57 (52/92)
F2	68 (23/34)	56 (5/9)	76 (19/25)	61 (11/18)
F3	39 (11/28)	38 (3/8)	67 (18/27)	62 (18/29)
F4	40 (19/47)	18 (2/11)	59 (17/29)	51 (23/45)
HCV 4	17 (5/29)	7 (1/15)	88 (7/8)	50 (4/8)

Achievement of an undetectable HCV-RNA at treatment week 12 was a strong predictor of sustained virologic response (SVR). In this trial, 1470 (64%) subjects did not achieve an undetectable HCV-RNA at treatment week 12, and were offered enrollment into long-term treatment trials, due to an inadequate treatment response. Of the 823 (36%) subjects who were HCV-RNA undetectable at treatment week 12, those infected with genotype 1 had an SVR of 48% (245/507), with a range of responses by fibrosis scores (F4-F2) of 39-55%. Subjects infected with genotype 2/3 who were HCV-RNA undetectable at treatment week 12 had an overall SVR of 70% (196/281), with a range of responses by fibrosis scores (F4-F2) of 60-83%. For all genotypes, higher fibrosis scores were associated with a decreased likelihood of achieving SVR.

14.2 Chronic Hepatitis C in Pediatrics

PegIntron/REBETOL Combination Therapy-Pediatric Study

Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV RNA were treated with REBETOL 15 mg/kg/day plus PegIntron 60 mcg/m² once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks post-treatment. A total of 107 subjects received treatment of whom 52% were female, 89% were Caucasian, and 67% were infected with HCV Genotype 1. Subjects infected with Genotype 1, 4 or Genotype 3 with HCV RNA ≥ 600,000 IU/mL received 48 weeks of therapy while those infected with Genotype 2 or Genotype 3 with HCV RNA < 600,000 IU/mL received 24 weeks of therapy. The study results are summarized in Table 15.

Table 15
Sustained Virologic Response Rates by Genotype and Treatment Duration – Pediatric Study

Genotype	All Subjects n=107	
	24 Weeks	48 Weeks
	Virologic Response n ^{a,b} (%)	Virologic Response n ^{a,b} (%)
All	26/27(96.3)	44/80(55.0)
1	-	38/72(52.8)
2	14/15(93.3)	-
3 ^c	12/12(100)	2/3(66.7)
4	-	4/5(80.0)

a: Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment.

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Subjects with genotype 3 low viral load (<600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load were to receive 48 weeks of treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

PegIntron REDIPEN

Each PegIntron REDIPEN Package Contains:	
A box containing one 50 mcg per 0.5 mL PegIntron REDIPEN and 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1323-01)
A box containing one 80 mcg per 0.5 mL PegIntron REDIPEN and 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1316-01)
A box containing one 120 mcg per 0.5 mL PegIntron REDIPEN and 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1297-01)
A box containing one 150 mcg per 0.5 mL PegIntron REDIPEN and 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1370-01)

Each PegIntron REDIPEN PAK 4 Contains:	
A box containing four 50 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1323-02)
A box containing four 80 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1316-02)
A box containing four 120 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1297-02)
A box containing four 150 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 B-D needle and 2 alcohol swabs.	(NDC 0085-1370-02)

PegIntron Vials

Each PegIntron Package Contains:	
A box containing one 50 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 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)
A box containing one 80 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 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)
A box containing one 120 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 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)
A box containing one 150 mcg per 0.5 mL vial of PegIntron Powder for Injection and one 1.25 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)

Storage

PegIntron REDIPEN

PegIntron REDIPEN should be stored at 2°-8°C (36°-46°F). After reconstitution, the solution should be used immediately, but may be stored up to 24 hours at 2°-8°C (36°-46°F). The reconstituted solution contains no preservative, and is clear and colorless. **DO NOT FREEZE.**

PegIntron Vials

PegIntron should be stored at 25°C (77°F); excursions permitted to 15°-30°C (59-86°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°-8°C (36°-46°F). The reconstituted solution contains no preservative, is clear and colorless. **DO NOT FREEZE.**

Disposal Instructions

Patients should be thoroughly instructed in the importance of proper disposal. After preparation and administration of the PegIntron for injection, patients should be advised to use a puncture-resistant container for the disposal of used syringes, needles, and the REDIPEN. The full container should be disposed of in accordance with state and local laws. Patients should also be cautioned against reusing or sharing needles, syringes, or the REDIPEN.

PATIENT COUNSELING INFORMATION

Patient should self-inject PegIntron only if it has been determined 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.

17.1 Medication Guide

Patients receiving PegIntron alone or in combination with REBETOL should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the MEDICATION GUIDES for PegIntron and, if applicable, REBETOL (ribavirin).

17.2 Pregnancy

Patients must be informed that REBETOL may cause birth defects and death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients during treatment with combination PegIntron/REBETOL therapy and for 6 months posttherapy. Combination PegIntron/REBETOL therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. It is recommended that patients undergo monthly pregnancy tests during therapy and for 6 months posttherapy [see *Contraindications (4)*, *Use in Specific Populations (8.1)* and *REBETOL package insert*].

17.3 HCV Transmission

Inform patients that there are no data regarding whether PegIntron therapy will prevent transmission of HCV infection to others. Also, it is not known if treatment with PegIntron will cure hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C virus.

17.4 Laboratory Evaluations, Hydration, "Flu-like" Symptoms

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter [see *Warnings and Precautions (5.15)*]. It is advised that patients be well hydrated, especially during the initial stages of treatment. "Flu-like" symptoms associated with administration of PegIntron may be minimized by bedtime administration of PegIntron or by use of antipyretics.

Manufactured by Schering Corporation, a subsidiary of Schering-Plough Corporation, Kenilworth, NJ 07033 USA.



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