

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**103949Orig1s5259**

*Trade Name:* PegIntron Selectdose injection

*Generic or Proper Name:* Pegylated Interferon Alfa-2b injection

*Sponsor:* Schering Corporation

*Approval Date:* December 18, 2013

*Indication:* This supplement provides for a new single-use, dual chamber pre-filled pen injector, PegIntron Selectdose (peginterferon alfa-2b) with recommendations for dose reductions, an updated Medication Guide and Instructions for Use (IFU).

PegIntron is an antiviral indicated for the treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease.

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*Application Number:*  
**103949Orig1s5259**

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*APPLICATION NUMBER:*

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**APPROVAL LETTER**



BLA 103949/5259

**SUPPLEMENT APPROVAL**

Schering Corporation  
a subsidiary of Merck & Co., Inc.  
Attention: David Robinson, Ph.D.  
Global CMC Regulatory Affairs-Biologics and Vaccines  
P.O. Box 2000, RY34-A327  
Rahway, NJ 07065

Dear Dr. Robinson:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received October 10, 2012, submitted under section 351(a) of the Public Health Service Act for PegIntron<sup>®</sup> (peginterferon alfa-2b), injection.

We acknowledge receipt of your amendments dated October 10, 2012, January 11, 2013, January 29, 2013, February 1, 2013, May 23, 2013, May 29, 2013, June 21, 2013, August 2, 2013, August 19, 2013, September 3, 2013, September 13, 2013, September 20, 2013, September 24, 2013, September 25, 2013, October 3, 2013, October 25, 2013, November 1, 2013, November 21, 2013, December 5, 2013 and December 12, 2013.

This Prior Approval supplemental biologics application provides for a new single-use, dual-chamber pre-filled pen injector, PegIntron<sup>®</sup> Selectdose<sup>™</sup> (peginterferon alfa-2b), with recommendations for dose reductions, an updated Medication Guide and Instructions for Use (IFU).

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being

Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on August 2, 2013 and August 19, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103949/5259.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

1. Submit a supplement to remove the trailing zeroes from the doses imprinted on the PegIntron® Selectdose™ (peginterferon alfa-2b) prefilled syringe to optimize dosing and patient use.

The timetable you submitted on December 5, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2014

Submit clinical protocols to your IND 7173 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827 or (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEBRA B BIRNKRANT  
12/18/2013

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

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**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**PEGINTRON® (peginterferon alfa-2b) injection, for subcutaneous use**  
Initial U.S. Approval: 2001

### 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. (5.2)

#### Use with Ribavirin

- Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients. (5.1)

### RECENT MAJOR CHANGES

|   |         |
|---|---------|
| Dosage and Administration,              |         |
| Dose Reduction (2.3)                    | 12/2013 |
| Preparation and Administration (2.6)    | 12/2013 |
| Warnings and Precautions                |         |
| Impact on Growth – Pediatric Use (5.18) | 11/2013 |

### INDICATIONS AND USAGE

PegIntron is an antiviral indicated for treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease. (1.1)

### DOSAGE AND ADMINISTRATION

- PegIntron is administered by subcutaneous injection. (2)

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

\*Refer to Tables 1-8 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

Injection: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL in single-use vial (with 1.25 mL diluent) and single-use pre-filled pens (3)

### 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)
  - Hepatic decompensation (Child-Pugh score greater than 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 less than 50 mL/min. (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 greater than 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 greater than 1000 mg/dL). (5.17)
- Weight loss and growth inhibition reported during combination therapy in pediatric patients. Long-term growth inhibition (height) reported in some patients. (5.18)
- Peripheral neuropathy when used in combination with telbivudine. (5.19)

### ADVERSE REACTIONS

Most common adverse reactions (greater than 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 (greater than 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, a subsidiary of Merck & Co., Inc., at 1-800-526-4099 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 (8.1)
- Pediatrics: safety and efficacy in pediatrics less than 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 and Medication Guide.

Revised: 12/2013

**WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS**

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

**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 ribavirin therapy may result in a worsening of cardiac disease. [See *ribavirin labeling*.]

**1 INDICATIONS AND USAGE**

**1.1 Chronic Hepatitis C (CHC)**

PegIntron<sup>®</sup>, as part of a combination regimen, is indicated for the treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease.

- PegIntron in combination with REBETOL<sup>®</sup> (ribavirin) and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor is indicated in adult patients with HCV genotype 1 infection (see labeling of the specific HCV NS3/4A protease inhibitor for further information).
- PegIntron in combination with REBETOL is indicated in patients with genotypes other than 1, pediatric patients (3-17 years of age), or in patients with genotype 1 infection where use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications or other clinical factors.

PegIntron monotherapy should only be used in the treatment of CHC in patients with compensated liver disease if there are contraindications to or significant intolerance of REBETOL and is indicated for use only in previously untreated adult patients. Combination therapy provides substantially better response rates than monotherapy [see *Clinical Studies (14.1, 14.2)*].

**2 DOSAGE AND ADMINISTRATION**

**2.1 PegIntron Combination Therapy**

Adults

The recommended dose of PegIntron is 1.5 mcg/kg/week. The volume of PegIntron to be injected depends on the strength of PegIntron and patient's body weight (see **Table 1**).

The recommended dose of REBETOL for use with PegIntron is 800 to 1400 mg orally based on patient body weight. REBETOL should be taken with food. REBETOL should not be used in patients with creatinine clearance less than 50 mL/min.

See labeling of the specific HCV NS3/4A protease inhibitor for information regarding dosing regimen and administration of the protease inhibitor in combination with PegIntron and ribavirin.

*Duration of Treatment – Treatment with PegIntron/REBETOL of 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 log<sub>10</sub> 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 – Re-treatment with PegIntron/REBETOL of Prior Treatment Failures*

For patients with genotype 1 infection, PegIntron and REBETOL without an HCV NS3/4A protease inhibitor should only be used if there are contraindications, significant intolerance or other clinical factors that would not warrant use of an HCV NS3/4A protease inhibitor. The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Re-treated 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, Selectdose Pre-filled pen or Vial Strength to Use | Amount of PegIntron to Administer (mcg) | Volume* of PegIntron to Administer (mL) | REBETOL Daily Dose | REBETOL Number of Capsules                           |
|----------------------|--|---|---|--------------------|--|
| <40 (<88)            | 50 mcg per 0.5 mL  | 50                                      | 0.5                                     | 800 mg/day         | 2 x 200 mg capsules A.M.<br>2 x 200 mg capsules P.M. |
| 40-50 (88-111)       | 80 mcg per 0.5 mL  | 64                                      | 0.4                                     | 800 mg/day         | 2 x 200 mg capsules A.M.<br>2 x 200 mg capsules P.M. |
| 51-60 (112-133)      |  | 80                                      | 0.5                                     | 800 mg/day         | 2 x 200 mg capsules A.M.<br>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.<br>2 x 200 mg capsules P.M. |
| 66-75 (145-166)      |  | 96                                      | 0.4                                     | 1000 mg/day        | 2 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| 76-80 (167-177)      |  | 120                                     | 0.5                                     | 1000 mg/day        | 2 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| 81-85 (178-187)      |  |   |   | 1200 mg/day        | 3 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| 86-105 (188-231)     | 150 mcg per 0.5 mL   | 150                                     | 0.5                                     | 1200 mg/day        | 3 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |

|                |   |   |   |             |  |
|----------------|---|---|---|-------------|--|
| >105<br>(>231) | † | † | † | 1400 mg/day | 3 x 200 mg capsules A.M.<br>4 x 200 mg capsules P.M. |
|----------------|---|---|---|-------------|--|

\* When reconstituted as directed.

† For patients weighing greater than 105 kg (greater than 231 pounds), the PegIntron dose of 1.5 mcg/kg/week should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

### 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 60 mcg/m<sup>2</sup>/week subcutaneously in combination with 15 mg/kg/day of REBETOL orally in 2 divided doses (see **Table 2**) for pediatric patients ages 3 to 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<br>kg (lbs) | REBETOL<br>Daily Dose | REBETOL Number of<br>Capsules                        |
|-------------------------|-----------------------|--|
| <47<br>(<103)           | 15<br>mg/kg/day       | Use REBETOL oral<br>solution†                        |
| 47-59<br>(103-131)      | 800 mg/day            | 2 x 200 mg capsules A.M.<br>2 x 200 mg capsules P.M. |
| 60-73<br>(132-162)      | 1000 mg/day           | 2 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| >73<br>(>162)           | 1200 mg/day           | 3 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |

\*REBETOL to be used in combination with PegIntron 60 mcg/m<sup>2</sup> 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 1 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 log<sub>10</sub> 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<br>kg (lbs) | PegIntron REDIPEN, Selectdose Pre-filled pen or Vial Strength to Use | Amount of<br>PegIntron to Administer<br>(mcg) | Volume of PegIntron to Administer<br>(mL)* |
|-------------------------|--|---|--|
| ≤45<br>(≤100)           | 50 mcg per 0.5 mL  | 40  | 0.4  |
| 46-56<br>(101-124)      |  | 50  | 0.5  |
| 57-72<br>(125-159)      | 80 mcg per 0.5 mL  | 64  | 0.4  |
| 73-88<br>(160-195)      |  | 80  | 0.5  |
| 89-106<br>(196-234)     | 120 mcg per 0.5 mL   | 96  | 0.4  |
| 107-136<br>(235-300)    |  | 120   | 0.5  |
| 137-160<br>(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 discontinue or modify the dosage of PegIntron and REBETOL until the adverse event abates or decreases in severity [see **Warnings and Precautions (5)**]. If persistent or recurrent serious adverse events develop despite adequate dosage adjustment, discontinue treatment. For guidelines for dose modifications and discontinuation based on depression or laboratory parameters see **Tables 4** and **5**. Dose reduction of PegIntron in adult patients on PegIntron/REBETOL combination therapy is accomplished in a two-step process from the original starting dose of 1.5 mcg/kg/week, to 1 mcg/kg/week, then to 0.5 mcg/kg/week, if needed. Dose reduction in patients on PegIntron monotherapy is accomplished by reducing the original starting dose of 1 mcg/kg/week to 0.5 mcg/kg/week. Instructions for dose reductions in adults are outlined in **Tables 6** (Monotherapy: REDIPEN/Selectdose/Vial), **7** (Combination therapy: REDIPEN/Vial) and **8** (Combination therapy: Selectdose).

In the adult combination therapy Study 2, 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. In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination

with REBETOL, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events [see Adverse Reactions (6.1)].

Dose reduction in pediatric patients is accomplished by modifying the recommended dose in a 2-step process from the original starting dose of 60 mcg/m<sup>2</sup>/week, to 40 mcg/m<sup>2</sup>/week, then to 20 mcg/m<sup>2</sup>/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/m<sup>2</sup> 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* | Initial Management (4-8 weeks)   |   | Depression Status   |   |                                   |
|----------------------|--|---|---|---|-----------------------------------|
|                      | 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: Adjust Dose*<br>Pediatrics: Decrease dose to 40 mcg/m <sup>2</sup> /week, then to 20 mcg/m <sup>2</sup> /week, if needed | Evaluate once weekly (office visit at least every other week) | Consider psychiatric consultation.<br>Continue reduced dosing | If symptoms improve and are stable for 4 weeks, may resume normal visit schedule.<br>Continue reduced dosing or return to normal dose | See severe depression             |
| Severe               | Discontinue PegIntron/REBETOL permanently  | Obtain immediate psychiatric consultation                     | Psychiatric therapy as necessary                              |   |                                   |

\* See DSM-IV for definitions. For patients on PegIntron/REBETOL combination therapy: 1<sup>st</sup> dose reduction of PegIntron is to 1 mcg/kg/week, 2<sup>nd</sup> dose reduction (if needed) of PegIntron is to 0.5 mcg/kg/week. For patients on PegIntron monotherapy: decrease PegIntron dose to 0.5 mcg/kg/week.

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

| Laboratory Parameters                                     | Reduce PegIntron Dose (see note 1) if:  | Reduce ribavirin Daily Dose (see note 2) if: | Discontinue Therapy if:                                  |
|---|---|--|--|
| WBC   | 1.0 to <1.5 x 10 <sup>9</sup> /L  | N/A  | <1.0 x 10 <sup>9</sup> /L                                |
| Neutrophils   | 0.5 to <0.75 x 10 <sup>9</sup> /L   | N/A  | <0.5 x 10 <sup>9</sup> /L                                |
| Platelets   | 25 to <50 x 10 <sup>9</sup> /L (adults)                                       | N/A  | <25 x 10 <sup>9</sup> /L (adults)                        |
|   | 50 to <70 x 10 <sup>9</sup> /L (pediatrics)                                   | N/A  | <50 x 10 <sup>9</sup> /L (pediatrics)                    |
| Creatinine  | N/A   | N/A  | >2 mg/dL (pediatrics)                                    |
| Hemoglobin in patients without history of cardiac disease | N/A   | 8.5 to <10 g/dL                              | <8.5 g/dL  |
|   | <b>Reduce PegIntron Dose by Half and the Ribavirin Dose by 200 mg/day if:</b> |  |  |
| Hemoglobin in patients with history of cardiac disease*†  | ≥2 g/dL decrease in hemoglobin during any four week period during treatment   |  | <8.5 g/dL or <12 g/dL after four weeks of dose reduction |

Note 1: Adult patients on combination therapy: 1<sup>st</sup> dose reduction of PegIntron is to 1 mcg/kg/week. If needed, 2<sup>nd</sup> dose reduction of PegIntron is to 0.5 mcg/kg/week.

Adult patients on PegIntron monotherapy: decrease PegIntron dose to 0.5 mcg/kg/week.

Pediatric patients: 1<sup>st</sup> dose reduction of PegIntron is to 40 mcg/m<sup>2</sup>/week, 2<sup>nd</sup> dose reduction of PegIntron is to 20 mcg/m<sup>2</sup>/week.

Note 2: Adult patients: 1<sup>st</sup> dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1400 mg, dose reduction should be by 400 mg/day). If needed, 2<sup>nd</sup> dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

Pediatric patients: 1<sup>st</sup> dose reduction of ribavirin is to 12 mg/kg/day, 2<sup>nd</sup> dose reduction of ribavirin is to 8 mg/kg/day.

\* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron /REBETOL combination therapy [see Warnings and Precautions (5.3)].

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

| Body Weight<br>kg (lbs) | PegIntron<br>REDIPEN/Vial         |                                  |                                 | PegIntron Selectdose |                                  |                                 |
|-------------------------|-----------------------------------|----------------------------------|---------------------------------|----------------------|----------------------------------|---------------------------------|
|                         | Strength to Use                   | Amount to<br>Administer<br>(mcg) | Volume to<br>Administer<br>(mL) | Strength to Use      | Amount to<br>Administer<br>(mcg) | Volume to<br>Administer<br>(mL) |
| ≤45<br>(≤100)           | 50 mcg per<br>0.5 mL <sup>†</sup> | 20                               | 0.2                             | 50 mcg per<br>0.5 mL | 20                               | 0.2                             |
| 46-56<br>(101-124)      | 50 mcg per<br>0.5 mL <sup>†</sup> | 25                               | 0.25                            | 50 mcg per<br>0.5 mL | 25                               | 0.25                            |
| 57-72<br>(125-159)      | 50 mcg per<br>0.5 mL              | 30                               | 0.3                             | 80 mcg per<br>0.5 mL | 32                               | 0.2                             |
| 73-88<br>(160-195)      | 50 mcg per<br>0.5 mL              | 40                               | 0.4                             | 50 mcg per<br>0.5 mL | 40                               | 0.4                             |
| 89-106<br>(196-234)     | 50 mcg per<br>0.5 mL              | 50                               | 0.5                             | 50 mcg per<br>0.5 mL | 50                               | 0.5                             |
| 107-136<br>(235-300)    | 80 mcg per<br>0.5 mL              | 64                               | 0.4                             | 80 mcg per<br>0.5 mL | 64                               | 0.4                             |
| ≥137<br>(≥301)          | 80 mcg per<br>0.5 mL              | 80                               | 0.5                             | 80 mcg per<br>0.5 mL | 80                               | 0.5                             |

\* When reconstituted as directed.

<sup>†</sup> Must use vial. Minimum delivery for REDIPEN 0.3 mL.

**Table 7: Two-Step Dose Reduction of PegIntron REDIPEN/Vial in Combination Therapy in Adults**

| First Dose Reduction to PegIntron 1 mcg/kg |  |   |   | Second Dose Reduction to PegIntron 0.5 mcg/kg |   |  |   |
|--|--|---|---|---|---|--|---|
| Body weight<br>kg (lbs)                    | PegIntron<br>REDIPEN/Vial<br>Strength to Use | Amount of<br>PegIntron (mcg)<br>to Administer | Volume<br>(mL) <sup>†</sup> of<br>PegIntron<br>to<br>Administer | Body weight<br>kg (lbs)                       | PegIntron<br>REDIPEN/<br>Vial<br>Strength to<br>Use | Amount of<br>PegIntron<br>(mcg) to<br>Administer | Volume (mL) <sup>†</sup><br>of PegIntron to<br>Administer |
| <40<br>(<88)                               | 50 mcg per 0.5 mL                            | 35  | 0.35  | <40<br>(<88)                                  | 50 mcg per<br>0.5 mL*                               | 20   | 0.2   |
| 40-50<br>(88-111)                          |  | 45  | 0.45  | 40-50<br>(88-111)                             |   | 25   | 0.25  |
| 51-60<br>(112-133)                         |  | 50  | 0.5   | 51-60<br>(112-133)                            |   | 30   | 0.3   |
| 61-75<br>(134-166)                         | 80 mcg per 0.5 mL                            | 64  | 0.4   | 61-75<br>(134-166)                            | 50 mcg per<br>0.5 mL                                | 35   | 0.35  |
| 76-85<br>(167-187)                         |  | 80  | 0.5   | 76-85<br>(167-187)                            |   | 45   | 0.45  |
| 86-104<br>(188-230)                        | 120 mcg per 0.5 mL                           | 96  | 0.4   | 86-104<br>(188-230)                           | 80 mcg per<br>0.5 mL                                | 50   | 0.5   |
| 105-125<br>(231-275)                       |  | 108   | 0.45  | 105-125<br>(231-275)                          |   | 64   | 0.4   |
| >125<br>(>275)                             | 150 mcg per 0.5 mL                           | 135   | 0.45  | >125<br>(>275)                                | 72  | 0.45   |   |

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

<sup>†</sup> When reconstituted as directed.

**Table 8: Two-Step Dose Reduction of PegIntron Selectdose Pre-filled Pen in Combination Therapy in Adults**

| First Dose Reduction to PegIntron 1 mcg/kg |   |   |  | Second Dose Reduction to PegIntron 0.5 mcg/kg |   |   |  |
|--|---|---|--|---|---|---|--|
| Body Weight kg (lbs)                       | PegIntron Selectdose Pre-filled Pen Strength to Use | Amount of PegIntron to Administer (mcg) | Volume of PegIntron to Administer (mL) | Body Weight kg (lbs)                          | PegIntron Selectdose Pre-filled Pen Strength to Use | Amount of PegIntron to Administer (mcg) | Volume of PegIntron to Administer (mL) |
| <40 (<88)                                  | 50 mcg per 0.5 mL                                   | 35                                      | 0.35                                   | <40 (<88)                                     | 50 mcg per 0.5 mL                                   | 20                                      | 0.2                                    |
| 40-50 (88-111)                             | 120 mcg per 0.5 mL                                  | 48                                      | 0.2                                    | 40-50 (88-111)                                | 50 mcg per 0.5 mL                                   | 25                                      | 0.25                                   |
| 51-60 (112-133)                            | 50 mcg per 0.5 mL                                   | 50                                      | 0.5                                    | 51-60 (112-133)                               | 80 mcg per 0.5 mL                                   | 32                                      | 0.2                                    |
| 61-75 (134-166)                            | 80 mcg per 0.5 mL                                   | 64                                      | 0.4                                    | 61-75 (134-166)                               | 50 mcg per 0.5 mL                                   | 35                                      | 0.35                                   |
| 76-85 (167-187)                            | 80 mcg per 0.5 mL                                   | 80                                      | 0.5                                    | 76-85 (167-187)                               | 120 mcg per 0.5 mL                                  | 48                                      | 0.2                                    |
| 86-104 (188-230)                           | 120 mcg per 0.5 mL                                  | 96                                      | 0.4                                    | 86-104 (188-230)                              | 50 mcg per 0.5 mL                                   | 50                                      | 0.5                                    |
| 105-125 (231-275)                          | 150 mcg per 0.5 mL                                  | 105                                     | 0.35                                   | 105-125 (231-275)                             | 80 mcg per 0.5 mL                                   | 64                                      | 0.4                                    |
| >125 (>275)                                | *   | *                                       | *                                      | >125 (>275)                                   | *   | *                                       | *                                      |

\* For patients weighing greater than 125 kg (>275 pounds), the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

## 2.4 Discontinuation of Dosing

### Adults

See labeling of the specific HCV NS3/4A protease inhibitor for information regarding discontinuation of dosing based on treatment futility.

In HCV genotype 1, interferon-alfa-naïve patients receiving PegIntron, alone or in combination with REBETOL, discontinuation of therapy is recommended if there is not at least a 2 log<sub>10</sub> drop or loss of HCV-RNA at 12 weeks of therapy, or if 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 is recommended.

### 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 less than 2 log<sub>10</sub> 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 less than 50 mL/min.

## 2.6 Preparation and Administration

A patient should self-inject PegIntron only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and has been trained in proper injection technique [see *illustrated FDA-approved Medication Guide and Instructions for Use for directions on injection site preparation and injection instructions*].

The reconstituted solution should be visually inspected for discoloration and particulate matter prior to administration. Do not use the solution if it is discolored or not clear, or if particulates are present.

**DO NOT REUSE THE VIAL OR PRE-FILLED PEN; 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.
- REDIPEN® single-use pre-filled pen: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL.
- Selectdose™ single-use pre-filled pen: 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 greater than 6 [class B and C]) in cirrhotic CHC patients before or during treatment

PegIntron/ribavirin combination therapy is additionally contraindicated in:

- women who are pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. Ribavirin is contraindicated in women who are or may become pregnant. If ribavirin is used during pregnancy, or if the patient becomes pregnant while taking ribavirin, the patient should be apprised of the potential hazard to her 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 less than 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

**Ribavirin may cause birth defects and death of the unborn child. Ribavirin 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 2 forms of contraception and have monthly pregnancy tests during treatment and during the 6-month period after treatment has been stopped [see *Contraindications (4)* and *ribavirin labeling*].**

#### Anemia

Ribavirin caused hemolytic anemia in 10% of PegIntron/REBETOL-treated subjects within 1 to 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 ribavirin therapy may result in a worsening of cardiac disease. Decrease in dosage or discontinuation of ribavirin may be necessary [see *Dosage and Administration (2.3)* and *ribavirin labeling*].

### 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 caution in patients with a history of psychiatric disorders. Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is initiated in patients with prior history or existence of psychiatric condition or with a history of substance use disorders, treatment considerations should include the need for drug screening and periodic health evaluation, including psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance use is recommended.

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 *Warnings and Precautions (5.15)*]. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron/ribavirin combination therapy [see *ribavirin labeling*].

### 5.4 Endocrine Disorders

PegIntron causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with PegIntron. Diabetes mellitus, including cases of new onset Type 1 diabetes, has been observed in patients treated with alpha interferons, including PegIntron. 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, papilledema, and serous retinal detachment 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 alfa-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 alfa-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) has been observed in patients receiving PegIntron.

PegIntron should be used with caution in patients with autoimmune disorders.

### 5.9 Pancreatitis

Fatal and nonfatal pancreatitis has 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. The colitis usually resolves within 1 to 3 weeks of discontinuation of alpha interferons.

### 5.11 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, 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.

Because of the fever and other "flu-like" symptoms associated with PegIntron administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease).

### 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 co-infected 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 greater than 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 less than 50 mL/min; the potential risks should be weighed against the potential benefits in these patients. Combination therapy with ribavirin must not be used in patients with creatinine clearance less than 50 mL/min [see *ribavirin labeling*].

### 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 were 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, complete blood counts (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, and 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 (2.1, 2.2, 2.4)*].

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

### 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 greater than 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 trial in 107 subjects, 3 through 17 years of age, in which weight and height changes are compared to US 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. Severely inhibited growth velocity (less than 3<sup>rd</sup> percentile) was observed in 70% of the subjects while on treatment. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that PegIntron in combination therapy with REBETOL may induce a growth inhibition that results in reduced adult height in some patients [see *Adverse Reactions (6.1)*].

### 5.19 Peripheral Neuropathy

Peripheral neuropathy has been reported when alpha interferons were given in combination with te bividine. In one clinical trial, an increased risk and severity of peripheral neuropathy was observed with the combination use of telbivudine and pegylated interferon alfa-2a as compared to telbivudine alone. The safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated.

## 6 ADVERSE REACTIONS

### 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.

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 *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, 5.3)], 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.

#### 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 clinical trials, nearly all subjects experienced one or more adverse reactions. Study 3 compared a PegIntron/weight-based REBETOL combination to a PegIntron/flat dose REBETOL regimen. Study 4 compared two PegIntron (1.5 mcg/kg/week and 1 mcg/kg/week) doses in combination with REBETOL and a third treatment group receiving Pegasys® (180 mcg/week)/Copegus® (1000-1200 mg/day).

Adverse reactions that occurred in Studies 1 and 2 at greater than 5% incidence are provided in **Table 9** by treatment group. Due to potential differences in ascertainment procedures, adverse reaction rate comparisons across trials should not be made. **Table 10** summarizes the treatment-related adverse reactions in Study 4 that occurred at a greater than or equal to 10% incidence.

**Table 9: Adverse Reactions Occurring in Greater than 5% of Subjects**

| Adverse Reactions                            | Percentage of Subjects Reporting Adverse Reactions* |                              |  |                                 |
|--|---|------------------------------|--|---------------------------------|
|  | Study 1   |                              | Study 2  |                                 |
|  | PegIntron<br>1 mcg/kg<br>(N=297)                    | INTRON A<br>3 MIU<br>(N=303) | PegIntron<br>1.5 mcg/kg/<br>REBETOL<br>(N=511) | INTRON A/<br>REBETOL<br>(N=505) |
| <b>Application Site</b>                      |   |                              |  |                                 |
| Injection Site<br>Inflammation/Reaction      | 47  | 20                           | 75   | 49                              |
| <b>Autonomic Nervous<br/>System</b>          |   |                              |  |                                 |
| Dry Mouth                                    | 6   | 7                            | 12   | 8                               |
| Increased Sweating                           | 6   | 7                            | 11   | 7                               |
| Flushing                                     | 6   | 3                            | 4  | 3                               |
| <b>Body as a Whole</b>                       |   |                              |  |                                 |
| 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<br>Pain                 | 8   | 8                            | 12   | 6                               |
| Chest Pain                                   | 6   | 4                            | 8  | 7                               |
| Malaise                                      | 7   | 6                            | 4  | 6                               |
| <b>Central/Peripheral<br/>Nervous System</b> |   |                              |  |                                 |
| Dizziness                                    | 12  | 10                           | 21   | 17                              |
| <b>Endocrine</b>                             |   |                              |  |                                 |
| Hypothyroidism                               | 5   | 3                            | 5  | 4                               |
| <b>Gastrointestinal</b>                      |   |                              |  |                                 |
| 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                               |
| <b>Hematologic Disorders</b>                 |   |                              |  |                                 |
| Neutropenia                                  | 6   | 2                            | 26   | 14                              |

| Percentage of Subjects Reporting Adverse Reactions* |                                  |                              |  |                                 |
|---|----------------------------------|------------------------------|--|---------------------------------|
| Adverse Reactions                                   | Study 1                          |                              | Study 2  |                                 |
|   | PegIntron<br>1 mcg/kg<br>(N=297) | INTRON A<br>3 MIU<br>(N=303) | PegIntron<br>1.5 mcg/kg/<br>REBETOL<br>(N=511) | INTRON A/<br>REBETOL<br>(N=505) |
| Anemia  | 0                                | 0                            | 12   | 17                              |
| Leukopenia  | <1                               | 0                            | 6  | 5                               |
| Thrombocytopenia                                    | 7                                | <1                           | 5  | 2                               |
| <b>Liver and Biliary System</b>                     |                                  |                              |  |                                 |
| Hepatomegaly  | 6                                | 5                            | 4  | 4                               |
| <b>Musculoskeletal</b>                              |                                  |                              |  |                                 |
| Myalgia   | 54                               | 53                           | 56   | 50                              |
| Arthralgia  | 23                               | 27                           | 34   | 28                              |
| Musculoskeletal Pain                                | 28                               | 22                           | 21   | 19                              |
| <b>Psychiatric</b>                                  |                                  |                              |  |                                 |
| 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                               |
| <b>Reproductive, Female</b>                         |                                  |                              |  |                                 |
| Menstrual Disorder                                  | 4                                | 3                            | 7  | 6                               |
| <b>Resistance Mechanism</b>                         |                                  |                              |  |                                 |
| Viral Infection                                     | 11                               | 10                           | 12   | 12                              |
| Fungal Infection                                    | <1                               | 3                            | 6  | 1                               |
| <b>Respiratory System</b>                           |                                  |                              |  |                                 |
| 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                               |
| <b>Skin and Appendages</b>                          |                                  |                              |  |                                 |
| Alopecia  | 22                               | 22                           | 36   | 32                              |
| Pruritus  | 12                               | 8                            | 29   | 28                              |
| Rash  | 6                                | 7                            | 24   | 23                              |
| Skin Dry  | 11                               | 9                            | 24   | 23                              |
| <b>Special Senses, Other</b>                        |                                  |                              |  |                                 |
| Taste Perversion                                    | <1                               | 2                            | 9  | 4                               |
| <b>Vision Disorders</b>                             |                                  |                              |  |                                 |
| 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.

**Table 10: Treatment-Related Adverse Reactions (Greater than or Equal to 10% Incidence)  
By Descending Frequency**

*Percentage of Subjects Reporting Treatment-Related Adverse Reactions*

**Study 4**

| Adverse Reactions        | PegIntron<br>1.5 mcg/kg with<br>REBETOL | PegIntron<br>1 mcg/kg with<br>REBETOL | Pegasys 180 mcg<br>with Copegus |
|--------------------------|---|---------------------------------------|---------------------------------|
|                          | (N=1019)                                | (N=1016)                              | (N=1035)                        |
| Fatigue                  | 67                                      | 68                                    | 64                              |
| Headache                 | 50                                      | 47                                    | 41                              |
| Nausea                   | 40                                      | 35                                    | 34                              |
| Chills                   | 39                                      | 36                                    | 23                              |
| Insomnia                 | 38                                      | 37                                    | 41                              |
| Anemia                   | 35                                      | 30                                    | 34                              |
| Pyrexia                  | 35                                      | 32                                    | 21                              |
| Injection Site Reactions | 34                                      | 35                                    | 23                              |
| Anorexia                 | 29                                      | 25                                    | 21                              |
| Rash                     | 29                                      | 25                                    | 34                              |
| Myalgia                  | 27                                      | 26                                    | 22                              |
| Neutropenia              | 26                                      | 19                                    | 31                              |
| Irritability             | 25                                      | 25                                    | 25                              |
| Depression               | 25                                      | 19                                    | 20                              |
| Alopecia                 | 23                                      | 20                                    | 17                              |
| Dyspnea                  | 21                                      | 20                                    | 22                              |
| Arthralgia               | 21                                      | 22                                    | 22                              |
| Pruritus                 | 18                                      | 15                                    | 19                              |
| Influenza-like Illness   | 16                                      | 15                                    | 15                              |
| Dizziness                | 16                                      | 14                                    | 13                              |
| Diarrhea                 | 15                                      | 16                                    | 14                              |
| Cough                    | 15                                      | 16                                    | 17                              |
| Weight Decreased         | 13                                      | 10                                    | 10                              |
| Vomiting                 | 12                                      | 10                                    | 9                               |
| Unspecified Pain         | 12                                      | 13                                    | 9                               |
| Dry Skin                 | 11                                      | 11                                    | 12                              |
| Anxiety                  | 11                                      | 11                                    | 10                              |
| Abdominal Pain           | 10                                      | 10                                    | 10                              |
| Leukopenia               | 9                                       | 7                                     | 10                              |

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 trials. In the PegIntron 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 for 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 31 subject deaths that occurred during treatment or during follow-up in these clinical trials. In Study 1, there was 1 suicide in a subject receiving PegIntron monotherapy and 2 deaths among subjects receiving INTRON A monotherapy (1 murder/suicide and 1 sudden death). In Study 2, there was 1 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 1 was an unexplained death in a person with a relevant medical history of depression. In Study 4, there were 12 deaths, 6 of which occurred in subjects receiving PegIntron/REBETOL combination therapy; 5 in the PegIntron 1.5 mcg/REBETOL arm (N=1019) and 1 in the PegIntron 1 mcg/REBETOL arm (n=1016); and 6 of which occurred in subjects receiving Pegasys/Copegus (N=1035). There were 3 suicides that occurred during the off-treatment follow-up period in subjects who received PegIntron (1.5 mcg/kg)/REBETOL combination therapy.

In Studies 1 and 2, 10% to 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 4, 13% of subjects in the PegIntron 1.5 mcg/REBETOL arm, 10% in the PegIntron 1 mcg/REBETOL arm, and 13% in the Pegasys 180 mcg/Copegus arm discontinued therapy due to adverse events.

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 more than PegIntron 0.5 mcg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose reduction for REBETOL was similar across all three groups, 33% to 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 weight-based dosing (WBD) compared to flat dosing (29% and 23%, respectively). In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with REBETOL, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events, compared to 15% of subjects in the Pegasys/Copegus arm, who required a dose reduction to 135 mcg/week with Pegasys, with an additional 7% requiring a second dose reduction to 90 mcg/week with Pegasys.

In the PegIntron/REBETOL combination trials the most common adverse reactions were psychiatric, which occurred among 77% of subjects in Study 2 and 68% to 69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30% to 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)]. In Study 4, psychiatric adverse reactions occurred in 58% of subjects in the PegIntron 1.5 mcg/REBETOL arm, 55% of subjects in the PegIntron 1 mcg/REBETOL arm, and 57% of subjects in the Pegasys 180 mcg/Copegus arm.

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) tended to decrease as treatment continued. 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% to 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% to 15% of subjects, weight loss, fatigue, and headache had not resolved.

Individual serious adverse reactions in Study 2 occurred at a frequency less than or equal to 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 re-treatment 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 trial, 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 trial 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; three with clinical hypothyroidism and two with asymptomatic TSH elevations. Weight and height gain of pediatric subjects treated with PegIntron plus REBETOL lagged behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment.

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

Adverse reactions that occurred with a greater than or equal to 10% incidence in the pediatric trial subjects are provided in **Table 11**.

**Table 11: Percentage of Pediatric Subjects with Treatment-related Adverse Reactions (in At Least 10% of All Subjects)**

| System Organ Class<br>Preferred Term | All Subjects<br>N=107 |
|--------------------------------------|-----------------------|
|--------------------------------------|-----------------------|

| <b>Blood and Lymphatic System Disorders</b>                 |     |
|---|-----|
| Neutropenia   | 33% |
| Anemia  | 11% |
| Leukopenia  | 10% |
| <b>Gastrointestinal Disorders</b>                           |     |
| Abdominal Pain  | 21% |
| Abdominal Pain Upper  | 12% |
| Vomiting  | 27% |
| Nausea  | 18% |
| <b>General Disorders and Administration Site Conditions</b> |     |
| Pyrexia   | 80% |
| Fatigue   | 30% |
| Injection-site Erythema                                     | 29% |
| Chills  | 21% |
| Asthenia  | 15% |
| Irritability  | 14% |
| <b>Investigations</b>                                       |     |
| Weight Decreased  | 19% |
| <b>Metabolism and Nutrition Disorders</b>                   |     |
| Anorexia  | 29% |
| Decreased Appetite  | 22% |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |     |
| Arthralgia  | 17% |
| Myalgia   | 17% |
| <b>Nervous System Disorders</b>                             |     |
| Headache  | 62% |
| Dizziness   | 14% |
| <b>Skin and Subcutaneous Tissue Disorders</b>               |     |
| Alopecia  | 17% |

Ninety-four of 107 subjects enrolled in a 5 year long-term follow-up trial. The long-term effects on growth were less in those subjects treated for 24 weeks than those treated for 48 weeks. Twenty-four percent of subjects (11/46) treated for 24 weeks and 40% of subjects (19/48) treated for 48 weeks had a >15 percentile height-for-age decrease from pre-treatment to the end of the 5 year long-term follow-up compared to pre-treatment baseline percentiles. Eleven percent of subjects (5/46) treated for 24 weeks and 13% of subjects (6/48) treated for 48 weeks were observed to have a decrease from pre-treatment baseline of >30 height-for-age percentiles to the end of the 5 year long-term follow-up. While observed across all age groups, the highest risk for reduced height at the end of long-term follow-up appeared to correlate with initiation of combination therapy during the years of expected peak growth velocity [see *Warnings and Precautions* (5.18)].

#### 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, 5.7)].

**Hemoglobin.** Hemoglobin levels decreased to less than 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 less than 11 g/dL. Reductions in hemoglobin to less than 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. In Study 4, subjects receiving PegIntron (1.5 mcg/kg)/REBETOL had decreases in hemoglobin levels to between 8.5 to less than 10 g/dL (28%) and to less than 8.5 g/dL (3%), whereas in subjects receiving Pegasys 180 mcg/Copegus these decreases occurred in 26% and 4% of subjects, respectively. Hemoglobin levels became stable by treatment Weeks 4 to 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 (less than  $0.5 \times 10^9/L$ ) 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 (less than 1%) required permanent discontinuation of treatment. Neutrophil counts generally returned to pretreatment levels 4 weeks after cessation of therapy [see *Dosage and Administration* (2.3)].

**Platelets.** Platelet counts decreased to less than  $100,000/mm^3$  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 (less than  $50,000/mm^3$ ) occur in less than 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 or without clinical manifestations, is associated with interferon therapies. In Study 2, clinically apparent thyroid disorders occurred 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% to 14% of subjects developed hyperbilirubinemia and 33% to 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 12**. Most of the changes in laboratory values in this trial were mild or moderate.

**Table 12: Selected Laboratory Abnormalities during Treatment Phase with PegIntron Plus REBETOL in Previously Untreated Pediatric Subjects**

| Laboratory Parameter*                   | All Subjects (N=107) |
|---|----------------------|
| <b>Hemoglobin (g/dL)</b>                |                      |
| 9.5 to <11.0                            | 30%                  |
| 8.0 to <9.5                             | 2%                   |
| <b>WBC (x 10<sup>9</sup>/L)</b>         |                      |
| 2.0-2.9                                 | 39%                  |
| 1.5 to <2.0                             | 3%                   |
| <b>Platelets (x 10<sup>9</sup>/L)</b>   |                      |
| 70-100                                  | 1%                   |
| 50 to <70                               | —                    |
| 25 to <50                               | 1%                   |
| <b>Neutrophils (x 10<sup>9</sup>/L)</b> |                      |
| 1.0-1.5                                 | 35%                  |
| 0.75 to <1.0                            | 26%                  |
| 0.5 to <0.75                            | 13%                  |
| <0.5                                    | 3%                   |
| <b>Total Bilirubin</b>                  |                      |
| 1.26-2.59 x ULN <sup>†</sup>            | 7%                   |
| Evidence of Hepatic Failure             | —                    |

\* 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.

<sup>†</sup> ULN=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 (less than or equal to 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. 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.

##### *Blood and Lymphatic System Disorders*

Pure red cell aplasia, thrombotic thrombocytopenic purpura

##### *Cardiac Disorders*

Palpitations

##### *Ear and Labyrinth Disorders*

Hearing loss, vertigo, hearing impairment

##### *Endocrine Disorders*

Diabetic ketoacidosis, diabetes

##### *Eye Disorders*

Vogt-Koyanagi-Harada syndrome, serous retinal detachment

##### *Gastrointestinal Disorders*

Aphthous stomatitis

##### *General Disorders and Administration Site Conditions*

Asthenic conditions (including asthenia, malaise, fatigue)

##### *Immune System Disorders*

Cases of acute hypersensitivity reactions (including anaphylaxis, angioedema, urticaria); Stevens-Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, erythema multiforme

##### *Infections and Infestations*

Bacterial infection including sepsis

#### *Metabolism and Nutrition Disorders*

Dehydration, hypertriglyceridemia

#### *Musculoskeletal and Connective Tissue Disorders*

Rhabdomyolysis, myositis

#### *Nervous System Disorders*

Seizures, memory loss, peripheral neuropathy, paraesthesia, migraine headache

#### *Psychiatric Disorders*

Homicidal ideation

#### *Respiratory, Thoracic, and Mediastinal Disorders*

Pulmonary hypertension

#### *Renal and Urinary Disorders*

Renal failure, renal insufficiency

#### *Skin and Subcutaneous Tissue Disorders*

Psoriasis

#### *Vascular Disorders*

Hypertension, hypotension

## 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 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 *labeling for individual NRTI product*]. 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 greater than 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 trial 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 co-infected 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 less than 500) and severe anemia (hemoglobin less than 8 g/dL) more frequently than similar subjects not receiving zidovudine.

#### Didanosine

Co-administration of ribavirin 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: Nonpegylated 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 trials 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. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant [see *Contraindications* (4) and *ribavirin labeling*].

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 ribavirin 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 ribavirin 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 subjects less than 3 years of age are not considered feasible due to the small proportion of patients in this age group requiring treatment for CHC.

Long-term follow-up data in pediatric subjects indicates that PegIntron in combination with REBETOL may induce a growth inhibition that results in reduced height in some patients [see *Warnings and Precautions* (5.18) and *Adverse Reactions* (6.1)].

### 8.5 Geriatric Use

In general, younger patients tend to respond better than older patients to interferon-based therapies. Clinical trials of PegIntron alone or in combination with REBETOL did not include sufficient numbers of subjects aged 65 and over 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/ r baviirin therapy, refer also to the ribavirin labeling.

### 8.6 Organ Transplant Recipients

The safety and efficacy of PegIntron alone or in combination with ribavirin 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 Co-infection

The safety and efficacy of PegIntron/ ribavirin 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 trials, 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 r baviirin 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, 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  $0.7 \times 10^8$  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 vials and REDIPEN and Selectdose single-use pre-filled pens 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 reconstitution 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, 120 mcg per 0.5 mL, or 150 mcg per 0.5 mL.

### REDIPEN and Selectdose single-use pre-filled pens

REDIPEN and Selectdose pre-filled pens are 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 pre-filled pen 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 pre-filled pen 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 pre-filled pen 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 *Microbiology (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 and 44 hours postdose, and are sustained for up to 48 to 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 22-60 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 nonpegylated 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 4 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 labeling*]. REBETOL should not be used in patients with creatinine clearance less than 50 mL/min [see *REBETOL labeling, 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 and older) 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 (28-44 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/m<sup>2</sup>/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 trial of REBETOL in combination with INTRON A in pediatric subjects and in adults.

#### Effect of Food on Absorption of Ribavirin

Both  $AUC_{0-24}$  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 trial [see *Dosage and Administration (2.1)*].

#### 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 greater than or equal to 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 trial 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 co-infected 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)*].

## **12.4 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 1 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 ( $EC_{50}$ ) value of 1 to 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/nonpegylated interferons and ribavirin.

## **12.5 Pharmacogenomics**

A retrospective genome-wide association analysis<sup>1,2</sup> of 1671 subjects (1604 subjects from Study 4 [see *Clinical Studies (14.1)*] and 67 subjects from another clinical trial) was performed to identify human genetic contributions to anti-HCV treatment response in previously untreated HCV genotype 1 subjects. A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (*IL28B rs12979860*) was associated with variable SVR rates.

The *rs12979860* genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1587), SVR rates by *rs12979860* genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to *IL28B* genotype was consistent across various racial/ethnic groups (see **Table 13**). Other variants near the *IL28B* gene (e.g., *rs8099917* and *rs8103142*) have been identified; however, they have not been shown to independently influence SVR rates during treatment with pegylated interferon alpha therapies combined with r bavinir.<sup>1</sup>

**Table 13: SVR Rates by *IL28B* Genotype\***

| Population       | CC            | CT            | TT           |
|------------------|---------------|---------------|--------------|
| Caucasian        | 69% (301/436) | 33% (196/596) | 27% (38/139) |
| African-American | 48% (20/42)   | 15% (22/146)  | 13% (15/112) |
| Hispanic         | 56% (19/34)   | 38% (21/56)   | 27% (7/26)   |

\* The SVR rates are the overall rates for subjects treated with PegIntron 1.0 mcg/kg/REBETOL, PegIntron 1.5 mcg/kg/REBETOL and Pegasys 180 mcg/Copegus according to self-reported race/ethnicity.

## 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:** See ribavirin labeling for additional warnings relevant to PegIntron therapy in combination with r bavinir.

#### Impairment of Fertility

PegIntron may impair human fertility. Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 mcg/m<sup>2</sup> PegIntron alone every other day for 1 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/m<sup>2</sup> (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 trial compared treatment with PegIntron (0.5, 1, or 1.5 mcg/kg once weekly subcutaneously) to treatment with INTRON A (3 million units 3 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 post-treatment.

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 post-treatment. 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 14**).

**Table 14: Rates of Response to Treatment – Study 1**

|   | A<br>PegIntron<br>0.5 mcg/kg<br>(N=315) | B<br>PegIntron<br>1 mcg/kg<br>(N=298) | C<br>INTRON A<br>3 MIU three<br>times weekly<br>(N=307) | B - C (95% CI)<br>Difference<br>between<br>PegIntron<br>1 mcg/kg and<br>INTRON A |
|---|---|---------------------------------------|---|--|
| Treatment Response<br>(Combined Virologic<br>Response and ALT<br>Normalization) | 17%                                     | 24%                                   | 12%   | 11 (5, 18)   |
| Virologic Response*   | 18%                                     | 25%                                   | 12%   | 12 (6, 19)   |
| ALT Normalization   | 24%                                     | 29%                                   | 18%   | 11 (5, 18)   |

\* 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 respond 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 (2.1)*].

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 4 treatment groups was observed.

#### *PegIntron/REBETOL Combination Therapy — Study 2*

A randomized trial 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 thrice weekly/REBETOL 1000 or 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 post-treatment. 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 post-treatment. The response rate to the PegIntron 1.5 mcg/kg plus REBETOL 800 mg dose was higher than the response rate to INTRON A/REBETOL (see **Table 15**). 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 15: 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 *† | 52% (264/511)   | 46% (231/505)  |
| Genotype 1          | 41% (141/348)   | 33% (112/343)  |
| Genotype 2-6        | 75% (123/163)   | 73% (119/162)  |

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

† Difference 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 post-treatment.

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 trial.

Liver biopsies were obtained before and after treatment in 68% of subjects. Compared to baseline, approximately two-thirds 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 trial, 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 to 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 post-treatment.

Treatment with PegIntron 1.5 mcg/kg and REBETOL 800 to 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 greater than 105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing greater than 85 to 105 kg (see **Table 16**). The benefit of WBD in subjects weighing greater than 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 16: SVR Rates by Treatment and Baseline Weight – Study 3**

| Treatment Group | Subject Baseline Weight |                      |                          |                   |
|-----------------|-------------------------|----------------------|--------------------------|-------------------|
|                 | <65 kg (<143 lb)        | 65-85 kg (143-188 b) | >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 greater than 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 — Study 4

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/REBETOL regimens [PegIntron 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with REBETOL 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg

subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3070 treatment-naïve adults with chronic hepatitis C genotype 1. In this trial, lack of early virologic response (undetectable HCV-RNA or greater than or equal to 2 log<sub>10</sub> reduction from baseline) by treatment Week 12 was the criterion for discontinuation of treatment. SVR was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks post-treatment (see **Table 17**).

**Table 17: SVR Rates by Treatment – Study 4**

|     | <b>PegIntron 1.5 mcg/kg/<br/>REBETOL</b> | <b>PegIntron 1 mcg/kg/<br/>REBETOL</b> | <b>Pegasys<br/>180 mcg/Copegus</b> |
|-----|--|--|------------------------------------|
| SVR | 40% (406/1019)                           | 38% (386/1016)                         | 41% (423/1035)                     |

Overall SVR rates were similar among the three treatment groups. Regardless of treatment group, SVR rates were lower in subjects with poor prognostic factors. Subjects with poor prognostic factors randomized to PegIntron (1.5 mcg/kg)/REBETOL or Pegasys/Copegus, however, achieved higher SVR rates compared to similar subjects randomized to PegIntron 1 mcg/kg/REBETOL. For the PegIntron 1.5 mcg/kg plus REBETOL dose, SVR rates for subjects with and without the following prognostic factors were as follows: cirrhosis (10% vs. 42%), normal ALT levels (32% vs. 42%), baseline viral load greater than 600,000 IU/mL (35% vs. 61%), 40 years of age and older (38% vs. 50%), and African American race (23% vs. 44%). In subjects with undetectable HCV-RNA at Week 12 who received PegIntron (1.5 mcg/kg)/REBETOL, the SVR rate was 81% (328/407).

***PegIntron/REBETOL Combination Therapy in Prior Treatment Failures — Study 5***

In a noncomparative trial, 2293 subjects with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/r bavinir were re-treated with PegIntron, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible subjects included prior nonresponders (subjects who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (subjects who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after post-treatment follow-up). Subjects who were negative at Week 12 were treated for 48 weeks and followed for 24 weeks post-treatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (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). Subjects with the following characteristics were less likely to benefit from re-treatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The re-treatment sustained virologic response rates by baseline characteristics are summarized in **Table 18**.

**Table 18: SVR Rates by Baseline Characteristics of Prior Treatment Failures**

| HCV<br>Genotype/<br>Metavir<br>Fibrosis<br>Score | Overall SVR by Previous Response and Treatment      |   |   |   |
|--|---|---|---|---|
|  | Nonresponder  |   | Relapser  |   |
|  | alfa interferon/ribavirin<br>% (number of subjects) | peginterferon (2a and 2b<br>combined)/r bavinir<br>% (number of subjects) | alfa interferon/ribavirin<br>% (number of subjects) | peginterferon (2a and 2b<br>combined)/r bavinir<br>% (number of subjects) |
| 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 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 Trial***

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/m<sup>2</sup> 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 which 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 greater than or equal to 600,000 IU/mL received 48 weeks of therapy while those infected with genotype 2 or genotype 3 with HCV-RNA less than 600,000 IU/mL received 24 weeks of therapy. The trial results are summarized in **Table 19**.

**Table 19: SVR Rates by Genotype and Treatment Duration – Pediatric Trial**

|          | All Subjects<br>N=107         |                               |
|----------|-------------------------------|-------------------------------|
|          | 24 Weeks                      | 48 Weeks                      |
|          | Virologic Response<br>N*† (%) | Virologic Response<br>N*† (%) |
| Genotype |                               |                               |

|                |              |              |
|----------------|--------------|--------------|
| All            | 26/27 (96.3) | 44/80 (55.0) |
| 1              | —            | 38/72 (52.8) |
| 2              | 14/15 (93.3) | —            |
| 3 <sup>†</sup> | 12/12 (100)  | 2/3 (66.7)   |
| 4              | —            | 4/5 (80.0)   |

\* Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.

<sup>†</sup> N = number of responders/number of subjects with given genotype, and assigned treatment duration.

<sup>‡</sup> Subjects with genotype 3 low viral load (less than 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.

## 15 REFERENCES

1. Ge, D., Fellay, J., Thompson, A.J., Simon, J.S., Shianna, K.V., Urban, T.J., Heinzen, E.L., Qiu, P., Bertelsen, A.H., Muir, A.J., Su kowski, M., McHutchison, J.G., Goldstein, D.B., Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance, *Nature* 2009;461(7262):399-401.
2. Thompson, A.J., Muir, A.J., Sulkowski, M.S., Ge, D., Fellay, J., Shianna, K.V., Urban, T., Afdhal, N.H., Jacobson, I.M., Esteban, R., Poordad, F., Lawitz, E.J., McCone, J., Shiffman, M.L., Galler, G.W., Lee, W.M., Reindollar, R., King, J.W., Kwo, P.Y., Ghalib, R.H., Freilich, B., Nyberg, L.M., Zeuzem, S., Poynard, T., Vock, D.M., Pieper, K.S., Patel, K., Tillmann, H.L., Noviello, S., Koury, K., Pedicone, L.D., Brass, C.A., Albrecht, J.K., Goldstein, D.B., McHutchison, J.G., Interlukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus, *Gastroenterology* 2010;139:120-129.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### PegIntron REDIPEN

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

|  |                    |
|--|--------------------|
| <b>Each PegIntron REDIPEN PAK 4 Contains:</b>  |                    |
| A box containing four 50 mcg per 0.5 mL PegIntron REDIPEN Units, each containing 1 BD 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 BD 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 BD 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 BD needle and 2 alcohol swabs. | (NDC 0085-1370-02) |

### PegIntron Selectdose single-use pre-filled pen

|  |                  |
|--|------------------|
| <b>Each PegIntron Selectdose Package Contains:</b>   |                  |
| A box containing one 50 mcg per 0.5 mL PegIntron Selectdose and 1 push-on needle and 2 alcohol swabs.  | NDC 0085-1902-01 |
| A box containing one 80 mcg per 0.5 mL PegIntron Selectdose and 1 push-on needle and 2 alcohol swabs.  | NDC 0085-1903-01 |
| A box containing one 120 mcg per 0.5 mL PegIntron Selectdose and 1 push-on needle and 2 alcohol swabs. | NDC 0085-1904-01 |

|  |                  |
|--|------------------|
| A box containing one 150 mcg per 0.5 mL PegIntron Selectdose and 1 push-on needle and 2 alcohol swabs. | NDC 0085-1905-01 |
|--|------------------|

|  |                  |
|--|------------------|
| <b>Each PegIntron Selectdose PAK 4 Contains:</b>   |                  |
| A box containing four 50 mcg per 0.5 mL PegIntron Selectdose units, each containing 1 push-on needle and 2 alcohol swabs.  | NDC 0085-1902-04 |
| A box containing four 80 mcg per 0.5 mL PegIntron Selectdose units, each containing 1 push-on needle and 2 alcohol swabs.  | NDC 0085-1903-04 |
| A box containing four 120 mcg per 0.5 mL PegIntron Selectdose units, each containing 1 push-on needle and 2 alcohol swabs. | NDC 0085-1904-04 |
| A box containing four 150 mcg per 0.5 mL PegIntron Selectdose units, each containing 1 push-on needle and 2 alcohol swabs. | NDC 0085-1905-04 |

#### PegIntron Vials

|  |                    |
|--|--------------------|
| <b>Each PegIntron Package Contains:</b>  |                    |
| 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 BD 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 BD 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 BD 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 BD Safety Lok syringes with a safety sleeve and 2 alcohol swabs. | (NDC 0085-1279-01) |

#### Storage

##### *PegIntron single-use pre-filled pens*

PegIntron pre-filled pens 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. Keep away from heat.**

##### *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, and is clear and colorless. **DO NOT FREEZE. Keep away from heat.**

#### Disposal Instructions

Patients should be thoroughly instructed in the importance of proper disposal. After preparation and administration of PegIntron for Injection, patients should be advised to use a puncture-resistant container for the disposal of used syringes, needles, and the pre-filled pens. 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 pre-filled pens.

#### 17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)

A patient should self-inject PegIntron only if it has been determined that it is appropriate, the patient agrees to medical follow-up as necessary, and training in proper injection technique has been given to him/her.

#### Pregnancy

Patients must be informed that REBETOL (r bavinir) 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/r bavinir therapy and for 6 months post-therapy. Combination PegIntron/ribavirin 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 post-therapy [see *Contraindications (4), Use in Specific Populations (8.1), and ribavirin labeling*].

### 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.

### 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.

Patients developing fever, cough, shortness of breath or other symptoms of a lung problem during treatment with PegIntron may need to have a chest X-ray or other tests to adequately treat them.

### Instructions for Use

Patients receiving PegIntron should be directed in its appropriate preparation, handling, measurement, and injection, and referred to the Instructions for Use for PegIntron Powder for Solution, PegIntron REDIPEN Single-use Pre-filled pen and Selectdose Single-use Pre-filled pen.

Patients should be directed to store PegIntron before mixing as follows:

- PegIntron pre-filled pens: store in the refrigerator between 36-46°F (2-8°C)
- PegIntron Powder for Solution: store at room temperature between 59-86°F (15-30°C)

Patients should be instructed on the importance of site selection for self-administering the injection, as well as the importance on rotating the injection sites.

Manufactured by: Schering Corporation, a subsidiary of  
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: [www.merck.com/product/patent/home.html](http://www.merck.com/product/patent/home.html)

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**MEDICATION GUIDE**  
**PegIntron®** (peg-In-tron)  
(Peginterferon alfa-2b)  
for injection, for subcutaneous use

Read this Medication Guide before you start taking PegIntron®, and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**If you are taking PegIntron with REBETOL (ribavirin) with or without an approved hepatitis C virus (HCV) protease inhibitor, also read the Medication Guides for those medicines.**

PegIntron, by itself or in combination with other approved medicines, is a treatment for some people who are infected with hepatitis C virus.

**What is the most important information I should know about PegIntron?**

**PegIntron can cause serious side effects that:**

- **may cause death, or**
- **may worsen certain serious diseases that you may already have.**

**Tell your healthcare provider right away if you have any of the symptoms listed below while taking PegIntron. If symptoms get worse, or become severe and continue, your healthcare provider may tell you to stop taking PegIntron permanently. In many, but not all, people, these symptoms go away after they stop taking PegIntron.**

- 1. Mental health problems and suicide.** PegIntron may cause you to develop mood or behavior problems that may get worse during treatment with PegIntron or after your last dose, including:
  - irritability (getting upset easily)
  - depression (feeling low, feeling bad about yourself, or feeling hopeless)
  - aggressive behavior
  - thoughts of hurting yourself or others, or suicide
  - former drug addicts may fall back into drug addiction or overdose

If you have these symptoms, your healthcare provider should carefully monitor you during treatment with PegIntron and for 6 months after your last dose.

- 2. Heart problems.** Some people who take PegIntron may get heart problems, including:
  - low blood pressure
  - fast heart rate or abnormal heart beat
  - trouble breathing or chest pain
  - heart attacks or heart muscle problems (cardiomyopathy)
- 3. Stroke or symptoms of a stroke. Symptoms may include weakness, loss of coordination, and numbness.** Stroke or symptoms of a stroke may happen in people who have some risk factors or no known risk factors for a stroke.

4. **New or worsening autoimmune problems.** Some people taking PegIntron develop autoimmune problems (a condition where the body's immune cells attack other cells or organs in the body), including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. In some people who already have an autoimmune problem, it may get worse during your treatment with PegIntron.
5. **Infections.** Some people who take PegIntron may get an infection. Symptoms may include:
  - fever
  - chills
  - bloody diarrhea
  - burning or pain with urination
  - urinating often
  - coughing up mucus (phlegm) that is discolored (for example, yellow or pink)

PegIntron in combination with REBETOL (ribavirin) may cause birth defects or the death of your unborn baby. Do not take PegIntron and ribavirin combination therapy if you or your sexual partner is pregnant or plan to become pregnant. Do not become pregnant within 6 months after discontinuing PegIntron and ribavirin combination therapy. You must use 2 forms of birth control when you take PegIntron and ribavirin and for the 6 months after treatment.

- Females must have a pregnancy test before starting PegIntron and ribavirin combination therapy, every month while on the combination therapy, and every month for the 6 months after the last dose of combination therapy.
- If you or your female sexual partner becomes pregnant while taking PegIntron and ribavirin combination therapy or within 6 months after you stop taking the combination therapy, tell your healthcare provider right away. You or your healthcare provider should contact the Ribavirin pregnancy registry by calling 1-800-593-2214. The Ribavirin pregnancy registry collects information about what happens to mothers and their babies if the mother takes ribavirin while she is pregnant.

While taking PegIntron, you should see a healthcare provider regularly for check-ups and blood tests to make sure that your treatment is working, and to check for side effects.

### **What is PegIntron?**

PegIntron is a prescription medicine that is used:

- with REBETOL (ribavirin) and an approved hepatitis C virus (HCV) protease inhibitor to treat chronic (lasting a long time) hepatitis C infection in adults.
- with REBETOL (ribavirin) to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with stable liver problems.
- alone, sometimes to treat adults who have chronic (lasting a long time) hepatitis C infection with stable liver problems and who can not take REBETOL (ribavirin).

People with hepatitis C have the virus in their blood and in their liver. PegIntron reduces the amount of virus in the body and helps the body's immune system fight the virus. REBETOL (ribavirin) is a drug that helps to fight the viral infection but does not work when used by itself to treat chronic hepatitis C.

It is not known if PegIntron use for longer than 1 year is safe and will work.

It is not known if PegIntron use in children younger than 3 years old is safe and will work.

## Who should not take PegIntron?

Do not take PegIntron:

- if you have had a serious allergic reaction to another alpha interferon or to any of the ingredients in PegIntron. See the end of this Medication Guide for a complete list of ingredients. Ask your healthcare provider if you are not sure.
- if you have certain types of hepatitis (autoimmune hepatitis).
- if you have certain other liver problems.
- with REBETOL (ribavirin) if you are pregnant, planning to get pregnant, or breastfeeding. See “What is the most important information I should know about PegIntron?”

Talk to your healthcare provider before taking PegIntron if you have any of these conditions.

## What should I tell my healthcare provider before taking PegIntron?

**Before you take PegIntron, see “What is the most important information I should know about PegIntron?”, and tell your healthcare provider if you:**

- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and suicidal behavior
- have or ever had any problems with your heart, including heart attack or high blood pressure
- have any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- have or ever had bleeding problems or a blood clot
- have or ever had low blood cell counts
- have ever been addicted to drugs or alcohol
- have liver disease (other than hepatitis C infection)
- have or had lung disease such as chronic obstructive pulmonary disease (COPD)
- have thyroid problems
- have diabetes
- have colitis (inflammation of your intestine)
- have a condition that suppresses your immune system, such as cancer
- have hepatitis B infection
- have HIV infection
- have kidney problems
- have high blood triglyceride levels (fat in your blood)
- have an organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)
- have any other medical conditions
- are pregnant or plan to become pregnant. PegIntron may harm your unborn baby. You should use effective birth control during treatment with PegIntron. Talk to your healthcare provider about birth control choices for you during treatment with PegIntron. Tell your healthcare provider if you become pregnant during treatment with PegIntron.
- are breastfeeding or plan to breastfeed. It is not known if PegIntron passes into your breast milk. You and your healthcare provider should decide if you will use PegIntron or breastfeed.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. PegIntron and certain other medicines may affect each other and cause side effects.

**Especially tell your healthcare provider if you take** the anti-hepatitis B medicine telbivudine (Tyzeka).

**Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.**

### **How should I take PegIntron?**

- Take PegIntron exactly as your healthcare provider tells you to. Your healthcare provider will tell you how much PegIntron to take and when to take it. Do not take more than your prescribed dose.
- Take your prescribed dose of PegIntron every week, on the same day of each week and at the same time.
- PegIntron is given as an injection under your skin (subcutaneous injection). Your healthcare provider should show you how to prepare and measure your dose of PegIntron, and how to inject yourself before you use PegIntron for the first time.
- You should not inject PegIntron until your healthcare provider has shown you how to use PegIntron the right way.
- PegIntron comes as a:
  - powder in a single-use vial
  - Selectdose™ single-use pre-filled pen
  - single-use REDIPEN

Your healthcare provider will prescribe the PegIntron that is right for you. See the Instructions for Use that comes with your PegIntron for detailed instructions for preparing and injecting a dose of PegIntron.

- If you miss a dose of PegIntron, take the missed dose as soon as possible during the same day or the next day, then continue on your regular dosing schedule. If several days go by after you miss a dose, check with your healthcare provider about what to do.
- Do not inject more than 1 dose of PegIntron in one week without talking to your healthcare provider.
- If you take too much PegIntron, call your healthcare provider right away. Your healthcare provider may examine you more closely, and do blood tests.
- Your healthcare provider should do regular blood tests before you start PegIntron, and during treatment to see how well the treatment is working and to check you for side effects.

### **What are the possible side effects of PegIntron?**

**PegIntron may cause serious side effects including:**

**See "What is the most important information I should know about PegIntron?"**

- **Serious eye problems.** PegIntron may cause eye problems that may lead to vision loss or blindness. You should have an eye exam before you start taking PegIntron. If you have eye problems or have had them in the past, you may need eye exams while you are taking PegIntron. Tell your healthcare provider or eye doctor right away if you have any vision changes while taking PegIntron.

- **Blood problems.** PegIntron can affect your bone marrow and cause low white blood cell and platelet counts. In some people, these blood counts may fall to dangerously low levels. If your blood counts become very low, you can get infections, and problems with bleeding and bruising.
- **Swelling of your pancreas (pancreatitis) or intestines (colitis).** Symptoms may include:
  - severe stomach area (abdomen) pain
  - severe back pain
  - nausea and vomiting
  - bloody diarrhea
  - fever
- **Lung problems including:**
  - trouble breathing
  - pneumonia
  - inflammation of lung tissue
  - new or worse high blood pressure of the lungs (pulmonary hypertension). This can be severe and may lead to death.

You may need to have a chest X-ray or other tests if you develop fever, cough, shortness of breath or other symptoms of a lung problem during treatment with PegIntron.

- **Severe liver problems, or worsening of liver problems, including liver failure and death.** Symptoms may include:
  - nausea
  - loss of appetite
  - tiredness
  - diarrhea
  - yellowing of your skin or the white part of your eyes
  - bleeding more easily than normal
  - swelling of your stomach area (abdomen)
  - confusion
  - sleepiness
  - you cannot be awakened (coma)
- **Thyroid problems.** Some people develop changes in their thyroid function. Symptoms of thyroid changes include:
  - problems concentrating
  - feeling cold or hot all of the time
  - weight changes
  - skin changes
- **Blood sugar problems.** Some people may develop high blood sugar or diabetes. If you have high blood sugar or diabetes that is not controlled before starting PegIntron, talk to your healthcare provider before you take PegIntron. If you develop high blood sugar or diabetes while taking PegIntron, your healthcare provider may tell you to stop PegIntron and prescribe a different medicine for you. Symptoms of high blood sugar or diabetes may include:
  - increased thirst
  - tiredness

- urinating more often than normal
- increased appetite
- weight loss
- your breath smells like fruit
- **Serious allergic reactions and skin reactions. Symptoms may include:**
  - itching
  - swelling of the face, eyes, lips, tongue, or throat
  - trouble breathing
  - anxiousness
  - chest pain
  - feeling faint
  - skin rash, hives, sores in your mouth, or your skin blisters and peels
- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with PegIntron and REBETOL. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with PegIntron and REBETOL.
- **Nerve problems.** People who take PegIntron or other alpha interferon products with telbivudine (Tyzeka) can develop nerve problems such as continuing numbness, tingling, or burning sensation in the arms or legs (peripheral neuropathy). Call your healthcare provider if you have any of these symptoms.
- **Dental and gum problems.**

**Tell your healthcare provider right away if you have any of the symptoms listed above.**

**The most common side effects of PegIntron include:**

- **Flu-like symptoms.** Symptoms may include: headache, muscle aches, tiredness, and fever. Some of these symptoms may be decreased by injecting your PegIntron dose at bedtime. Talk to your healthcare provider about which over-the-counter medicines you can take to help prevent or decrease some of these symptoms.
- **Tiredness.** Many people become very tired during treatment with PegIntron.
- **Appetite problems.** Nausea, loss of appetite, and weight loss can happen with PegIntron.
- **Skin reactions.** Redness, swelling, and itching are common at the site of injection.
- **Hair thinning.**

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PegIntron. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

**How should I store PegIntron?**

- Before mixing, store PegIntron Selectdose single-use pre-filled pen or single-use REDIPEN in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Before mixing, store PegIntron vials at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep PegIntron away from heat.
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- **Keep PegIntron and all medicines out of the reach of children.**

### **General Information about PegIntron**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PegIntron for a condition for which it was not prescribed. Do not give PegIntron to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about PegIntron. If you would like more information, ask your healthcare provider. You can ask your healthcare provider or pharmacist for information about PegIntron that was written for healthcare professionals.

For more information, go to [www.PegIntron.com](http://www.PegIntron.com) or call 1-800-526-4099.

### **What are the ingredients in PegIntron?**

**Active ingredients:** peginterferon alfa-2b

**Inactive ingredients:** dibasic sodium phosphate anhydrous, monobasic sodium phosphate dihydrate, sucrose, polysorbate 80. Sterile water for injection is supplied as a diluent.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

 Manufactured by: Schering Corporation, a subsidiary of  
**MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Revised: 12/2013

For patent information: [www.merck.com/product/patent/home.html](http://www.merck.com/product/patent/home.html)

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## Instructions for Use

PegIntron<sup>®</sup> (peg-In-tron)

(Peginterferon alfa-2b)

Selectdose<sup>™</sup> single-use pre-filled pen

**This Instructions for Use is only for use with the Selectdose single-use pre-filled pen. If your healthcare provider prescribes the REDIPEN for you, use only those Instructions for Use.**

Be sure that you read, understand and follow these instructions before injecting PegIntron<sup>®</sup>. Your healthcare provider should show you how to prepare and inject PegIntron properly using the Selectdose pre-filled pen before you use it for the first time. Ask your healthcare provider if you have any questions.

### Important:

- Make sure you have the correct strength of Selectdose pre-filled pen prescribed by your healthcare provider.
- Throw away the pre-filled pen after you use it. **Do not re-use your pre-filled pen.** See “**Disposal of used needles and pre-filled pens**” in this Instructions for Use.

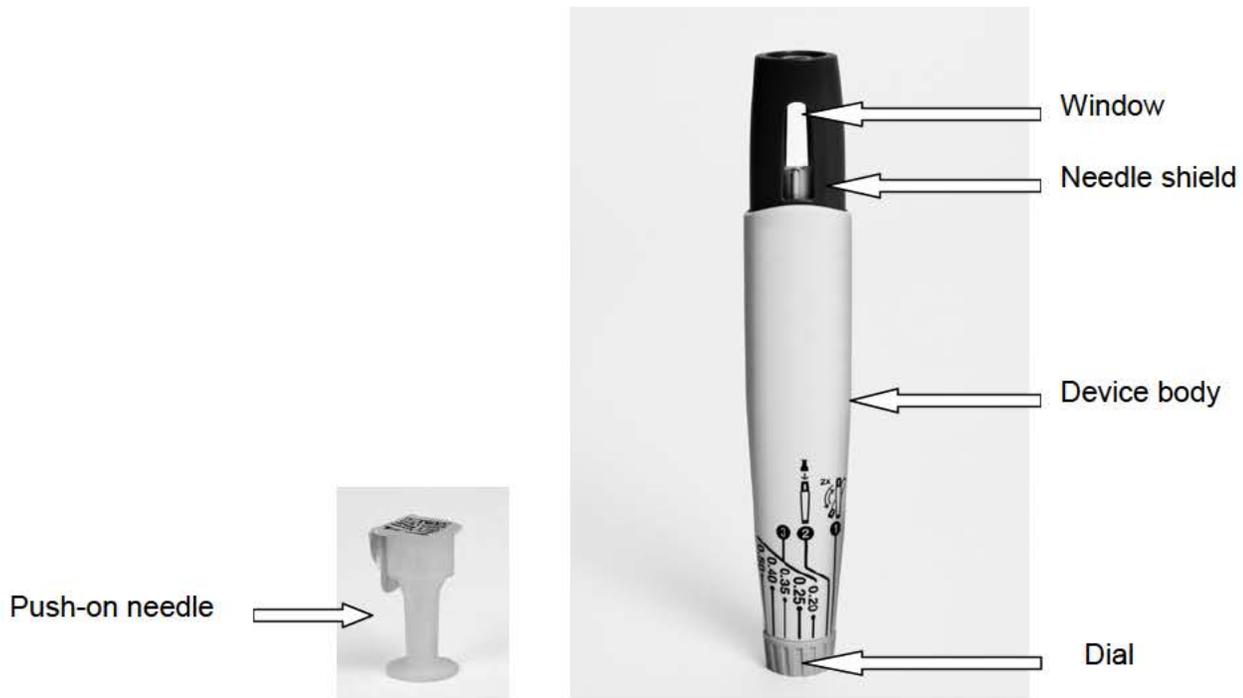
### Gather the supplies for your injection

You will need these supplies for an injection of PegIntron. These supplies are included in the package:

- 1 PegIntron Selectdose single-use pre-filled pen
- 1 push-on needle
- 2 alcohol swabs

You will also need 1 sharps disposal container for throwing away your used pre-filled pen. See “**Disposal of used needles and pre-filled pens**” in this Instructions for Use.

The figure below shows the push-on needle, and the pre-filled pen in an upright position. See Figure A.



**Figure A**

**Prepare a dose of PegIntron using the Selectdose pre-filled pen**

- Find a well-lit, clean flat work surface such as a table.
- Take the pre-filled pen out of the refrigerator. Remove the pre-filled pen from the carton.
- Look at the date printed on the carton and on the pre-filled pen to make sure that the expiration date has not passed. See Figure B. Do not use if the expiration date has passed.



**Figure B**

- Lay the pre-filled pen on a flat clean surface and wait a few minutes until it reaches room temperature.
- Wash your hands well with soap and warm water. Keep your work area, your hands, and the injection site clean to decrease the risk of infection.

## 1. Mix the PegIntron

- **Hold the pre-filled pen upright with the dial on the bottom.** See Figure C.
- **Turn the dial to number 1.** See Figure D. You may or may not hear a "click" sound when you turn the dial. This starts the PegIntron mixing.

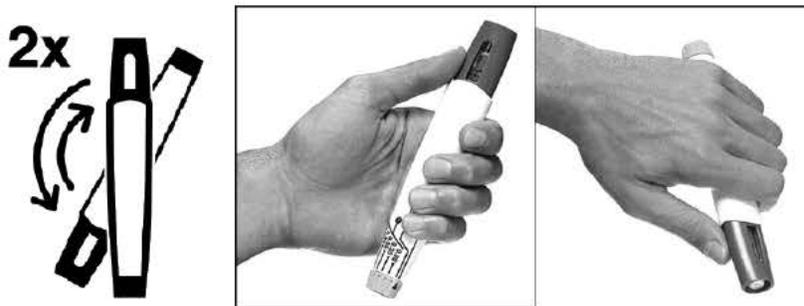


**Figure C (start position)**



**Figure D**

- **Do not shake to mix.** Gently turn the pre-filled pen up-side-down two times to mix. See Figure E.



**Figure E**

- **Look in the window.** See Figure F. The solution should be clear and colorless before use. Do not use the Selectdose pre-filled pen if it is discolored or if you see particles in it.



**Figure F**

## 2. Attach push-on needle

- **Turn the dial to number 2.** See Figure G. You may or may not hear a "click" sound when you turn the dial.



**Figure G**

- Use an alcohol swab to wipe the pre-filled pen where the needle attaches. See Figure H.



**Figure H**

- **Remove the paper from the push-on needle cap before attaching to the pre-filled pen.** See Figure I.



**Figure I**

- Support the pre-filled pen in the upright position. Carefully turn the needle cap upside down and push it straight down firmly to attach it to the pre-filled pen. See Figure J. You might hear a squishing sound. Attaching the needle correctly helps you to receive the full dose of PegIntron.



**Figure J**

- Carefully remove needle cap by pulling it straight up. Do not let the needle touch anything. You may see some liquid come out of the needle. See Figure K. This is normal.



Figure K

### 3. Dial the dose

- **Turn the dial to your prescribed dose.** See Figure L. The dose shown in Figure L may be different than your prescribed dose. You may hear clicking sounds as you dial. The needle shield will automatically make a loud “Snap” sound and pop up as you dial. See Figure M. You may dial up or down to the correct dose before injecting.



Figure L



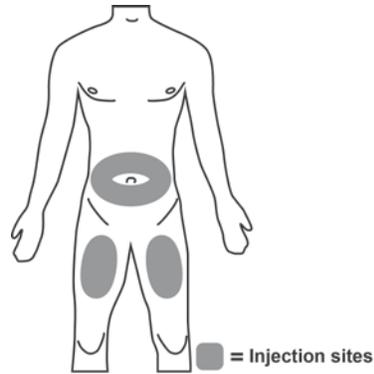
Figure M

**If you dial your dose before attaching the push-on needle your device will not work and should not be used.** Call your healthcare provider for instructions.

### Inject PegIntron using the Selectdose pre-filled pen

- Lay the pre-filled pen on a flat clean surface while you select and prepare the injection site.
- Choose an injection site on your stomach or thigh. See Figure N. Avoid your belly-button (navel) and waistline. If you are very thin, you

should only use the thigh for injection. You should use a different place each time you give yourself an injection. **Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.**



**Figure N**

- Wipe the injection site with alcohol swab. Let the skin air dry.
- Pinch a fold of loose skin in the area you have cleaned for injection.
- **Press the pre-filled pen firmly against your skin at the injection site.** See Figure O. The shield will glide back to allow the needle to inject the medicine.
- **Hold the pre-filled pen against your skin for 15 seconds to be sure that you receive your full dose of PegIntron.** See Figure O. You may hear the pre-filled pen click during that time.
- Remove the pre-filled pen from your skin. The needle shield should lock in place.



**Figure O**

**If you see leakage around the injection site, you may not have received your full dose of PegIntron.**

- **Do not** try to re-use the pre-filled pen.
- **Do not** repeat the injection with another pre-filled pen.
- **Call your healthcare provider for instructions.**

## Disposal of the used needles and pre-filled pens

- Put your used needles and pre-filled pens in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and pre-filled pens in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes and pre-filled pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

## How should I store PegIntron Selectdose pre-filled pen?

- Before mixing, store PegIntron Selectdose pre-filled pen in a refrigerator, at 36°F to 46°F (2°C to 8°C).
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- Keep PegIntron away from heat.

**Keep PegIntron and all medicines out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Schering Corporation, a subsidiary of  
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Issued 12/2013

U.S. Patent Nos. 5,951,974; 6,180,096; and 6,610,830.

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## Instructions for Use

PegIntron<sup>®</sup> (peg-In-tron)  
(Peginterferon alfa-2b)

REDIPEN<sup>®</sup> single-use pre-filled pen

**This Instructions for Use is only for use with the REDIPEN single-use pre-filled pen. If your healthcare provider prescribes the Selectdose single-use pre-filled pen for you, use only those Instructions for Use.**

Be sure that you read, understand, and follow these instructions before injecting PegIntron. Your healthcare provider should show you how to prepare and inject PegIntron properly using the REDIPEN single-use pre-filled pen before you use it for the first time. Ask your healthcare provider if you have any questions.

### **Important:**

- Make sure that you have the correct strength of REDIPEN pre-filled pen prescribed by your healthcare provider.
- Throw away REDIPEN after you use it. **Do not re-use your pre-filled pen or needle.** See “**Disposal of used needles and pre-filled pens**” in this Instructions for Use.

Before starting, collect all of the supplies that you will need to use for preparing and injecting PegIntron. For each injection you will need a package that contains:

- 1 PegIntron REDIPEN single-use pre-filled pen
- 1 disposable needle
- 2 alcohol swabs
- dosing tray (the dosing tray is the bottom half of the REDIPEN package)
- You will need gauze or a cotton ball to press to the injection site after injecting. You will also need 1 sharps disposal container for throwing away your used pre-filled pen. See “**Disposal of used needles and pre-filled pens**” in this Instructions for Use.

The REDIPEN single-use pre-filled pen should only be used with the injection needle that comes in the package. If you use other needles, the pen may not work the right way.

- Figures A and B below show the different parts of the REDIPEN single-use pre-filled pen and the injection needle. Figure C

below shows the dosing tray with the pre-filled pen. The parts of the pre-filled pen you need to know are:

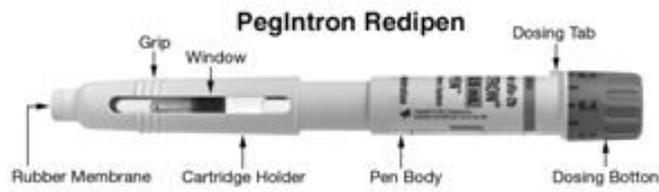


Figure A

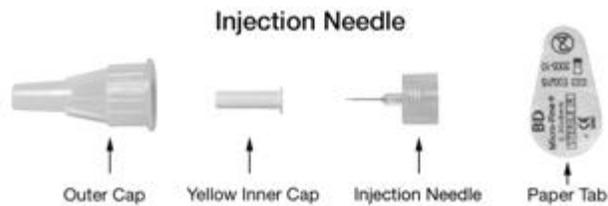


Figure B



Figure C

**How should I prepare a dose of PegIntron using the REDIPEN single-use pre-filled pen?**

1. Find a clean, well-lit, flat work surface.
2. Take the pre-filled pen out of the refrigerator and allow the medicine to come to room temperature. Look at the date printed on the carton to make sure that the expiration date has not passed. Do not use if the expiration date has passed.
3. After taking the pre-filled pen out of the carton, look in the window of the pre-filled pen and make sure the PegIntron in the cartridge holder window is a white to off-white tablet that is whole, or in pieces, or powdered.

4. Wash your hands well with soap and water. It is important to keep your work area, your hands, and the injection site clean to decrease the risk of infection. See Figure D.



Figure D

### Mix the PegIntron

5. **Place the pre-filled pen upright** in the dosing tray on a hard, flat, non-slip surface with the dosing button down. See Figure E. You may want to hold the pre-filled pen using the grip.



Figure E

6. To mix the powder and the liquid, keep the pre-filled pen upright in the dosing tray and press the top half of the pre-filled pen downward toward the hard, flat, non-slip surface **until you hear the “click” sound.** See Figure F. When you hear the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flat with the pen body.



**Figure F**

7. Wait several seconds for the powder to completely dissolve. Do not shake. If the solution does not dissolve, gently turn the pre-filled pen upside down two times. See Figure G.



**Figure G**

8. Keep the pre-filled pen **UPRIGHT**, with the dosing button down. Look through the pre-filled pen window to see that the mixed PegIntron solution is completely dissolved. The solution should be clear and colorless **before use**. It is normal to see some small bubbles in the pre-filled pen window, near the top of the solution. Do not use the REDIPEN pre-filled pen if the solution is discolored, or is not clear, or if it has particles in it.
9. Place the pre-filled pen back into the dosing tray provided in the packaging. See Figure H. The dosing button will be on the bottom.



**Figure H**

### **Attach the Needle**

10. Before you attach the needle to the pre-filled pen, wipe the rubber membrane of the pre-filled pen with an alcohol swab.
11. Remove the protective paper tab from the injection needle, but do not remove either the outer cap or the yellow inner cap from the injection needle.
12. Keep the pre-filled pen upright in the dosing tray and push the injection needle straight into the pre-filled pen rubber membrane. Screw the needle onto the pre-filled pen by turning it in a clockwise direction. See Figure I.
  - Remember to leave the needle caps in place when you attach the needle to the pre-filled pen. Pushing the needle through the rubber membrane "primes" the needle and allows the extra liquid and air in the pen to be removed.



**Figure I**

NOTE: Some fluid will trickle out. This is **normal**. The dark stoppers move up and you will no longer see the fluid in the window once the needle is successfully primed.

- Remove the outer clear needle cap on the pre-filled pen, but leave the yellow cap on. See Figure J.



**Figure J**

**How should I set the dose prescribed by my healthcare provider?**

### **Dial the Dose**

13. Holding the pre-filled pen firmly, pull the dosing button out as far as it will go. See Figure K. You will see a dark band.

**Do not push the dosing button in until you are ready to self-inject the PegIntron dose.**



**Figure K**

- Turn the dosing button until your prescribed dose is lined up with the dosing tab. See Figure L. The dosing button will turn freely. If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go. See Figure M.



**Figure L**

**Figure M**

- Carefully lay the pre-filled pen down on the dosing tray or on a hard, flat, non-slip surface. Do not remove the yellow needle cap and do not push the dosing button in until you are ready to self-inject the PegIntron dose.

### **Choosing an Injection Site**

The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. See Figure N. Do not inject yourself in the area near your belly-button (navel) or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.



**Figure N**

You should use a different site each time you inject PegIntron to avoid soreness at any one site. Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

### How should I Inject a dose of PegIntron?

16. Clean the skin where the injection is to be given with the second alcohol swab provided, and wait for the skin to dry.
17. There may be some liquid around the yellow inner needle cap. See Figure O. This is normal.



**Figure O**

18. Remove the **yellow** inner needle cap when the injection site is dry. See Figure P. You are now ready to inject.



**Figure P**

19. Hold the pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button. See Figure Q.



**Figure Q**

20. With your other hand, pinch the skin in the area you have cleaned for injection.
21. Insert the needle into the pinched skin at an angle of 45° to 90°. See Figure R.



**Figure R**

22. Press the dosing button down slowly and firmly until you can not push it any further. Keep your thumb pressed down on the dosing button for an additional 5 seconds to make sure that you get the complete dose.
23. Slowly release the dosing button and remove the needle from your skin.

24. Gently press the injection site with a small bandage or sterile gauze if needed for a few seconds but do not massage the injection site. If there is bleeding, cover with an adhesive bandage. Do not recap the needle and do not reuse the pre-filled pen.

### **Disposal of the used needles and pre-filled pens**

- Put your used needles and pre-filled pens in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and pre-filled pens in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes and pre-filled pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

### **How should I store PegIntron REDIPEN pre-filled pen?**

- Before mixing, store PegIntron REDIPEN pre-filled pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- Keep PegIntron away from heat.

**Keep PegIntron and all medicines out of reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Schering Corporation, a subsidiary of **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA.

Revised: 12/2013

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U.S. Patent Nos. 5,951,974; 6,180,096; and 6,610,830.

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## Instructions for Use

PegIntron<sup>®</sup> (peg-In-tron)  
(Peginterferon alfa-2b)  
Powder for Injection

**This Instructions for Use is only for use with the single-use vials of Powder for injection. If your healthcare provider prescribes the REDIPEN or Selectdose Pre-filled Pen for you, use only those Instructions for Use.**

Be sure that you read, understand and follow these instructions before injecting PegIntron. Your healthcare provider should show you how to prepare, measure, and inject PegIntron properly using a vial before you use it for the first time. Ask your healthcare provider if you have any questions.

Important:

- Make sure that you have:
  - the correct strength of PegIntron vial prescribed by your healthcare provider.
  - the correct syringe and needle to use with PegIntron. Your healthcare provider should tell you what syringes and needles to use to inject PegIntron.
- Throw away the syringe and needle after you use it. Do not re-use your syringes and needles. See “Disposal of the used needles, syringes and vials” in this Instructions for Use.
- The vial of mixed PegIntron should be used right away. Do not mix more than 1 vial of PegIntron at a time. If you do not use the vial of the prepared solution right away, store it in a refrigerator and use within 24 hours. See the end of these Instructions for Use for information about “How should I store PegIntron?”

Before starting, collect all of the supplies that you will need to use for preparing and injecting PegIntron. For each injection you will need a PegIntron vial package that contains:

- 1 vial of PegIntron powder for injection
- 1 vial of sterile water for injection (diluent)
- 2 single-use disposable syringes (BD Safety Lok syringes with a safety sleeve)
- 2 alcohol swabs

You will also need:

- 1 cotton ball or gauze

- 1 sharps disposal container for throwing away your used syringes, needles, and vials.

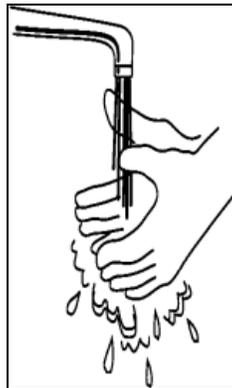
### How should I prepare a dose of PegIntron?

Before you inject PegIntron, the powder must be mixed with 0.7 mL of the sterile water for injection (diluent) that comes in the PegIntron vial package.

1. Find a clean, well-lit, flat work surface.
2. Get 1 of your PegIntron vial packages. Check the date printed on the PegIntron carton. Make sure that the expiration date has not passed. Do not use your PegIntron vial packages if the expiration date has passed. The medicine in the PegIntron vial should look like a white to off-white tablet that is whole, or in pieces, or powdered.

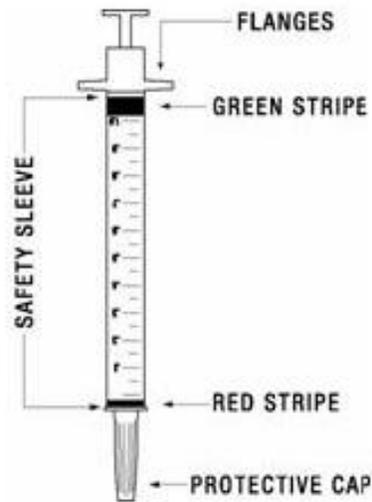
If you have already mixed the PegIntron solution and stored it in the refrigerator, take it out of the refrigerator before use and allow the solution to come to room temperature. See the Medication Guide section “How should I store PegIntron?”

3. Wash your hands well with soap and water, rinse and towel dry (See Figure A). Keep your work area, your hands, and injection site clean to decrease the risk of infection.



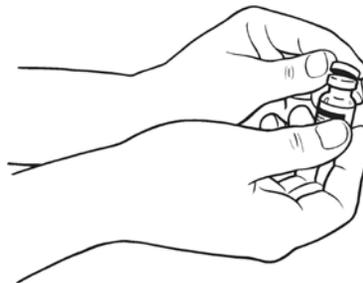
**Figure A**

The disposable syringes have needles that are already attached and cannot be removed. Each syringe has a clear plastic safety sleeve that is pulled over the needle for disposal after use. The safety sleeve should remain tight against the flange while using the syringe and moved over the needle only when ready for disposal. (See Figure B)



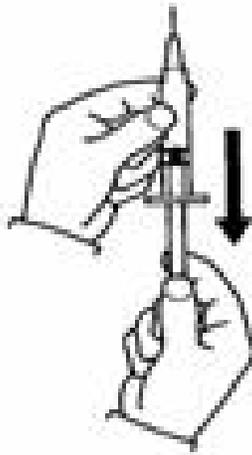
**Figure B**

4. Remove the protective wrapper from one of the syringes provided. Use the syringe for steps 4 through 15. Make sure that the syringe safety sleeve is sitting against the flange. (See Figure B)
5. Remove the protective plastic cap from the tops of both the sterile water for injection (diluent) and the PegIntron vials (See Figure C). Clean the rubber stopper on the top of both vials with an alcohol swab.



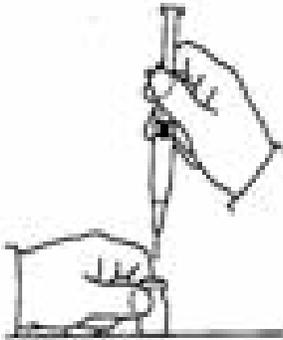
**Figure C**

6. Carefully remove the protective cap straight off of the needle to avoid damaging the needle point.
7. Fill the syringe with air by pulling back on the plunger to 0.7 mL. (See Figure D)



**Figure D**

8. Hold the diluent vial upright. Do not touch the cleaned top of the vial with your hands.
  - Push the needle through the center of the rubber stopper of the diluent vial. (See Figure E)
  - Slowly inject all the air from the syringe into the air space above the diluent in the vial. (See Figure F)

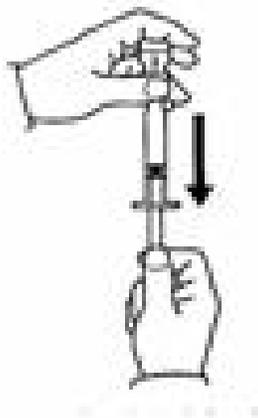


**Figure E**



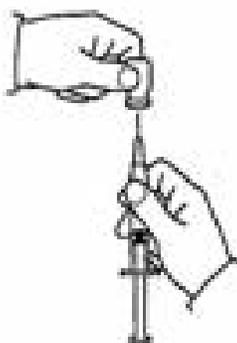
**Figure F**

9. Turn the vial upside down and make sure the tip of the needle is in the liquid.
10. Withdraw only 0.7 mL of diluent by pulling the plunger back to the 0.7 mL mark on the side of the syringe. (See Figure G)



**Figure G**

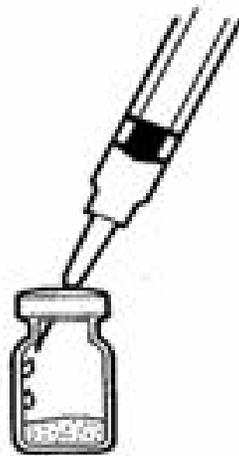
11. With the needle still inserted in the vial, check the syringe for air bubbles.
  - If there are any air bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe.
  - Slowly push the plunger up to remove the air bubbles.
  - If you push diluent back into the vial, slowly pull back on the plunger to draw the correct amount of diluent back into the syringe.
12. Remove the needle from the vial (See Figure H). Do not let the syringe touch anything.



**Figure H**

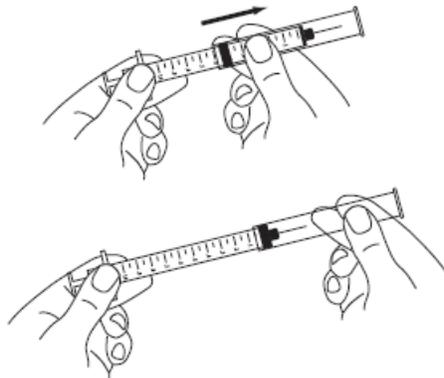
13. Throw away any diluent that is left over in the vial.
14. Insert the needle through the center of the rubber stopper of the PegIntron powder vial. Do not touch the cleaned rubber stopper.
  - Place the needle tip, at an angle, against the side of the vial. (See Figure I)
  - Slowly push the plunger down to inject the 0.7 mL diluent. The stream of diluent should run down the side of the vial.

- To prevent bubbles from forming, do not aim the stream of diluent directly on the medicine in the bottom of the vial.



**Figure I**

15. Remove the needle from the vial.
- Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click (See Figure J). The green stripe on the safety sleeve will completely cover the red stripe on the needle. Throw away the syringe, needle, and vial in the sharps disposal container (See “Disposal of the used needles, syringes, and vials”).



**Figure J**

16. Gently swirl the vial in a gentle circular motion, until the PegIntron is completely dissolved (mixed together). (See Figure K)
- Do not shake the vial. If any powder remains undissolved in the vial, gently turn the vial upside down until all of the powder is dissolved.
  - The solution may look cloudy or bubbly for a few minutes. If air bubbles form, wait until the solution settles and all bubbles rise to the top.

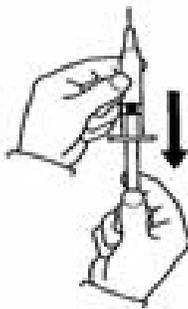


**Figure K**

17. After the PegIntron completely dissolves, the solution should be clear, colorless and without particles. It is normal to see a ring of foam or bubbles on the surface.

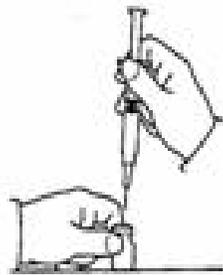
Do not use the mixed solution if you see particles in it, or it is not clear and colorless. Throw away the syringe, needle, and vial in the sharps disposal container (See the section "Disposal of the used needles, syringes, and vials"). Then, repeat steps 1 through 17 with a new vial of PegIntron and diluent to prepare a new syringe.

18. After the PegIntron powder completely dissolves, clean the rubber stopper again with an alcohol swab before you withdraw your dose.
19. Unwrap the second syringe provided. You will use it to give yourself the injection.
  - o Carefully remove the protective cap from the needle. Fill the syringe with air by pulling the plunger to the number on the side of the syringe (mL) that matches your prescribed dose. (See Figure L)



**Figure L**

- o Hold the PegIntron vial upright. Do not touch the cleaned top of the vial with your hands. (See Figure M)



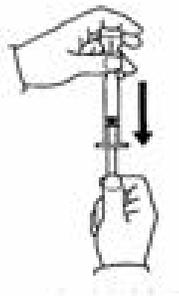
**Figure M**

- Insert the needle into the vial containing the PegIntron solution. Inject the air into the center of the vial. (See Figure N)



**Figure N**

20. Turn the PegIntron vial upside down. Be sure the tip of the needle is in the PegIntron solution.
- Hold the vial and syringe with one hand. Be sure the tip of the needle is in the PegIntron solution. With the other hand, slowly pull the plunger back to fill the syringe with the exact amount of PegIntron into the syringe your healthcare provider told you to use. (See Figure O)



**Figure O**

21. Check for air bubbles in the syringe. If you see any air bubbles, hold the syringe with the needle pointing up. Gently tap the syringe until the air bubbles rise. Then, slowly push the plunger up to remove any air bubbles. If you push

solution into the vial, slowly pull back on the plunger again to draw the correct amount of PegIntron back into the syringe. When you are ready to inject the medicine, remove the needle from the vial. (See Figure P)

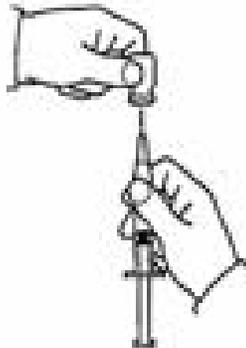


Figure P

### How should I choose a site for injection?

The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen (See Figure Q). Do not inject yourself in the area near your belly-button (navel) or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection.

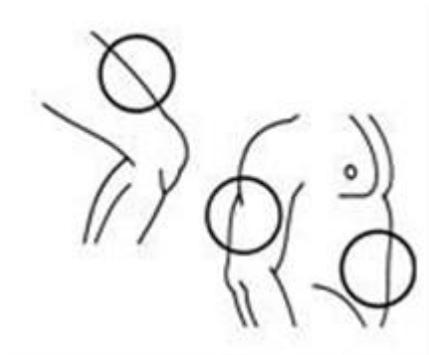
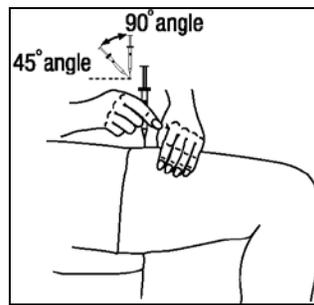


Figure Q

You should use a different site each time you inject PegIntron to avoid soreness at any one site. **Do not inject PegIntron solution into an area where the skin is irritated, red, bruised, infected or has scars, stretch marks, or lumps.**

### How should I inject a dose of PegIntron?

22. Clean the skin where the injection is to be given with an alcohol swab. Wait for the area to dry.
  - Make sure the safety sleeve of the syringe is pushed firmly against the syringe flange so that the needle is fully exposed.
23. With one hand, pinch a fold of skin. With your other hand, pick up the syringe and hold it like a pencil.
  - Insert the needle into the pinched skin at a 45- to 90-degree angle with a quick dart-like motion. (See Figure R)

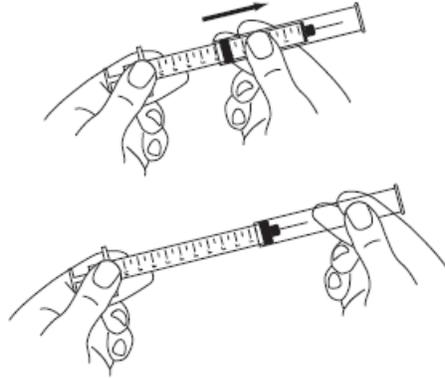


**Figure R**

- After the needle is inserted, remove the hand that you used to pinch your skin. Use it to hold the syringe barrel.
  - Pull the plunger of the syringe back very slightly.
  - **If no blood is present in the syringe**, inject the medicine by gently pressing the plunger all the way down the syringe barrel, until the syringe is empty.
  - **If blood comes into the syringe**, the needle has entered a blood vessel. Do not inject.
    - Withdraw the needle and throw away the syringe and needle in the sharps disposal container. (See "Disposal of the used needles, syringes, and vials")
    - Then, repeat steps 1 through 23 with a new vial of PegIntron and diluent to prepare a new syringe, and inject the medicine at a new site.
24. When the syringe is empty, pull the needle out of the skin.
    - Place a cotton ball or gauze over the injection site and press for several seconds. Do not massage the injection site.
    - If there is bleeding, cover it with a bandage.

25. After injecting your dose:

- o Firmly grasp the safety sleeve and pull it over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle. (See Figure S)



**Figure S**

### **Disposal of the used needles, syringes, and vials**

- Put your used needles, syringes and vials in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles, syringes and vials in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - o made of a heavy-duty plastic,
  - o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - o upright and stable during use,
  - o leak-resistant, and
  - o properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Always keep the sharps disposal container out of the reach of children.

**How should I store PegIntron?**

- Before mixing, store PegIntron vials at room temperature, between 68°F to 77°F (20°C to 25°C).
- After mixing, use PegIntron right away or store it in the refrigerator for up to 24 hours between 36°F to 46°F (2°C to 8°C).
- Do not freeze PegIntron.
- Keep PegIntron away from heat.

**Keep PegIntron and all medicines out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Schering Corporation, a subsidiary of **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA.

Revised 12/2013

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U.S. Patent Nos. 5,951,974; 6,180,096; and 6,610,830.

B-D is a registered trademark of Becton, Dickinson and Company.

ifu-vial-4031131101rXXX

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**103949Orig1s5259**

**OFFICER/EMPLOYEE LIST**

**Officer/Employee List**  
**Application: 103949/5259**

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

1. Asante, Kemi
2. Fischer, Carl
3. Fox, Jessica
4. Fuller, Barbara
5. Genca, Emre
6. Holquist, Carol
7. Lewis, Linda
8. Miele, Peter
9. Mills, Sharon
10. Murray, Jeffrey
11. Obenhuber, Donald
12. Rains, Kimberly
13. Ryan, Jacqueline
14. Tejero, Isabel
15. Thompson, Elizabeth
16. Tyson, Victoria
17. Walker, Morgan

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103949Orig1s5259**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

|  |   |
|--|---|
| <b>Date</b>  | July 19, 2013   |
| <b>From</b>  | Linda L. Lewis, M.D.<br>Medical Officer Team Leader<br>DAVP/OAP/CDER/DAVP   |
| <b>Subject</b>   | Cross-Discipline Team Leader Review   |
| <b>NDA/BLA #<br/>Supplement#</b>                       | 103949/5259   |
| <b>Applicant</b>                                       | Schering Corporation<br>A subsidiary of Merck & Company, Inc.   |
| <b>Date of Submission</b>                              | October 10, 2012  |
| <b>PDUFA Goal Date</b>                                 | August 9, 2013  |
| <b>Proprietary Name /<br/>Established (USAN) names</b> | PegIntron <sup>®</sup> Selectdose <sup>™</sup><br>Pegylated interferon alfa-2b  |
| <b>Dosage forms / Strength</b>                         | Prefilled single-use syringe to deliver multiple dose choices   |
| <b>Proposed Indication(s)</b>                          | PegIntron <sup>®</sup> in combination with REBETOL <sup>®</sup> (ribavirin) is indicated for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease |
| <b>Recommended:</b>                                    | <b>Approval</b> – pending satisfactory completion of all product manufacturing/device assembly inspections  |

### 1. Introduction

PegIntron<sup>®</sup> (peginterferon alfa-2b), a polyethylene glycol-conjugated formulation of interferon alfa-2b, is currently approved for the treatment of chronic hepatitis C (HCV) in patients greater than 3 years of age with compensated liver disease. This submission includes the Applicant's design validation testing and proposed new labeling for a new pre-filled, single-use, dual-chamber PegIntron auto-injector. The agreed upon proprietary name for this new device is PegIntron<sup>®</sup> Selectdose<sup>™</sup>.

The purpose of this CDTL Review is to summarize the FDA conclusions described in the primary reviews and consults contributed by multiple review disciplines and to identify any unresolved issues. The CDTL review will describe the review team's overall risk-benefit assessment of the Applicant's proposed revisions to the labeling for PegIntron<sup>®</sup> Selectdose<sup>™</sup>. In this review the new device will be referred to as the new dual-chamber injector (DCI) or by the agreed upon proprietary name.

## 2. Background

PegIntron was initially approved as monotherapy for the treatment of chronic hepatitis C in patients not previously treated with interferon alfa who have compensated liver disease and are at least 18 years of age in January, 2001. In October, 2003, a single-use pen injector with a dual-chamber cartridge containing lyophilized drug and sterile water diluent was approved. The original REDIPEN<sup>®</sup> device has been marketed since that time [REDACTED] (b)(4)

Members of a combined CDER and CDRH review team met with the Applicant in December, 2011, discussed the development of a new dosing device, and described the data needed for approval of a BLA supplement for a new dual chamber injector (DCI). This meeting was followed with additional teleconferences and written communications to discuss the iterative development and testing of the new device. No clinical trial data is submitted with this application but the results of a Human Use Factors/Usability Design Validation Study were provided to support use of the new device and the proposed Instructions for Use.

With this BLA supplement submission, the Applicant requests approval of the PegIntron<sup>®</sup> Selectdose<sup>™</sup> device and changes in several aspects of the product labeling including:

- Replacement of the current PEGINTRON<sup>®</sup> REDIPEN<sup>®</sup> with a new (dual-chamber) pre-filled pen for self injection. This new pre-filled pen will use the currently-approved PEGINTRON<sup>®</sup> drug product cartridge and incorporates a needle shield to aid in the prevention of accidental needle sticks.
- Modification of the currently approved REDIPEN<sup>®</sup> dose settings that allow administration of a broader range of dosing volumes, including lower dosing volumes.
- Replacement of the current screw-on needle supplied with REDIPEN<sup>®</sup> with a push-on needle [REDACTED] (b)(4)
- Revised Package Insert and Medication Guide based on the current FDA approved versions containing information for both the vial and pre-filled pen and

new Instructions for Use (IFU) that provides instructions for administration of PEGINTRON® with the new pre-filled pen.

- New carton and pen labeling reflecting the tradename (PegIntron® Selectdose™) of the new pre-filled pen.
- Replacement of the current PEGINTRON® REDIPEN® dose-accuracy release test for drug product with a dose-accuracy test during incoming pen component release.

### 3. CMC/Device

This submission provides data to support the use of a new pre-filled, single-use, variable dose injector. The new device is designed to deliver the correct dose of PegIntron for an adult patient, subcutaneously, allowing for a variety of starting doses and dose adjustments. Because PegIntron® Selectdose™ represents a combination (drug+device) product, this submission was reviewed by both CDER and CDRH reviewers and both centers cooperated in performing facility evaluations.

- *General product quality considerations:*

The new PegIntron® Selectdose™ uses the currently approved PegIntron dual chamber cartridge, assembled inside a disposable, single unit, spring-powered, adjustable delivery device. The one chamber of the cartridge contains lyophilized peginterferon alfa and the second chamber contains sterile water used as a diluent. The pen injector twists and “clicks” into different dose increments marked on the barrel to allow selection of the correct volume to be injected.

A new push-on needle was designed for the new DCI device. The needle is a sterile, single-use, 30 gauge needle assembled in a protective (b)(4) cap; the needle assembly is sealed with a sterile barrier blister paper. The cap provides a shield against accidental needle sticks.

The Applicant describes intended use of the new DCI as follows:

“.....Each operation is initiated by a turn of the dial which mechanically must be performed sequentially. Additionally, each operation is accompanied by numbers and icons on the device to support the injection preparation steps. The design requires needle insertion to activate the injection and deliver the drug. In this manner, the design facilitates the correct sequential operation of the preparation and injection steps, (b)(4). After dose delivery, a needle shield extends and locks into place to help prevent against needle stick injury and exposure to a potentially contaminated needle.”

Reviewers from CDER's Office of Compliance/Office of Manufacturing and Product Quality/Division of Good Manufacturing Practice Assessment, Biotech Manufacturing Assessment Branch (OC/OMPQ/DGMPA/BMAB), Dr. Donald Obenhuber found that from a sterility assurance perspective and microbiology

product quality perspective the DCI could be recommended for approval. His review found documentation of container/closure integrity was acceptable. Evaluation of shipping and transportation studies found the qualification sufficient to protect the product during routine transportation and distribution.

As noted in the additional review memo from Dr. Jinhai Wang, Quality Reviewer for CDER's Division of Therapeutic Proteins, there were no product quality issues to be addressed in this submission. The PegIntron drug product cartridges are currently approved and no changes were made that would require additional testing.

- *Facilities review/inspection*

[REDACTED] (b)(4)  
[REDACTED]. According to the Therapeutic Biological Establishment Evaluation Request form, the MSD International GmbH (Singapore Branch) facility that manufactures the PegIntron cartridges and performs [REDACTED] (b)(4) testing was evaluated in March, 2013, as part of a routine GMP surveillance inspection. This site was acceptable. [REDACTED] (b)(4)  
[REDACTED].

The Schering-Plough Labo NV facility in Heist-op-den-Berg, Belgium assembles the new DCI, provides [REDACTED] (b)(4) of the assembled pen injector, and performs packaging operations. This is the same facility that assembles and tests the currently approved REDIPEN<sup>®</sup> injector. CDRH/Office of Compliance staff reviewed the previous OC/OMPQ/DGMPA/BMAB reports of REDIPEN<sup>®</sup> assembly inspection (last inspected in October, 2012) and indicated that this site should be inspected for the new DCI because of a lack of device inspection history. The device inspection is currently scheduled for September 2-5, 2013. All recommendations for approval of the DCI are contingent upon successful completion of this device facility inspection.

- *Other notable issues (resolved or outstanding)*

The new DCI device was reviewed by Jacqueline Ryan, Combination Products Team Leader, General Hospital Devices Branch, DAGID, ODE, CDRH. Specifically, she assessed the pen injector performance and biocompatibility. She noted that the tested DCI pens met the upper and lower limit specification for three dose volumes evaluated at different environmental settings. She also confirmed that the new push-on needle and needle shield met the performance testing requirements for needle-stick injury prevention. However, her review identified DCI injection failures the Applicant attributed to blockage of the needles. The Applicant noted that they had taken corrective actions and that additional performance testing had been performed and met pre-determined acceptance criteria. The CDRH reviewer did not have access to this final study report and has asked that the performance qualification documentation be submitted.

In summary, the new DCI uses approved PegIntron cartridges so this product quality review focused on the performance of the new pen injector device. The new PegIntron

Selectdose has been reviewed from a quality perspective and been found to be acceptable based on sterility assessment and device performance. However, recommendation for approval is contingent upon submission of the final performance qualification testing documentation and completion of the device facility inspection.

## **4. Nonclinical Pharmacology/Toxicology**

No new animal toxicology studies were submitted with this supplement.

## **5. Clinical Pharmacology/Biopharmaceutics**

No new clinical pharmacology/biopharmaceutics information was submitted with this supplement. Minor changes to delivered dose with the new DCI device are addressed in the Clinical Review.

## **6. Clinical Microbiology**

No new clinical microbiology information was submitted with this supplement.

## **7. Clinical/Statistical- Efficacy**

Although no new clinical trial data was submitted with this supplement, the usability and performance of the new DCI were assessed during repeated product evaluations. Initial “Contextual Inquiry and Expert Review” sessions with HCV-experienced and non-experienced health care providers were used to develop test scenarios. The first “Formative Test” evaluated seven device use scenarios and results were used to improve the device design. The second “Formative Test” introduced the revised DCI device and retested the same seven scenarios. The Applicant notes that, “Throughout the formative studies, information was gathered to identify and to resolve unforeseen hazards, and optimize the device design and the instructions for use.” Finally, a Design Validation Study was conducted to assess the optimized device and determine whether the new DCI is safe and effective for the intended users, uses, and use environment. The human factors studies were reviewed by Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH, as well as Morgan Walker, Division of Medication Error Prevention and Analysis (DMEPA), CDER. For additional details of the human factors use assessment, please see their full reviews.

The Design Validation Study represents the critical assessment to support use of the new DCI device and is summarized here. The study evaluated multiple user groups including: health care providers, caregivers, and both treatment-naïve and treatment-experienced patients. The study was conducted in two rounds of testing; the first focused on training

prior to simulated device use and the second focused on unassisted simulated use. During the first round, participants were provided one-on-one training support, asked to watch a training video and then read the Instructions for Use (IFU). Users were then asked to perform a simulated injection with the DCI and scored on whether critical or non-critical steps were completed correctly. Users who did not correctly complete any step received additional instruction and re-tested with the DCI. During the second round, subjects who completed round one were asked to perform a simulated injection one week after the initial round of training. A final (different) test cohort was asked to perform an injection using only the IFU as their reference material.

Because the product is intended to be used after training by a health care provider, the CDRH human factors review focused on the cohort of subjects who received training and their ability to correctly perform self injection. Overall, 85 subjects received training and were evaluated in round one of the protocol. Only a single subject failed to successfully complete a simulated injection after three attempts. The Applicant notes that, in general, such a subject would not be an appropriate candidate for self injection. However, the **CDRH reviewer identified reports of failures and “close calls” in attempts to use the DCI** and noted that many subjects were unaware of having used the DCI incorrectly. Depending on the specific error, the potential harm could include a missed dose or over- or under-dosing events that could represent a single event or multiple events. As noted in the DMEPA review, the types of errors observed in the Design Validation Study were not the same types of errors reported to FDA associated with the currently approved REDIPEN®.

A request for information regarding the observed dosing errors was sent and the Applicant provided additional explanation. They noted that of the eight subjects observed making a DCI use error in round 2 of the protocol, three recognized that an error had been made. The Applicant anticipated that such subjects would likely seek additional guidance from their health care provider or the available customer service telephone number. Also, post-test interviews documented that some subjects had explanations for their incorrect DCI use actions that might be easily mitigated in a real-world patient care setting (e.g., dialing in the dose pictured in the IFU rather than the **subjects’ dose**). In addition, the review team recommended changes to the IFU to clarify each step of DCI use to further mitigate the risk of incorrect dosing. Overall, the review team considered the Applicant’s responses adequate.

**In summary, the results of the Applicant’s Design Validation Study for the new DCI identified about 10% of those tested used the device incorrectly. The review team considered the Applicant’s explanation for these failures acceptable. However, they suggested revisions to the IFU and minor changes to the DCI markings in an attempt to further decrease critical dosing errors. The revised IFU will be retested as a post-marketing requirement (see Section 13).**

## 8. Safety

The current supplement provides no new safety data and identifies no new risks of toxicity of PegIntron. However, some aspects of the new DCI have implications for dosing recommendations. For a more detailed discussion of the proposed revisions to dosing recommendation required for the new DCI, please refer to the Clinical Review conducted by Dr. Peter Miele.

The new DCI [REDACTED] (b)(4)  
[REDACTED]  
[REDACTED] Many issues related to ease and accuracy of use of the new DCI (described in the Design Validation Study report) have been discussed in Section 7 of this CDTL review.

The new DCI was also designed to provide a broader range of adult starting doses of PegIntron at the lower end of the adult weight range and allow for subsequent dose adjustments. Consequently, the dose volumes are somewhat different than those delivered with the REDIPEN®. As noted in Dr. Miele's review, the strengths of the PegIntron cartridges (50 µg, 80 µg, 120 µg and 150 µg per 0.5 mL) to be used with the new DCI device are the same as those currently used with the REDIPEN®. Like the REDIPEN®, the new DCI device also has the capability to dial five different volume settings and accommodate any strength cartridge, but the settings (0.20, 0.25, 0.35, 0.40 and 0.50 mL) allow lower doses of PegIntron to be administered. As shown in Table 1 from the proposed Package Insert, all starting doses of PegIntron for patients up to 105 kg can be accommodated with the new DCI without any differences in delivered dose compared to REDIPEN®.

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

| Body Weight kg (lbs) | PegIntron Pre-filled pen or Vial Strength to Use | Amount of PegIntron to Administer (mcg) | Volume* of PegIntron to Administer (mL) | REBETOL Daily Dose | REBETOL Number of Capsules                           |
|----------------------|--|---|---|--------------------|--|
| <40 (<88)            | 50 mcg per 0.5 mL                                | 50                                      | 0.5                                     | 800 mg/day         | 2 x 200 mg capsules A.M.<br>2 x 200 mg capsules P.M. |
| 40-50 (88-111)       | 80 mcg per 0.5 mL                                | 64                                      | 0.4                                     | 800 mg/day         | 2 x 200 mg capsules A.M.<br>2 x 200 mg capsules P.M. |
| 51-60 (112-133)      |  | 80                                      | 0.5                                     | 800 mg/day         | 2 x 200 mg capsules A.M.<br>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.<br>2 x 200 mg capsules P.M. |
| 66-75 (145-166)      |  | 96                                      | 0.4                                     | 1000 mg/day        | 2 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| 76-80 (167-177)      |  | 120                                     | 0.5                                     | 1000 mg/day        | 2 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| 81-85 (178-187)      |  |   |   | 1200 mg/day        | 3 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| 86-105 (188-231)     | 150 mcg per 0.5 mL                               | 150                                     | 0.5                                     | 1200 mg/day        | 3 x 200 mg capsules A.M.<br>3 x 200 mg capsules P.M. |
| >105 (>231)          | †  | †                                       | †                                       | 1400 mg/day        | 3 x 200 mg capsules A.M.<br>4 x 200 mg capsules P.M. |

\* When reconstituted as directed.

† For patients weighing greater than 105 kg (greater than 231 pounds), the PegIntron dose of 1.5 mcg/kg/week should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

The altered volume settings provide slightly different delivered doses for some dose reductions at some weights. None of the differences in delivered dose is large (2-3 mcg) or represent a clinically significant proportion of the total dose (no more than 3% lower dose or 7% higher dose). Table 2 abstracted from Dr. Miele's review illustrates the magnitude of the changes proposed in delivered dose, with the new DCI dose in mcg shown compared to REDIPEN® in brackets. He concluded that the small differences in dose were unlikely to have a negative impact on treatment outcome.

**Table 2: Proposed Two-Step Dose Reduction of PegIntron Combination Dosing Using DCI (Adults)**

| First Dose Reduction to PegIntron 1 mcg/kg |   |   |   | Second Dose Reduction to PegIntron 0.5 mcg/kg |   |   |   |
|--|---|---|---|---|---|---|---|
| Body Weight kg (lbs)                       | PegIntron Pre-filled Pen/Vial Strength to Use | Amount of PegIntron to Administer (mcg) | Volume *of PegIntron to Administer (mL) | Body Weight kg (lbs)                          | PegIntron Pre-filled Pen/Vial Strength to Use | Amount of PegIntron to Administer (mcg) | Volume* of PegIntron to Administer (mL) |
| <40 (<88)                                  | 50 mcg per 0.5 mL                             | 35                                      | 0.35                                    | <40 (<88)                                     | 50 mcg per 0.5 mL                             | 20                                      | 0.2                                     |
| 40-50 (88-111)                             | 120 mcg per 0.5 mL                            | 48 [45]                                 | 0.2                                     | 40-50 (88-111)                                | 50 mcg per 0.5 mL                             | 25                                      | 0.25                                    |
| 51-60 (112-133)                            | 50 mcg per 0.5 mL                             | 50                                      | 0.5                                     | 51-60 (112-133)                               | 80 mcg per 0.5 mL                             | 32 [30]                                 | 0.2                                     |
| 61-75 (134-166)                            | 80 mcg per 0.5 mL                             | 64                                      | 0.4                                     | 61-75 (134-166)                               | 50 mcg per 0.5 mL                             | 35                                      | 0.35                                    |
| 76-85 (167-187)                            | 80 mcg per 0.5 mL                             | 80                                      | 0.5                                     | 76-85 (167-187)                               | 120 mcg per 0.5 mL                            | 48 [45]                                 | 0.2                                     |
| 86-104 (188-230)                           | 120 mcg per 0.5 mL                            | 96                                      | 0.4                                     | 86-104 (188-230)                              | 50 mcg per 0.5 mL                             | 50                                      | 0.5                                     |
| 105-125 (231-275)                          | 150 mcg per 0.5 mL                            | 105 [108]                               | 0.35                                    | 105-125 (231-275)                             | 80 mcg per 0.5 mL                             | 64                                      | 0.4                                     |
| >125 (>275)                                | †   | † [135]                                 | †                                       | >125 (>275)                                   | †   | † [72]                                  | †                                       |

Numbers in [ ] indicate current recommended dose administered with REDIPEN in U.S. PegIntron label.

† For patients weighing greater than 125 kg (>275 pounds), the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

The Applicant has proposed a transition plan for the period of time during which REDIPEN remains available and (b)(4).

They anticipate (b)(4).

(b)(4). The review team considers this (b)(4) to be a time at high risk for medication errors. The Applicant intends to have an (b)(4).

In summary, the new DCI cartridges will be available in the same concentrations and the new device will deliver the same starting doses as the currently marketed injector. It will provide for dial-in dose adjustments for patients at the lower weight range but will not

allow dosing of those in the heaviest weight range. Minor differences in dose will result when some patients using the new DCI require dose adjustments but these differences are unlikely to have a negative impact on treatment.

## 9. Advisory Committee Meeting

Review and approval of this supplement did not warrant convening an Advisory Committee Meeting.

## 10. Pediatrics

This supplement does not trigger PREA and no additional pediatric studies are in progress or requested.

## 11. Other Relevant Regulatory Issues

No other relevant regulatory issues need to be addressed for this supplement.

## 12. Labeling

The Applicant submitted the proprietary name PegIntron® Selectdose™ for review. This name was considered acceptable by DMEPA reviewers.

The package insert for PegIntron® Selectdose™ has been revised to provide changes in the DOSAGE AND ADMINISTRATION sections 2.1, 2.2 and 2.3 regarding the new dose recommendations, specifically the new DCI volume increments and the doses delivered during dose reduction. In addition, section 2.6 describing Preparation and Administration has been revised with language appropriate for the new PegIntron® Selectdose™. In addition, section 11 Description and section 16 How Supplied/Storage and Handling have been updated with information regarding the new DCI.

Carton and container labels were reviewed by the DMEPA reviewer and several recommendations were forwarded to the Applicant. Please see Dr. Walker's review for a complete description. She recommended that the new Selectdose carton and container labeling be better differentiated from the currently available REDIPEN® and that the new packaging be flagged for the first six months after launch to alert users and health care providers that this is a new device.

No changes are proposed to the current Medication Guide.

The IFU have been completely rewritten to provide instructions on correct needle attachment, dial-in dose selection, and injection of PegIntron using the new DCI. Revised IFU language was provided by both the CDRH and DMEPA reviewers.

### **13. Recommendations/Risk Benefit Assessment**

- *Recommended Regulatory Action and Risk Benefit Assessment*

In summary, I agree with Dr. Miele and other members of the Review Team who recommend approval of this supplement. Although additional testing of the proposed revised IFU will be required post-approval, the new DCI appears to address many of the use issues related to the currently approved injector. In addition, the new DCI device includes a shielded needle which is likely to provide much better protection against accidental needle sticks compared to the approved device which has no needle shield. Dose delivery with the new performance-tested DCI is certainly likely to be more accurate and reliable than use of individual vials and syringes, a dosing method that is difficult for patients and caregivers. I agree that minor variations in dosing between the new DCI and the approved injector are unlikely to have a clinically significant impact on treatment outcomes.

I recommend the PegIntron Selectdose injector be approved for use, contingent upon successful completion of all necessary facility inspections. As the final inspection will not be performed until after this CDTL review is completed, a review addendum explaining the final regulatory decision will be submitted after the inspection report is available.

- *Recommendation for Postmarketing Risk Evaluation and Management Strategies*

A postmarketing REMS will not be requested for this product.

- *Recommendation for other Postmarketing Requirements and Commitments*

The review team considered further revision and testing of the IFU necessary to ensure optimal use of the new DCI. The following post-marketing study will be required; study milestone dates and exact language may vary slightly:

Conduct additional testing of the Instructions for Use (IFU) after incorporating the recommendations listed below. The goal of the PMR is to revise the IFU based upon the additional testing to help mitigate user errors and failures identified in the initial Design Validation Study. Please submit an Instructions for Use re-validation Study Protocol for review and comment prior to initiating the study. The study must be completed within 6 months after approval.

IFU Recommendations:

- a. During all printings in the [REDACTED] (b)(4) period between Redipen and Selectdose, until all lots of the Redipen expire, place a statement at the beginning of the IFU alerting patients, healthcare practitioners, and caregivers that this is a new pen device that is different from the Redipen and the steps to deliver a dose will be different.
- b. Emphasize the importance of critical steps [REDACTED] (b)(4) identified in the Design Validation Summary with bold text.
- c. Upon removal of the trailing zeros from the pen device, replace all current pictures with new pictures of the pen device without trailing zeros.
- d. Secondary to multiple errors identified in the Design Validation Summary, in [REDACTED] (b)(4) expand the pictures to show the entire pen and [REDACTED] (b)(4) add language that the pen is in an upright position.
- e. Secondary to multiple errors identified in the Design Validation Summary such as failure to remove the yellow paper from the push-on needle and placing the needle at the wrong end of the pen device, ensure that all pictures are presented in color instead of black and white to clearly illustrate the supplies needed to administer a dose of PegIntron.

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/s/  
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LINDA L LEWIS  
07/19/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103949Orig1s5259**

**CLINICAL REVIEW**

Medical Officer's Review of Prior Approval Supplement  
BLA 103949/5259

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Date submitted: October 10, 2012  
Date received: October 10, 2012  
Date completed: July 2, 2013

Sponsor: Merck Sharp & Dohme Corp.  
2000 Galloping Hill Rd.  
Kenilworth, NJ 07033

Drug: PEGINTRON<sup>®</sup> REDIPEN<sup>®</sup> (peginterferon alfa-2b powder for injection)

Indication: Treatment of chronic hepatitis C infection

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#### Executive Summary

This submission contains a prior approval supplement for BLA 103949 for PegIntron<sup>®</sup> to replace the currently approved REDIPEN<sup>®</sup> single-use pen injector with a newly designed dual-chamber injector (DCI) device (SELECTDOSE<sup>™</sup>) for drug delivery. The new

(b)(4)  
be simpler and more intuitive; it also has a new needle shield lock to minimize the risk of needle stick accidents. The volume settings on the new device are different than on the REDIPEN, a change that was purposefully done to provide greater convenience to patients of lower body weight and to minimize the use of vials and syringes. As a consequence, a few of the proposed new doses in the dose-reduction schema for mono and combination PegIntron therapy are different than the current REDIPEN recommendations. These differences are minor (2-3µg or 3-7% change from current dose recommendations) and unlikely to have a negative clinical impact; although the effect of these changes on efficacy or user/prescriber error has not been formally evaluated. The proposed labeling for PegIntron

(b)(4)  
proposed labeling adequately conveys the dosage recommendations (both initial and reduced) for the new device. In addition, the Sponsor plans

(b)(4)  
The proposed labeling and Instructions for Use (IFU) are

(b)(4)  
labeling, Medication Guide and IFU. Although the Sponsor reports an 89% success rate with the new DCI

device in a 2012 US Design Validation study, there were reports of multiple failures and close calls when users performed critical tasks under simulated use conditions. Most concerning, subjects who failed to use the device correctly were not aware of having made errors or what to do to prevent future errors; it was evident these users did not understand the device-user interface features, including the markings on the device and audible feedback "clicks" which were intended to facilitate correct use. As such, the proposed IFU was revised during this review cycle with Agency input and will be revalidated in a repeat study as a postmarketing requirement. From a clinical standpoint, approval of this supplement is recommended.

### 1.0 Background and Rationale

Biologics License Application (BLA) 103949 for PegIntron<sup>®</sup> (peginterferon alfa-2b) was approved on January 19, 2001 for the treatment of chronic hepatitis C virus (HCV) infection. On October 10, 2003, supplemental BLA (sBLA) 103949/5063 was approved to include the REDIPEN<sup>®</sup>, a single-use pen injector with a dual-chamber cartridge containing lyophilized drug product and Sterile Water for Injection, as the primary delivery device for PegIntron. After reconstitution with diluent, PegIntron is currently administered subcutaneously using the REDIPEN pre-filled pen.

(b)(4)

(b)(4) the Sponsor has developed a new injector device to ultimately replace the REDIPEN. In developing the new device, user needs were identified, with priority given to patient complaints and use error data obtained through postmarketing surveillance. The new injector device (Dual Chamber Injector [DCI]), like the current REDIPEN, is designed to deliver an adjustable, subcutaneous dose from the same dual-chamber PegIntron cartridges with automatic reconstitution of drug product from the cartridge. The new DCI device, however, was purposefully developed based on user feedback and is specifically designed to provide patients with a simpler, more intuitive sequence of steps for injection. The new device also incorporates a needle shield to help prevent accidental needle sticks.

The new DCI device has been under development since 2005. The Sponsor has sought to address (b)(4) using a thorough Human Factors, Usability Engineering and Risk Management approach. Meetings with patients and health care professionals in focus groups and Human Factors Evaluation (HFE) studies were carried out. Between 2008 and 2011, four formative HFE studies were done to evaluate the DCI and push-on needle device designs as well as the IFU and labeling. User errors were detected and mitigated in an iterative development.

cycle based on the results of these studies. The design of the new device evolved over time, with incrementally improved results. In a 2009 Quality Study, the Sponsor observed a successful injection rate [REDACTED] (b)(4). In a 2012 US Design Validation Study, with protocol input from FDA, the Sponsor reports that 89% of participants correctly using the DCI given appropriate training, a result that compares favorably to published data for other common self-administration devices, such as metered-dose respiratory inhalers.

The current submission provides a prior approval supplement to replace the current REDIPEN with the new DCI pre-filled device (submitted proprietary name: SELECTDOSE™). Because the new DCI device has different volume settings than the REDIPEN for the delivery of PegIntron, a new label, Medication Guide, and IFU have been submitted. A clinical overview with a risk-benefit analysis of the new DCI device is included in Module 2; however, no new clinical data are submitted.

## 2.0 Review Strategy

For the review of this sBLA, consultation was requested from the Center for Devices and Radiological Health (CDRH) to review the specifics of the device design and push-on needle as well as the results of the submitted HFE studies. Because the sBLA contains no new clinical data, this clinical review will be limited to the dose volume modifications proposed in labeling.

## 3.0 PegIntron Dose Volume Considerations

The strengths of the PegIntron cartridges (50 µg, 80 µg, 120 µg and 150 µg per 0.5 mL) to be used with the new DCI device are the same as those currently used with the REDIPEN. The REDIPEN provides five different volume settings (0.30, 0.35, 0.40, 0.45 and 0.50 mL) which can be dialed for administration with any strength PegIntron cartridge. The new DCI device also has the capability to dial-in five different volume settings and accommodate any strength cartridge, but the settings (0.20, 0.25, 0.35, 0.40 and 0.50 mL) are slightly different to accommodate lower doses of PegIntron.

The Sponsor chose these settings on the new DCI device to support both initial PegIntron dosing and dose reduction regimens for both the mono and combination regimens. A primary consideration was to replace or minimize the use of vials and syringes wherever possible and to preserve the 0.40 mL and 0.50 mL volumes since those are critical volumes for initial dosing. Another goal was to include doses appropriate for patients of lower body weight; therefore, the 0.2 mL and 0.25 mL volumes were added. Consequently, two of the five dose volumes available with the current REDIPEN had to be eliminated. The decision to eliminate the 0.3 mL and 0.45 mL dose volumes was based partly on limiting the impact to the dosing tables where the other three volume settings are currently used and partly to accommodate lower doses of PegIntron for patients of lower body weight without having to use vials and syringes.

In some cases of dose reduction, the volume settings and the PegIntron cartridge strengths recommended for the new DCI device differ slightly from those of the REDIPEN. The delivered dose, however, is still within a clinically acceptable range and the Sponsor does not anticipate any negative clinical impact. Specifically, there are four instances where the recommended DCI dose is slightly higher (i.e., 2-3 $\mu$ g or 6.7% increase) than the REDIPEN dose and one instance where the new dose is slightly lower (i.e., 3 $\mu$ g or 2.7% decrease). Such approximations to the target doses, which were themselves calculated based on the mean of the weight range as administered via vials and syringes, have been found to be acceptable in clinical practice based on current use of REDIPEN.

For monotherapy dose reductions, patients weighing  $\leq 45$  kg ( $\leq 100$  lbs) and 46-56 kg (101-124 lbs) will now be able to use the DCI device to continue dosing using the 0.20 and 0.25 mL volume settings, respectively, for dose reductions instead of using vials; the cartridge strength remains the same. In addition, patients weighing 57-72 kg (125-159 lbs) will be able to use the DCI device in the same strength (80 mcg/0.5mL) for their initial (starting) dose as well as for their dose reduction, but the volume will change to 0.2 mL (32 mcg) (Table 1). Patients in the remaining weight categories (73-88 kg, 89-106 kg, 107-136 kg and  $\geq 137$  kg) will use the same strength and dose volume as with the current REDIPEN.

For patients following the two-step dose reduction of PegIntron for combination therapy, there are four instances where the dose volume and strength of the new DCI device differ slightly from those currently used for REDIPEN (Table 2). These dose reduction modifications are minor and the delivered doses are still consistent with those of the REDIPEN. As an added benefit, the dose strength of the new DCI device for the initial dose in some instances will be consistent with the dose strength required for the dose reductions, thereby providing added convenience. Again for low-weight patients, i.e. weight  $< 40$  kg ( $< 88$  lbs), these patients can now continue to use the DCI device during a second dose reduction, unlike with the REDIPEN where vials are required. For patients weighing more than 275 lbs, the new DCI pen does not allow for a reduction dose that closely approximates the one in the current PegIntron label; therefore, the Sponsor proposes using various combinations of PegIntron dose strengths and volumes to achieve the appropriate dose.

Table 1 and 2 show proposed dose reduction tables for PegIntron Monotherapy and Combination therapy in adults. In those cases where the new DCI dose differs from the currently recommended dose using the REDIPEN injector, the current REDIPEN dose is shown in square brackets.

Table 1: Recommended Dose Reduction of PegIntron Monotherapy (0.5 mcg/kg) Using DCI (Adults)

| Body weight<br>kg (lbs)  | PegIntron <sup>®</sup><br>Strength to Use | Amount of<br>PegIntron <sup>®</sup> (mcg)<br>to Administer | Volume (mL) of<br>PegIntron <sup>®</sup> to Administer |
|--------------------------|---|--|--|
| ≤45<br>(≤100)            | 50 mcg per 0.5 mL                         | 20   | 0.2  |
| 46 – 56<br>(101 – 124)   | 50 mcg per 0.5 mL                         | 25   | 0.25   |
| 57 – 72<br>(125 – 159)   | 80 mcg per 0.5 mL                         | 32 [30]  | 0.2  |
| 73 – 88<br>(160 – 195)   | 50 mcg per 0.5 mL                         | 40   | 0.4  |
| 89 – 106<br>(196 – 234)  | 50 mcg per 0.5 mL                         | 50   | 0.5  |
| 107 – 136<br>(235 – 300) | 80 mcg per 0.5 mL                         | 64   | 0.4  |
| ≥137<br>(≥301)           | 80 mcg per 0.5 mL                         | 80   | 0.5  |

Numbers in [ ] indicate current recommended administered with Redipen<sup>®</sup> in US PegIntron<sup>®</sup> label.

Table 2: Proposed Two-Step Dose Reduction of PegIntron Combination Dosing Using DCI (Adults)

| First Dose Reduction to PegIntron <sup>®</sup> 1 mcg/kg |   |   |   | Second Dose Reduction to PegIntron <sup>®</sup> 0.5 mcg/kg |   |   |   |
|---|---|---|---|--|---|---|---|
| Body weight<br>kg (lbs)                                 | PegIntron <sup>®</sup><br>Strength to Use | Amount of<br>PegIntron <sup>®</sup><br>(mcg) to<br>Administer | Volume (mL)<br>of PegIntron <sup>®</sup><br>to Administer | Body weight<br>kg (lbs)                                    | PegIntron <sup>®</sup><br>Strength to Use | Amount of<br>PegIntron <sup>®</sup><br>(mcg) to<br>Administer | Volume (mL)<br>of PegIntron <sup>®</sup><br>to Administer |
| <40<br>(<88)  | 50 mcg<br>per 0.5 mL                      | 35  | 0.35  | <40<br>(<88)   | 50 mcg<br>per 0.5 mL                      | 20  | 0.2   |
| 40 – 50<br>(88 – 111)                                   | 120 mcg<br>per 0.5 mL                     | 48 [45]   | 0.2   | 40 – 50<br>(88 – 111)                                      | 50 mcg<br>per 0.5 mL                      | 25  | 0.25  |
| 51 – 60<br>(112 – 133)                                  | 50 mcg<br>per 0.5 mL                      | 50  | 0.5   | 51 – 60<br>(112 – 133)                                     | 80 mcg<br>per 0.5 mL                      | 32 [30]   | 0.2   |
| 61 – 75<br>(134 – 166)                                  | 80 mcg<br>per 0.5 mL                      | 64  | 0.4   | 61 – 75<br>(134 – 166)                                     | 50 mcg<br>per 0.5 mL                      | 35  | 0.35  |
| 76 – 85<br>(167 – 187)                                  | 80 mcg<br>per 0.5 mL                      | 80  | 0.5   | 76 – 85<br>(167 – 187)                                     | 120 mcg<br>per 0.5 mL                     | 48 [45]   | 0.2   |
| 86-104<br>(188-230)                                     | 120 mcg<br>per 0.5 mL                     | 96  | 0.4   | 86-104<br>(188-230)  | 50 mcg<br>per 0.5 mL                      | 50  | 0.5   |
| 105-125<br>(231-275)                                    | 150 mcg<br>per 0.5 mL                     | 105 [108]   | 0.35  | 105-125<br>(231-275)                                       | 80 mcg<br>per 0.5 mL                      | 64  | 0.4   |
| >125<br>(>275)  | *   | *[135]  | *   | >125<br>(>275)   | *   | *[72]   | *   |

Numbers in [ ] indicate current recommended administered with Redipen<sup>®</sup> in US PegIntron<sup>®</sup> label.

\* For patients weighing greater than 125 kg (>275 pounds), the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

There are no differences between the new DCI device and the REDIPEN with regards to initial (starting) PegIntron dose recommendations.

*Medical Officer's Comments:*

*The differences between the new DCI device and the current REDIPEN injector with respect to PegIntron dose reduction recommendations are minor and in only one instance does the recommended DCI dose represent a lower dose (-3%) than the REDIPEN dose. This reviewer agrees with the Sponsor that the proposed dose modifications are not likely to have a negative clinical impact.*

*For patients on combination PegIntron/REBETOL therapy weighing greater than 125 kg (>275 lbs), the new DCI device does not offer a straightforward dose reduction option like the REDIPEN. That said, PegIntron labeling recommends that initial dosing in patients weighing greater than 105 kg (>231 pounds) should be calculated based on the individual patient weigh, which may require combinations of various PegIntron dose strengths and volumes. Thus, the language for dose reduction recommendations in obese patients with the new DCI device is consistent with current initial dosing instructions and should not constitute a significant new burden to these patients.*

(b)(4)

*Medical Officer's Comments:*

*In a Type C meeting held on December 20, 2011, the Agency requested that the new dose modifications be evaluated as part of the usability study to ensure healthcare providers can calculate the differences in doses. Based on the submitted US Design Validation Summary Report, however, this issue does not appear to have been explored.*

**4.0 Proposed Labeling**

The major proposed revisions to the PegIntron label relate to those modifications to the dose reduction tables discussed above and are primarily found in Section 2, DOSAGE AND ADMINISTRATION. (b)(4)

?. No other substantive changes are proposed to either the USPI or Medication Guide.

This Medical Officer defers to the reviewers from CDRH and Division of Medication Error Prevention and Analysis (DMEPA) for review of the IFU for the new DCI device, and the reviewer from the Division of Medical Policy Programs (DMPP) for additional review of the Medication Guide.

## 5.0 Risk Management

This application is made to provide another administration option for PegIntron in the treatment of chronic hepatitis C. The introduction of the new DCI device (b)(4)

(b)(4) There are no modifications to the active ingredient(s) or therapeutic properties with the new device compared to the REDIPEN injector. Therefore, the safety specifications, pharmacovigilance plans, and risk minimization activities of the new DCI device are considered sufficiently addressed within the current, routine pharmacovigilance measures in place for PegIntron REDIPEN.

The Sponsor (b)(4)

## 6.0 Medical Reviewer's Assessment

The Sponsor contends that the new DCI device provides important advantages compared to the REDIPEN injector by offering more convenient dosing, especially for patients in the lower weight groups, and incorporating increased safety modifications. This reviewer defers to the CDRH consultant regarding whether the new DCI device and the accompanying IFU adequately address (b)(4)

(b)(4)

From a clinical standpoint, the dose reduction changes associated with the new DCI device are few and minor. Although, the clinical impact of these changes has not been formally evaluated, it is unlikely that these small differences in dosing (2-3 µg), representing a 7% increase or 3% decrease compared to current dose recommendations, will have a significant negative effect. Moreover, the proposed labeling has clear recommendations for dose reduction with the new device so that (b)(4)

(b)(4) it is unlikely that prescribers will confuse the dose reduction schemes for the new DCI device with the old REDIPEN, although this too has not been formally explored. Although there is potential for medication error by having both devices on the (b)(4) (b)(4) the Sponsor has indicated that each device will be (b)(4) (b)(4) with labeling, Medication Guide and IFU (b)(4) included in the packaging.

**7.0 Recommendation for Regulatory Action**

From a clinical standpoint, approval of this supplement is recommended.

Peter Miele, M.D.  
Medical Officer  
FDA/CDER/OAP/DAVP

Concurrence:  
HFD-530/TL/Lewis

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PETER S MIELE  
07/02/2013

LINDA L LEWIS  
07/03/2013

I concur with the clinical reviewer's assessment and recommendations.

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PETER S MIELE  
12/06/2012

LINDA L LEWIS  
12/06/2012

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103949Orig1s5259**

**MICROBIOLOGY REVIEW**

September 13, 2013

To: BLA103949

Approved by: Susan Kirshner, Ph. D., Associate Chief, LIM, DTP, OBP, CDER

From: Jinhai Wang, M.D., Medical Officer, DTP, OBP, CDER, HFD-122

Re: Supplement 103949-5259

**Subject: PEGINTRON® REDIPEN® (peginterferon alfa-2b powder for injection)  
Prior Approval Supplement - New Pre-Filled Pen  
REQUEST FOR PRIORITY REVIEW**

Date received: Oct. 10, 2012

#### **Recommendation**

Pending the recommendation from CDRH, DTP recommends approval of this application. There are no changes to the primary container closure, only secondary closures and packaging. Therefore there are no product quality concerns to be addressed in this submission.

#### **Review**

The PegIntron® pre-filled pen is a newly developed drug delivery device that is provided with a push-on needle, (b)(4) for administration of all strengths of the approved PegIntron drug product cartridges.

CDRH is responsible for reviewing the device.

There were no product changes except replacement of the injector device. There are no new primary packaging materials. Therefore, compatibility studies for the new device are not needed.

SCH-054031/MK-4031

#### **Claim of Categorical Exclusion**

Restricted Confidential – Limited Access

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(a). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the drug. To the best of the firm's knowledge, no extraordinary circumstances exist in regards to this action.

This sBLA involves the replacement of the PegIntron injector device by a new injector. No increase in the use of the drug from this action is expected.

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/s/  
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VICTORIA L TYSON  
12/13/2013

SUSAN L KIRSHNER  
12/13/2013



Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** June 19, 2013  
**To:** Administrative File, STN 103949/5259  
**From:** Donald C. Obenhuber, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsement** Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** PAS: efficacy supplement submitted to replace REDIPEN with a new single-use, dual chamber prefilled pen with a push on needle with Instructions for Use and recommendations for dose reductions.  
**Applicant:** Schering Corporation  
**US License:** 0994  
**Facility:** Schering-Plough Labo NV  
Industriepark 30 Zone A  
2220 Heist-op-den-Berg, Belgium  
FEI 3003974846  
**Product:** PEGINTRON® (peginterferon alfa-2b, Lyophilized powder for injection)  
**Dosage:** Subcutaneous injection (50, 80, 120 and 150 micrograms/0.5ml)  
**Indication:** Chronic Hepatitis C  
**PDUFA date:** Aug 10, 2013

**Recommendation:** This submission is recommended for approval from a product quality microbiology perspective.

**Review Summary**

A PAS from Schering Corp., a subsidiary of Merck & Co., Inc. requests replacement of the current Redipen with the new PegIntron prefilled pen. The PegIntron prefilled pen is a single-use, variable dose, disposable, spring-powered drug delivery device designed to inject the required dose of peginterferon alfa-2b. The medication is administered as a subcutaneous injection of a single weekly dose up to 24 or 48 weeks and is indicated for the treatment of chronic Hepatitis C. The PegIntron prefilled pen is supplied with (b)(4)

(b)(4) 30-gauge sterile push-on needle (b)(4)  
(b)(4)  
(b)(4)

(b)(4). The previously approved PegIntron cartridges are provided by the Singapore Branch of MSD International GmbH. Quality control inspection/testing of all components, labeling, and final assembly and release take place at Schering-Plough Labo NV, Industriepark 30-Zone A, 2220 Heist-op-den-Berg, Belgium, FEI No. 3003974846.

## Assessment

### 3.2.P.1 DESCRIPTION/COMPOSITION OF THE DRUG PRODUCT (32p1-desc-comp)

#### 1.0 DESCRIPTION AND COMPOSITION OF PEGINTRON PRE-FILLED PEN

##### 1.1 Introduction

Merck is switching to a newly developed pen referred to as the (b)(4). The PegIntron pre-filled pen uses the current approved PegIntron dual chamber glass cartridges; one chamber of the cartridge contains the lyophilized powder formulation of PegIntron and the second chamber contains sterile water for injection as diluent. Both the PegIntron pre-filled pen and the accompanying separate push-on needle were developed by Merck (b)(4). (b)(4) The classification of the PegIntron pre-filled pen and push-on needle are outlined in Table 1.

| Item  | Classification  |
|---|---|
| PegIntron pre-filled pen                    | The pen is classified as a Syringe Needle Introducer having Product Code KZH and identified in 21 CFR 880.6920 as a Class II device. (b)(4)<br>(b)(4) |
| Push-on needle                              | Class II as governed by 21 CFR 880.5570. (b)(4)   |
| PegIntron pre-filled pen and push-on needle | The PegIntron pre-filled pen and push-on needle are classified as a Combination Product governed by 21 CFR 3.2(e).                                    |

The PegIntron pre-filled pen is a single-use, disposable, spring-powered drug delivery device. The medication is administered as a subcutaneous injection of a single weekly dose over a prolonged period up to 24 or 48 weeks. The intended users are adult patients, healthcare professionals and caregivers.

#### 2.0 GENERAL DESCRIPTION OF PEGINTRON PRE-FILLED PEN

The PegIntron pre-filled pen is assembled from (b)(4):  
(b)(4)

The PegIntron pre-filled cartridge is assembled inside the pen.



The PegIntron pre-filled pen single-unit market package includes the preassembled pen (i.e. loaded with a PegIntron glass cartridge) and a separate sterile push-on needle that is attached to the pen just prior to use.

### 3.0 GENERAL DESCRIPTION OF THE PUSH-ON NEEDLE

The push-on needle (see Figure 4) is a sterile, non toxic, non-pyrogenic, single use needle consisting of a 30 Gauge (0.3 x 8 mm) surgical grade stainless steel cannula in a  (b)(4) hub and is intended to be used for the hypodermic injection of fluids into the body when attached to the PegIntron pre-filled pen.

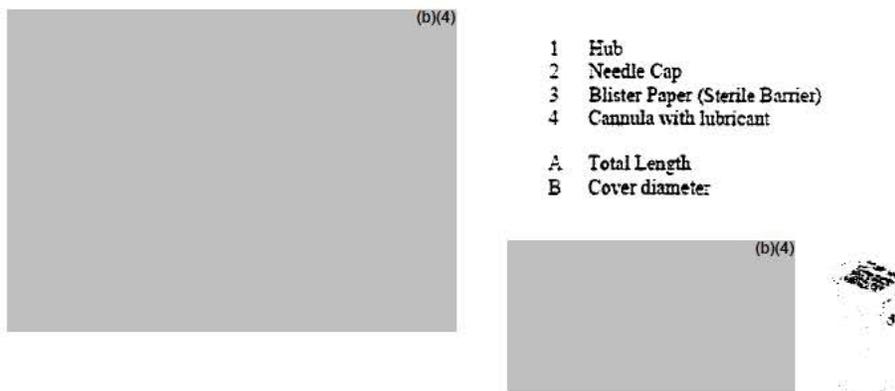


Figure 4 Push-on needle

The push-on needle is assembled into a  (b)(4) needle cap which is sealed with a sterile barrier blister paper. The needle cap serves as a protective cap when the user places the needle on the PegIntron pre-filled pen. After the needle is properly seated on the PegIntron pre-filled pen, the user can grip the knob at the end of the needle cap and separate the needle cap from the needle, leaving the needle firmly attached to the PegIntron pre-filled pen.

## 2.3.P DRUG PRODUCT

### 4.4.4 Product Container Closure Integrity

The container closure integrity (CCI) was tested following the assembly process validation runs at Schering-Plough Labo N.V. (Heist-op-den Berg, Belgium) and the shipping and transportation studies (see Section 4.4.5), to determine if the container closure integrity of the glass cartridge in the PegIntron pre-filled pen was compromised after assembly, labeling, packaging, and shipping conditions which simulated worst case shipment conditions..

The CCI test was performed using a (b)(4) method (see Section 3.2.P.8.2 for a summary of the procedure). The components of the PegIntron pens were assembled with placebo-containing glass cartridges at Schering-Plough Labo N.V. (Heist-op-den Berg, Belgium). Eighty (80) pens were collected after assembly and then subjected to the simulated shipping test, as described in the following section. The PegIntron pre-filled pen samples were then carefully disassembled and the cartridges tested for CCI. No (b)(4) was found in any of the samples or in the negative controls. (b)(4) occurred on all the positive controls.

### 4.4.5 Shipping and Transportation studies

The effect of shipping on the PegIntron pre-filled pen performance and packaging was evaluated before and after simulated ship testing. The simulated ship testing was conducted by (b)(4) (b)(4) to evaluate the protective performance of the packaged product related to vibrations, shocks, and other stresses normally encountered during handling and transportation. After simulated ship testing container closure integrity testing of the cartridges (see Section 4.4.4) were performed to demonstrate that the packaging provides sufficient protection of the product during shipment. The applied test conditions simulate worst case shipment conditions. Shipping presentations with maximum and minimum loads were packaged and shipped from Schering-Plough Labo NV operations (Heist) to (b)(4) testing.

After performing the simulation the shipping cartons and individual components were visually inspected for damage. The packaging was deemed acceptable provided there was no critical failure in the packaging due to simulated shipping test which would affect protection of the product as per post-shipment evaluation. Minor damage to the primary packaging (such as denting/scuffing) and damage to the secondary packaging (such as denting/torn carton) due to drop and vibration testing as well as due to shipping and handling was not considered a failure unless excessive as defined in the sampling plan. (b)(4) CCI testing was conducted on these units as described in the previous section. All cartridges remained intact and demonstrated that the transport simulation did not impact container closure integrity of the cartridges of the PegIntron pre-filled pen.

## 3.2.P.2 PHARMACEUTICAL DEVELOPMENT (32p2-pharm-dev)

### 8.4 Product Container Closure Integrity

The container closure integrity (CCI) was tested following the assembly process validation runs at Schering-Plough Labo N.V. (Heist-op-den Berg, Belgium) and the shipping and transportation studies (see Section 8.5), to determine if the container closure integrity of the glass cartridge in the PegIntron pre-filled pen was compromised after assembly, labeling, packaging, and shipping conditions which simulated worst case shipment conditions..

The CCI test was performed using a (b)(4) method (see Section 3.2.P.8.2 for a summary of the procedure). Eighty (80) pens were collected after assembly and then subjected to the simulated shipping test, as described in the following section. The PegIntron pre-filled pen samples were then carefully disassembled and the cartridges tested for CCI. (b)(4) (b)(4) was found in any of the samples or in the negative controls. (b)(4) occurred on all the positive controls.

*Comment 1: IR: With regard to container/closure integrity testing, please indicate the sensitivity of the test and describe how the sensitivity was measured.*

#### RESPONSE 1:

The sensitivity of the (b)(4) test was proven to be sufficient during the method development. Five (5) needle gauges (b)(4) were used to create defects (positive controls) in the glass cartridges from either the lyophilized powder or the Water for Injection (WFI) compartments. The results showed that:

1. Defects from the lyophilized powder compartment: The solid white powder (cake) in the lyophilized compartment immediately turns (b)(4) once the compartment is exposed to moisture regardless of the needle gauges. This change can be easily detected by visual observation.
2. Defects from the Water for Injection (WFI) compartment: the water (b)(4) for all needle gauges. Even though the (b)(4) depends on the needle gauge, the (b)(4) in all samples. This change can also be easily detected by visual observation.

The PEGINTRON pre-filled pen (b)(4) test (b)(4) Validation Report is provided.

*Comment: The method was demonstrated to be suitable to detect failures in cartridge integrity using the smallest needle gauge selected for testing, 31 gauge needle.*

#### 8.5 Shipping and Transportation studies

The effect of shipping on the PegIntron pre-filled pen performance and packaging was evaluated before and after simulated ship testing. The simulated ship testing was conducted by (b)(4) (b)(4) to evaluate the protective performance of the packaged product related to vibrations, shocks, and other stresses normally encountered during handling and transportation. After simulated ship testing, dose accuracy testing and container closure integrity

testing of the cartridges (see Section 8.4) were performed. The applied test conditions simulate worst case shipment conditions.

Shipping presentations with maximum and minimum loads (Table 20) were packaged and shipped from Schering-Plough Labo NV operations (Heist) (b)(4) for testing.

| <b>Presentation</b>            | <b>Quantity – Maximum load</b>  | <b>Quantity – Minimum load</b>  |
|--------------------------------|---|---|
| Single pack – small quantities | (b) shipper containing (b) single packs per shipper. (b)(4) placed in (b)(4)    | 1 shipper containing (b) single pack with buffer materials. (b)(4) placed in (b)(4)   |
| Single pack – large quantities | (b) shippers containing (b) single packs per shipper. Shipper placed in (b)(4). | (b) shippers containing (b) single packs per shipper and 1 shipper containing (b) single packs per shipper with buffer materials. Shipper placed into (b)(4) with buffer materials. |

(b)(4) CCI testing was conducted on these units. All cartridges remained intact and demonstrated that the transport simulation did not impact container closure integrity of the cartridges of the PegIntron pre-filled pen.

*Comment 2: IR: With regard to shipping validation please describe the worst case shipping conditions (time and temperature) and provide validation data with acceptance criteria.*

**RESPONSE 2:**

The PEGINTRON Redipen, which has the same package configuration as the PEGINTRON pre-filled pen, has been shipped in (b)(4) and (b)(4) thermal containers since 2003. The PEGINTRON pre-filled pen will be air shipped in the (b)(4) and (b)(4) thermal containers. The current (b)(4) cold chain shipping procedures will apply to the PEGINTRON pre-filled pen.

All product will be placed into shipping cartons at Schering-Plough Labo NV (Heistop-den-Berg, Belgium). The shipping cartons will then be transported to the distribution center, (b)(4). The shipping containers are then de-palletized at (b)(4) and packed into (b)(4) thermal containers. The thermal containers will then be transported to (b)(4) followed by a (b)(4) to local distribution centers. The maximum shipping duration is (b)(4). See Figure 1 for reference.



**Figure 1: Shipping configurations used for the PEGINTRON pre-filled pen**

#### Distribution Qualification Testing

Distribution testing was conducted by Heist in the (b)(4) thermal containers to provide qualification data to support shipments of PEGINTRON pre-filled pens. The testing successfully concluded that the (b)(4) thermal containers will protect the PEGINTRON pre-filled pen finished goods images from hazards normally encountered during routine transportation and distribution.

PEGINTRON pre-filled pen samples were collected after the PegIntron pre-filled pen shipping study for dose accuracy and container closure integrity testing.

The Container Closure Integrity Test was performed by using validated method (b)(4) (b)(4) for PEGINTRON Dual Chamber Wet/Dry Cartridge” on the glass Cartridge. No (b)(4) was found on any of the test samples and negative controls. In contrast, (b)(4) (b)(4) was shown on all the positive controls.

#### Thermal Qualification Testing

The validation provided the worst case scenario with stress tests at +50 °C and at -20 °C per box and per Load (Max and Min load), a total 4 stress test for each box. The acceptance criteria were +2° and +8°C (+/- 0.5°C) for a shipping duration (b)(4) hours. The temperature was recorded using (b)(4) temperature sensors.

|                   |  |                           |                       |
|-------------------|--|---------------------------|-----------------------|
| <b>PQP 03-518</b> | <b>VALIDATION SUMMARY OF THE</b><br>(b)(4) | <b>Date :</b><br>13/08/09 | <b>Page:</b><br>3 / 6 |
|-------------------|--|---------------------------|-----------------------|

5.1. (b)(4)

**Maximum load**

|                            | Test number | Maximum temperature | Minimum temperature | Duration between min/max temperature |
|----------------------------|-------------|---------------------|---------------------|--------------------------------------|
| Cyclic profile             | 04-0085     | (b)(4)              | (b)(4)              | (b)(4)                               |
|                            | 04-0098     |                     |                     |                                      |
|                            | 04-0118     |                     |                     |                                      |
| Constant temperature +20°C | 04-0155     | (b)(4)              | (b)(4)              | (b)(4)                               |
|                            | 04-0159     |                     |                     |                                      |
|                            | 04-0166     |                     |                     |                                      |
| Stress test +50°C          | 04-0175     | (b)(4)              | (b)(4)              | (b)(4)                               |
| Stress test -20°C          | 04-0185     |                     |                     |                                      |

**Minimum load**

|                            | Test number | Maximum temperature | Minimum temperature | Duration between min/max temperature |
|----------------------------|-------------|---------------------|---------------------|--------------------------------------|
| Cyclic profile             | 04-3086     | (b)(4)              | (b)(4)              | (b)(4)                               |
|                            | 04-3099     |                     |                     |                                      |
|                            | 04-3181     |                     |                     |                                      |
| Constant temperature +20°C | 04-3154     | (b)(4)              | (b)(4)              | (b)(4)                               |
|                            | 04-3167     |                     |                     |                                      |
|                            | 04-3168     |                     |                     |                                      |
| Stress test +50°C          | 04-3176     | (b)(4)              | (b)(4)              | (b)(4)                               |
| Stress test -20°C          | 04-3186     |                     |                     |                                      |

5.2. (b)(4)

**Maximum load**

|                            | Test number | Maximum temperature | Minimum temperature | Duration between min/max temperature |
|----------------------------|-------------|---------------------|---------------------|--------------------------------------|
| Cyclic profile             | 04-0068     | (b)(4)              | (b)(4)              | (b)(4)                               |
|                            | 04-0100     |                     |                     |                                      |
|                            | 04-0120     |                     |                     |                                      |
| Constant temperature +20°C | 04-0158     | (b)(4)              | (b)(4)              | (b)(4)                               |
|                            | 04-0169     |                     |                     |                                      |
|                            | 04-0170     |                     |                     |                                      |
| Stress test +50°C          | 04-0177     | (b)(4)              | (b)(4)              | (b)(4)                               |
| Stress test -20°C          | 04-0187     |                     |                     |                                      |

|            |                                     |                    |                |
|------------|-------------------------------------|--------------------|----------------|
| PQP 03-518 | VALIDATION SUMMARY OF THE<br>(b)(4) | Date :<br>13/08/09 | Page:<br>4 / 6 |
|------------|-------------------------------------|--------------------|----------------|

Minimum load

|                            | Test number | Maximum temperature | Minimum temperature | Duration between min/max temperature |
|----------------------------|-------------|---------------------|---------------------|--------------------------------------|
| Cyclic profile             | 04-0088     | (b)(4)              |                     |                                      |
|                            | 04-0101     |                     |                     |                                      |
|                            | 04-0121     |                     |                     |                                      |
| Constant temperature +20°C | 04-0157     | (b)(4)              |                     |                                      |
|                            | 04-0171     |                     |                     |                                      |
|                            | 04-0172     |                     |                     |                                      |
| Stress test +50°C          | 04-0178     | (b)(4)              |                     |                                      |
| Stress test -20°C          | 04-0188     | (b)(4)              |                     |                                      |

5.3. (b)(4)

Maximum load

|                            | Test number | Maximum temperature | Minimum temperature | Duration between min/max temperature |
|----------------------------|-------------|---------------------|---------------------|--------------------------------------|
| Cyclic profile             | 04-0235     | (b)(4)              |                     |                                      |
|                            | 04-0240     |                     |                     |                                      |
|                            | 04-0245     |                     |                     |                                      |
| Constant temperature +20°C | 04-0257     | (b)(4)              |                     |                                      |
|                            | 04-0273     |                     |                     |                                      |
|                            | 04-0313     |                     |                     |                                      |
| Stress test +50°C          | 04-0326     | (b)(4)              |                     |                                      |
| Stress test -20°C          | 04-0292     | (b)(4)              |                     |                                      |

Minimum load

|                            | Test number | Maximum temperature | Minimum temperature | Duration between min/max temperature |
|----------------------------|-------------|---------------------|---------------------|--------------------------------------|
| Cyclic profile             | 04-0236     | (b)(4)              |                     |                                      |
|                            | 04-0241     |                     |                     |                                      |
|                            | 04-0246     |                     |                     |                                      |
| Constant temperature +20°C | 04-0258     | (b)(4)              |                     |                                      |
|                            | 04-0274     |                     |                     |                                      |
|                            | 04-0314     |                     |                     |                                      |
| Stress test +50°C          | 04-0327     | (b)(4)              |                     |                                      |
| Stress test -20°C          | 04-0293     | (b)(4)              |                     |                                      |

*Comment: The qualification is sufficient to maintain PEGINTRON pre-filled pen at 2° - 8°C for a maximum duration (b)(4) hours. The thermal containers will protect the PEGINTRON pre-filled pen during routine transportation and distribution.*

Satisfactory

**3.2.P.3.1 MANUFACTURER  
(32p3-manuf)**

STN 103949/5259, Schering Corporation, PEGINTRON® (peginterferon alfa-2b)

The PegIntron® pre-filled pen uses the same PegIntron dual chamber glass cartridges (PegIntron cartridge) as the current REDIPEN® injector. Manufacturer information on the PegIntron dual chamber cartridge is unchanged as described in our PegIntron BLA (BL 103949).

MSD International GmbH (Singapore Branch)

60 Tuas West Drive

Singapore, 638413

FEI 3004611169

Manufacture of the PegIntron cartridges (compounding, sterile filling, lyophilization and inspection) and (b)(4) control testing, QC release and stability testing

Inspected by IOG July 12-16, 2010 (as Schering Plough Ltd.) and classified NAI. This inspection covered sterile biotech drug product manufacturing operations. The TRP profile was updated and is acceptable. A routine GMP surveillance inspection of this site has been requested for the beginning of FY2013.



Schering-Plough Labo NV

Industriepark 30 Zone A

2220 Heist-op-den-Berg, Belgium

FEI 3003974846

Assembly and (b)(4) testing of the PegIntron pre-filled pens

Inspected by IOG October 22-26, 2012 with no initial classification entered in FACTS. Manufacturing, packaging, and testing operations were covered. The control testing profiles are currently listed as acceptable.

### 3.2.P.3.3 DESCRIPTION OF MANUFACTURING PROCESS/PROCESS CONTROLS

#### 1.0 DESCRIPTION OF THE PEGINTRON PRE-FILLED PEN MANUFACTURING

##### 1.1 Introduction

The PegIntron® pre-filled pen uses the same PegIntron dual chamber glass cartridges (PegIntron cartridge) as per the current approved CMC information in our PegIntron BLA (BL 103949). A

description of the manufacturing process for the PegIntron pre-filled pen at Schering-Plough Labo N.V. (Heist-op-den Berg), Belgium (b)(4) packaging site) is provided in this section.

(b)(4) PegIntron pre-filled pen are received at the Schering-Plough Labo N.V. (Heist-op-den Berg, Belgium) facility (b)(4) final product release. The supply of the individual components required for the PegIntron pre-filled pen manufacturing process is outlined in Figure 1.



Figure 1 Flow Diagram of PegIntron Pre-filled Pen Components

## 2.0 PROCESSING OF THE PEGINTRON PRE-FILLED CARTRIDGES

All the current approved CMC information in our PegIntron BLA (BL 103949) for both the Peginterferon alfa-2b drug substance and the PegIntron pre-filled dual chamber cartridges remains unchanged.

The Peginterferon alfa-2b drug substance is manufactured and tested at the Schering-Plough (Brinny) Co, facility in Co. Cork, Ireland. The dual chamber PegIntron pre-filled cartridges are manufactured at the MSD International GmbH (Singapore Branch) facility in Singapore. When the release testing of the PegIntron pre-filled cartridges has been successfully completed, the shipment is released to Schering-Plough Labo N.V. (Heist-op-den Berg), Belgium for assembly and packaging operations.

## 5.0 INJECTOR ASSEMBLY PROCESS

The pre-filled PegIntron

(b)(4)  
(b)(4)

(b)(4)

The PegIntron pre-filled pen assembly process consists of the following steps:

(b)(4)

### 3.2.P.5.2 ANALYTICAL PROCEDURES (32p52-analyt-proc)

The analytical procedures for the PegIntron® pre-filled pen remain unchanged when compared to the current approved PegIntron® REDIPEN® analytical procedures.

### 3.2.P.5.3 VALIDATION OF ANALYTICAL PROCEDURES (32p53-val-analyt-proc)

The current approved analytical method validations detailed in our PegIntron BLA (BL 103949) for PegIntron® REDIPEN® are also applicable to PegIntron® pre-filled pen.

### 3.2.P.7 CONTAINER CLOSURE SYSTEM

#### 1.0 PEGINTRON PRE-FILLED PEN

The PegIntron pre-filled pen uses the same PegIntron dual chamber glass cartridges (PegIntron cartridge) as the current RediPen injector. The PegIntron is contained in a two chamber cartridge as a lyophilized powder separated from the diluent (sterile water for injection) (b)(4)

Detailed information on the dual chamber cartridge primary container closure system was previously submitted to our PegIntron BLA as part of the following PegIntron Redipen prior approval

supplements (STN: BL 103949/5063 approved Oct 10, 2003 and STN: BL 103949/5091 approved Sept 09, 2004).

A separate sterile push-on needle, provided with the PegIntron pre-filled pen, is attached to the PegIntron pre-filled pen by the end user prior to injection. Figure 3 shows the assembled PegIntron pre-filled pen and the pre-packaged sterile 30 Gauge push-on needle.

## 2.1 Description

The PegIntron pre-filled pen sub-assembly (Figure 4) is composed of (b)(4) plastic parts and metal parts (e.g. springs).



1 – Filled Cartridge

2 – Cartridge Retainer

3 – Push-on Needle

**Figure 4 PegIntron pre-filled pen and push-on needle**

## (b)(4) PUSH-ON NEEDLE

### 3.1 Description

The push-on needle is a sterile, non-toxic, non-pyrogenic, single use needle consisting of a 30 Gauge Type 304 surgical grade stainless steel cannula in a (b)(4) hub. The needle extends 8 mm from the hub. The push-on needle is intended to be used for the hypodermic injection of fluids into the body when attached to the PegIntron pre-filled pen. It is assembled into a (b)(4) needle cap which is sealed with a sterile barrier blister paper. The needle cap serves as a protective cap when the user places the needle on the PegIntron pre-filled pen.

(b)(4) The product is sterilized by a validated (b)(4) sterilization process, using the (b)(4) at Schering-Plough Labo NV (Heist-op den Berg, Belgium). Additional information on the push-on needle can be found in (b)(4), (b)(4). The only product contact material is the 304 stainless steel cannula of the needle.

3.2.P.8.2 POST-APPROVAL STABILITY PROTOCOL/STABILITY COMMITMENT

1.0 PEGINTRON PRE-FILLED PEN POST MARKETING STABILITY STUDY

The tests and testing intervals used in this stability study are listed in Table 1. At each time point, fifty (50) injectors were tested, ten (10) injectors per each of the five (5) dose settings.

| <b>Table 1 Study Design for the PegIntron Pre-Filled Pen Post Marketing Stability Study</b>   |                                  |           |           |           |           |           |
|---|----------------------------------|-----------|-----------|-----------|-----------|-----------|
| <b>Test</b>   | <b>Time points (months)</b>      |           |           |           |           |           |
|   | <b>T<sub>0</sub><sup>a</sup></b> | <b>12</b> | <b>18</b> | <b>24</b> | <b>30</b> | <b>36</b> |
| CCI <sup>b</sup>  | X                                | X         | X         | X         | X         | X         |
| Dose Accuracy   | X                                | X         | X         | X         | X         | X         |
| Visual Inspection   | X                                | X         | X         | X         | X         | X         |
| <p>a T<sub>0</sub> is the date that the samples are stored at the prescribed condition (temperature, humidity and orientation), and thus the start date of the stability study. This test point is used to calculate the other test points.</p> <p>b Container Closure Integrity (b)(4) for Peg-Intron Wet/Dry Cartridges</p> |                                  |           |           |           |           |           |

2.0 ANALYTICAL PROCEDURES

The analytical procedures used in the stability study.

2.1 Container Closure Integrity (b)(4) for Peg-Intron wet/dry cartridges

The PegIntron pre-filled pen samples were carefully disassembled and the cartridges tested for CCI. Cartridges are completely immersed in a (b)(4) and exposed sequentially to the following conditions for a minimum (b)(4) minutes each: a (b)(4) at least (b)(4). After rinsing the exterior of the cartridges with water, the contents of the cartridges are visually examined for the presence of (b)(4).

Acceptance criteria:

No (b)(4) should be observed on any sample or any negative control. The positive controls should contain (b)(4) in the cartridges. Reconstitution should not be observed on any test samples except the positive controls.

*Comment: Stability testing intervals are acceptable.*

Satisfactory

*Comment: All text in italics provides the reviewers comments, all other text is derived from the submission and is used either directly or paraphrased to provide information to support the reviewer's evaluation.*

**GMP Status:**

TBD

**Conclusion**

- I. This supplement is recommended for approval from a product quality microbiology perspective.
- II. Information and data in this submission not related to the drug product quality microbiology perspective was not evaluated and should be reviewed by an OBP reviewer.
- III. No additional inspectional follow-up items were identified.

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/s/  
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DONALD C OBENHUBER  
07/03/2013

COLLEEN THOMAS  
07/03/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

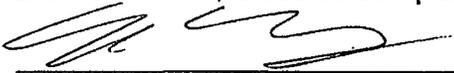
**103949Orig1s5259**

**OTHER REVIEW(S)**

## QUALITY SYSTEM EIR REVIEW

**DATE:** November 5, 2013

**FROM:** General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH

**THROUGH:** Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH  
 11/18/13

**TO:** Ranjani Prabhakara, Generic Drug Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

**CC:** Francis Godwin, Generic Drug Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

Victoria Tyson, Division of Antiviral Products, Office of Antimicrobial Products, Office of New Drugs, CDER

Office of Combination Products at [combination@fda.gov](mailto:combination@fda.gov)

**SUBJECT:** Review of Establishment Inspection Report (EIR) and Exhibits

EI dates September 2-5, 2013  
CDRH Receipt Date of EIR: October 17, 2013

**Site Inspected:** Schering Plough Labo NV  
Industriepark 30, Zone A  
2220 Heist-op-den-Berg, Belgium

**Type of Establishment:** Assembler, Packager, Labeler

**FEI/CFN:** 3003974846

**COMBINATION PRODUCT:** Selectdose PegIntron Drug Delivery System

**INVESTIGATOR:** Angela E. Glenn, FLA-DO

**ORA**

**RECOMMENDATION:** NAI

**CDRH OC**

**DECISION:** NAI for QS reg; Overall Classification Pending

## **I. Purpose and Type of Inspection**

The purpose for this inspection was to conduct a pre-approval inspection for the Selectdose PegIntron, a combination product, under BLA 103949/5259. It was conducted in accordance with CP 7382.845, Inspection of Medical Device Manufacturers (FACTS No. 1505975). The current CDER-requested inspection was a comprehensive baseline Level 2 inspection.

## **II. Background Information**

Schering Plough Labo NV is an assembler, packager, labeler of the Selectdose PegIntron, a single use, variable dose, disposable, spring-powered drug delivery system. It is indicated for the treatment of chronic Hepatitis C.

The firm is currently registered and listed as a drug manufacturer. There have been no previous regulatory actions against the firm.

## **III. Regulatory History**

This is the firm's initial medical device inspection. Previous inspections of the firm conducted on July 10-11, 2008, March 19-22, 2012, and October 22-26, 2012 covered drug-related activities. All these inspections were classified as NAI.

## **IV. Current Inspection**

The General Hospital Devices Branch of the Division of Enforcement A has completed its good manufacturing practices review and evaluation under the Quality System (QS) regulation of the Establishment Inspection Report (EIR) and exhibits for the inspection which closed on September 5, 2013, and which took place at Schering Plough Labo NV, Heist-op-den-Berg, Belgium, facility. The inspection of this firm indicates that it meets the criteria of a Situation II, in Compliance Program, CP 7382.845, Part V, dated February 2, 2011, in that there is minimal probability that the establishment will produce nonconforming

and/or defective medical devices and the inspection is being classified NAI.

CDRH concurs with the classification recommendation of NAI based on the information present.

**V. Quality System Review**

The review of the EIR and exhibits did not disclose any QS regulation violations or objectionable conditions that justify further FDA action.

**VI. Observations Pertaining To Other Regulations**

There are no observations pertaining to other regulations.

**VII. Nonsupportable FDA 483 Observations**

There are no nonsupportable FDA 483 observations.

**VIII. CDRH Recommendation and Follow-up**

CDRH has classified the inspection NAI under the QS regulation based on the EIR dated September 2-5, 2013. CDRH defers to CDER, the lead Center for this inspection, to make a final decision on the overall classification of the inspection.

  
\_\_\_\_\_  
Emre Genca

Drafted: EGenca: 11/5/13  
Reviewed: MITejero: 11/6/13  
Reviewed: CFischer:  
Final:

cc:  
WO66-3513 (OC Division Chron. File)  
HFR-SE250 (AEGlenn)  
WO66-3548 (EGenca)

CTS No.: ICC1300558

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/s/

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VICTORIA L TYSON  
11/20/2013 .

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance, Division of Enforcement A  
General Hospital Devices Branch

**DATE:** November 5, 2013

**TO:** Ranjani Prabhakara, Generic Drug Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

**CC:** Francis Godwin, Generic Drug Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

Victoria Tyson, Division of Antiviral Products, Office of Antimicrobial Products, Office of New Drugs, CDER

Office of Combination Products at [combination@fda.gov](mailto:combination@fda.gov)

**THROUGH:** Carl Fischer, Ph.D., Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO66, Room 3526



Handwritten signature of Emre Genca with date 11/14/13.

**FROM:** Emre Genca, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO66, Room 3548

**APPLICANT:** Merck & Co., Inc.  
One Merck Drive  
Whitehouse Station, NJ 08889-0100

**INSPECTION SITE:** Schering Plough Labo NV  
Industriepark 30, Zone A  
2220 Heist-op-den-Berg, Belgium  
FEI No. 3003974846

**APPLICATION NO.:** BLA 103949/5259

**PRODUCT NAME:** Selectdose PegIntron Drug Delivery System

**CONSULT INSTRUCTIONS:** The request is to perform a post-inspection compliance review of Schering Plough Labo NV (FEI No. 3003974846) in support of BLA 103949/5259. Original classification of the inspection, which ended on September 5, 2013, was NAI.

---

The Office of Compliance at CDRH received a consult request from CDER/OC/OMPQ/DGMPA/GDMAB to perform a post-inspection compliance review of Schering Plough Labo NV (FEI No. 3003974846) in support of BLA 103949/5259.

Through BLA 103949/5259, Merck & Co., Inc. requested that the Selectdose PegIntron Drug Delivery System be approved for marketing and distribution. In a memorandum dated December 13, 2012, CDRH/OC recommended that Schering Plough Labo NV, the facility where final assembly of the finished combination product takes place, be inspected prior to the approval of BLA 103949/5259.

#### **Application Documents Evaluation**

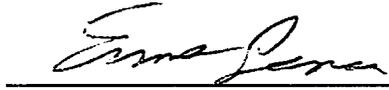
Please see the attached Quality System EIR Review Memorandum.

#### **Regulatory History Evaluation**

Please see the attached Quality System EIR Review Memorandum for a review of the Schering Plough Labo NV regulatory history.

#### **CDRH Office of Compliance Recommendation**

The Office of Compliance at CDRH has completed the evaluation of the EIR dated September 2-5, 2013, for the inspection which took place at Schering Plough Labo NV, Heist-op-den-Berg, Belgium, facility, in support of BLA 103949/5259, and recommends that the inspection be classified as NAI for the device Quality System regulation. CDRH defers to CDER to make a final decision on the overall classification of the inspection and on BLA approval.



Emre Genca

Attachment:

Schering Plough Labo NV Quality System EIR Review Memorandum

Prepared: EGenca: 11/5/13

Reviewed: MITejero: 11/6/13

Reviewed: CFischer:

Final:

CTS No.: ICC1300558

BLA 103949/5259

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/s/  
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VICTORIA L TYSON  
11/20/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** October 16, 2013

**To:** Victoria Tyson, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Kemi Asante, Pharm.D., Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

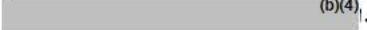
**CC:** Samuel Skariah, Pharm.D., Group Leader  
OPDP

**Subject:** **BLA 103949 PegIntron (Peginterferon alfa-2b) for Injection, for Subcutaneous Use**  
 (b)(4) Training Materials and Marketing Resources

---

As requested in DAVP's email dated September 25, 2013, OPDP has reviewed the following proposed materials for PegIntron:

-  (b)(4)
- 
- 
- 
- 
- 
- 
- 

The purpose of these materials is to educate patients and healthcare professionals about the PegIntron Selectdose pre-filled pen which will  (b)(4).  
 (b)(4).

OPDP offers the following comments regarding the proposed materials:

## **GENERAL COMMENTS**

- We are not commenting on the proposed (b)(4) and (b)(4) because they are mainly promotional in nature and OPDP would be happy to provide comments to the sponsor separately. Please ask the sponsor to submit annotated versions of these items directly to OPDP if they would like advisory comments from us on these pieces.
- Several images in the proposed materials are designated “FPO”. OPDP is unable to comment on the acceptability of images labeled “FPO.”
- The proposed materials are considered to be promotional labeling. Therefore, please remind the sponsor, pursuant to 21 CFR 314.81(b)(3)(i), to submit the final version of the materials under cover of Form FDA 2253 at the time of initial dissemination.

## **SPECIFIC COMMENTS**



Thank you for the opportunity to provide comments on these proposed materials. If you have any questions, please contact me at 301-796-7425 or at [Kemi.Asante@fda.hhs.gov](mailto:Kemi.Asante@fda.hhs.gov).

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/s/  
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OLUWASEUN A ASANTE  
10/16/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance, Division of Enforcement A  
General Hospital Devices Branch

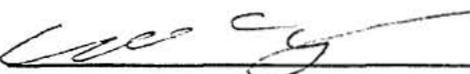
**DATE:** August 26, 2013

**TO:** Peter Miele, OND/OAP/DAVP, CDER, WO22, Room 6380,  
[peter.miele@fda.hhs.gov](mailto:peter.miele@fda.hhs.gov)

Victoria Tyson, OND/OAP/DAVP, CDER, WO22, Room 6392,  
[victoria.tyson@fda.hhs.gov](mailto:victoria.tyson@fda.hhs.gov)

Office of Combination Products at [combination@fda.gov](mailto:combination@fda.gov)

**THROUGH:** Carl Fischer, Chief, General Hospital Devices Branch, Division of  
Enforcement A, Office of Compliance, CDRH, WO66, Room 3526

 8/28/13

**FROM:** Emre Genca, General Hospital Devices Branch, Division of Enforcement  
A, Office of Compliance, CDRH, WO66, Room 3548

**APPLICANT:** Schering Corp., a subsidiary of Merck & Co., Inc.

**APPLICATION NO.** BLA 103949/5259

**PRODUCT NAME:** PegIntron Selectdose

**CONSULT INSTRUCTIONS:** Review the Performance Qualification Data submitted (b)(4)  
(b)(4) Schering Corp.

The Office of Compliance at CDRH received a consult request from CDER to evaluate BLA  
103949/5259, specifically the Performance Qualification Data submitted (b)(4)  
(b)(4) Schering Corp.

PegIntron Selectdose is a single-use, variable dose, disposable, spring-powered drug delivery  
device designed to inject the required dose of peginterferon alfa-2b. The medication is  
administered as a subcutaneous injection of a single weekly dose up to 24 or 48 weeks and is  
indicated for the treatment of chronic Hepatitis C. This product includes a (b)(4)  
(b)(4) 30-gauge, sterile push-on needle (b)(4)

PegIntron Selectdose. Drug product cartridges are provided by the Singapore Branch of MSD International GmbH. Quality control inspection/testing of all components, labeling, and final assembly and release take place at Schering-Plough Labo NV, Industriepark 30-Zone A, 2220 Heist-op-den-Berg, Belgium, FEI No. 3003974846.

#### Application Documents Evaluation

The following documents were evaluated:

PQ-P-0139-001-1201 Assembly Process Performance Qualification Protocol  
PQ-R-0139-001-1201 Assembly Process Performance Qualification Report

The performance qualification (PQ) of the push-on needle assembly process was conducted to demonstrate consistent, reproducible results meeting pre-established test acceptance criteria. It

(b)(4)

It should be noted that an initial, post-market inspection in accordance with CP 7382.845, Inspection of Medical Device Manufacturers, was conducted from (b)(4)

(b)(4)

Push-on needle (b)(4)

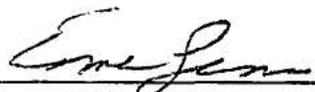
Needle appearance tests, stylet tests, needle dimension tests (outside diameter, patient-end length), and final functional tests (b)(4) were conducted with pre-established test acceptance criteria. The PQ was performed on three consecutive assembly batches of (b)(4) push-on needles. The needles were randomly collected and tested according to the sampling plan. Passing results were shown for all tests.

The review of these documents showed no apparent deficiencies.

#### CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application BLA 103949/5259 and has the following recommendation:

The desk review of the Performance Qualification Data submitted by the sponsor appeared to show no deficiencies. PegIntron Selectdose approvability under the Medical Device Regulations should be delayed until the inspections of Schering-Plough Labo (b)(4) have been conducted and are deemed acceptable.

  
Emre Genca

Prepared: EGenca: 8/26/13  
Reviewed: MITejero: 8/27/2013  
Reviewed: CFischer:  
Final:

CTS No.: ICC1300355  
BLA 103949/5259

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/s/  
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VICTORIA L TYSON  
09/04/2013



Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** July 18, 2013  
**From:** Jacqueline Ryan, Combination Products Team Leader, WO66, RM 2556  
General Hospital Devices Branch, DAGID, ODE, CDRH  
**To:** Victoria Tyson, CSO, OMPT/CDER/OND/OAP/DAVP  
**Subject:** CDRH Consult, ICC, sBLA 103949/5259, Pre-filled pen injector to deliver  
PegIntron alfa-2b

## 1. Issue

The Center for Drug Evaluation and Research (CDER)] has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding sBLA103949/5259. The device constituent of this combination product consists of a Pre-filled pen injector to deliver PegIntron alfa-2b.

## 2. Device Description

### Pre-filled Pen

The (b)(4) pen is a single-use, variable dose, disposable, spring powered drug delivery device designed to deliver the required dose of Peg interferon alfa-2b drug product (see **Figure 1**). The PegIntron pre-filled pen is non-product contact and is thus considered functional secondary packaging<sup>1</sup> with the purpose of delivering the intended dose and ensuring safety by preventing needle sticks.



Figure 1 PegIntron pre-filled pen

The PegIntron pre-filled pen uses the same PegIntron dual chamber glass cartridges (PegIntron cartridge) as the current RediPen injector. The PegIntron is contained in a two chamber cartridge as a lyophilized powder separated from the diluent (sterile water for injection) (b)(4)

(b)(4) Detailed information on the dual chamber cartridge primary container closure system was previously submitted to the PegIntron BLA as part of the following PegIntron Redipen prior approval supplements (STN: BL 103949/5063 approved Oct 10, 2003 and STN: BL 103949/5091 approved Sept 09, 2004).

The PegIntron pre-filled pen sub-assembly is composed of (b)(4) plastic parts and metal parts (e.g. springs). A drawing of the PegIntron prefilled pen sub assembly detailing the individual components is provided as **Figure 5**.



- 1 - Filled Cartridge
- 2 - Cartridge Retainer
- 3 - Push-on Needle

**Figure 4 PegIntron pre-filled pen and push-on needle**





**Figure 5 PegIntron pre-filled pen sub assembly components**

| Table 1 Sub-Assembly: Materials of Construction |        |
|---|--------|
| Component Name                                  | (b)(4) |
| (b)(4)  | (b)(4) |
| N/A: Not Applicable                             |        |
| 1)  | (b)(4) |

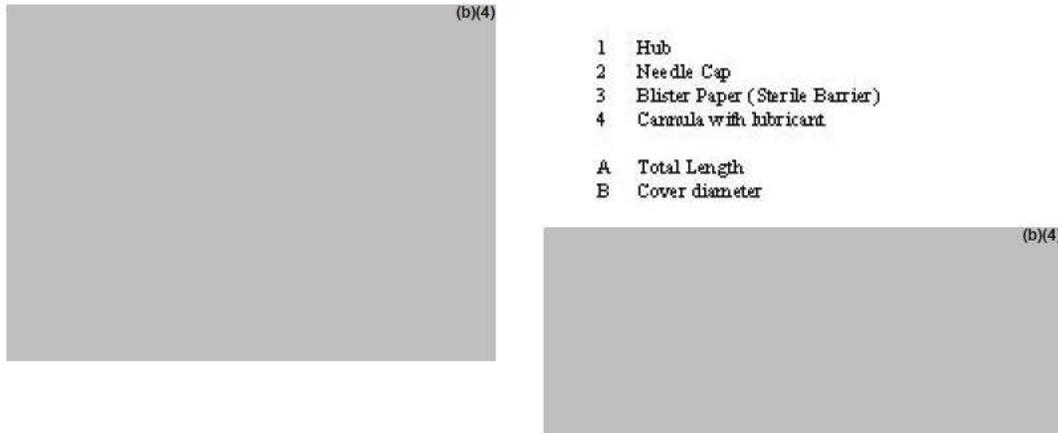
**Push –On Needle**

A separate pre-packaged sterile 30 gauge push-on needle, provided with the PegIntron pre-filled pen, is attached to the PegIntron pre-filled pen by the end user prior to injection.

The push-on needle is a sterile, non toxic, non-pyrogenic, single use needle consisting of a 30 Gauge Type 304 surgical grade stainless steel cannula in a (b)(4) hub. The needle extends 8 mm from the hub. The push-on needle is intended to be used for the hypodermic injection of fluids into the body when attached to the PegIntron pre-filled pen. It is assembled into a (b)(4) needle cap which is sealed with a sterile barrier blister paper.

The needle cap serves as a protective cap when the user places the needle on the PegIntron pre-filled pen. (b)(4)

(b)(4). The product is sterilized by a validated (b)(4) process, using the (b)(4) at Schering-Plough Labo NV (Heist-op den Berg, Belgium). Additional information on the push-on needle can be found in (b)(4)



**Figure 7 Diagram of Sterile Push-on Needle in Blister Pack**

| Table 5 Dimensions of the push-on needle |                   |
|--|-------------------|
| Description                              | Dimensions        |
| Total Length of:                         | 31.4 mm           |
| Cover diameter:                          | 15.4 mm           |
| Gauge:                                   | 30 G (0.3 x 8 mm) |
| Total Length of Cannula:                 | 17.75 mm          |
| Cannula length from Hub:                 | 8.00 mm           |
| Primary bevel angle:                     | 9.5°              |

**Reviewer's Comment:**

***During dose accuracy testing 34 pens were found to have delivered a low dose. A root cause analysis determined that the failures were due to blocked needles?***

***The following is from (b)(4):***



In addition, an internal study ( (b)(4) ) has been performed to verify that the performance of the DCI Injector and the new push on needles meet ISO 11608-1 requirements. All test results meets the pre-determined acceptance criteria.

***Performance qualification testing for the push-on needle should be submitted for review as well as test report (b)(4) to verify performance of the new push on needle with the pen injector meets ISO 11608 standards..***

**Secondary Packaging**

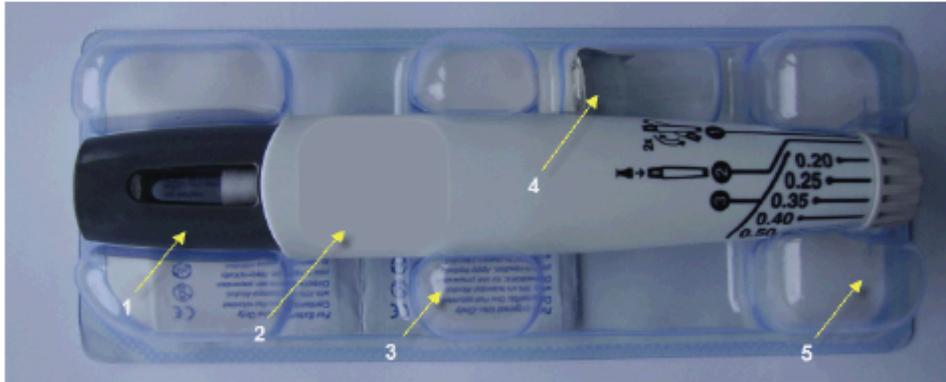
The assembled PegIntron pre-filled pen is presented in a blister kit consisting of a formed (b)(4) tray containing the push-on needle and two alcohol swabs. The push-on needle and the two alcohol swabs fit underneath the (b)(4) tray. The underside of the tray is sealed by means of a (b)(4) film. The blister kit is then packaged together with the Patient Package Insert (PPI) in an outer carton.

Side view:



- 1 – PegIntron pre-filled pen
- 2 – Push-on Needle
- 3 – Injector Label
- 4 – Alcohol Swabs
- 5 – Blister

From the top:



- 1 – PegIntron pre-filled pen
- 2 – Injector Label
- 3 – Alcohol Swabs
- 4 – Push-on Needle
- 5 – Blister

**Figure 8 PegIntron pre-filled pen Blister kit Components**

### **3. Documents Reviewed**

(b)(4)

sBLA 103949/5259, Module/ sections 3.2.P.7 and 3.2.P.2.8

### **4. CDRH Review and Comments**

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of: **pen injector performance and biocompatibility**. The pen injector is not sterile. Usability studies will be reviewed by CDRH Human Factors.

Performance, sterility and biocompatibility of the push-on needle were documented in the cleared 510(k).

### **Performance- Dose Accuracy**

Dose accuracy testing was performed according to ISO 11608-1:200, Pen-injectors for medical use – Part 1: pen-injectors- Requirements and test methods. The sponsor used placebo cartridges rather than actual drug cartridges to determine dose accuracy with the following justification:

The concentrations of all excipients in the PegIntron placebo cartridges are identical to those in PegIntron cartridges and in addition the concentration of the Peginterferon alfa-2b drug substance is very low. The concentrations and the physical properties, including specific gravity and viscosity of the reconstituted solution are the same for the placebo and all active strengths of the reconstituted drug. Therefore, dose accuracy testing performed using PegIntron placebo cartridges should be representative of all commercial strengths of PegIntron. The suitability of using PegIntron placebo cartridges for dose accuracy measurements was confirmed in a comparative study between PegIntron placebo cartridges and PegIntron cartridges at the (worst case) lowest dose volume setting (0.2 mL). Both placebo and PegIntron dose accuracy results met the ISO 11608-1 limits (i.e. error pre-set dose $\pm$ 10%, k-values greater than 2.638). Statistical analysis showed that there was no significant difference in dose accuracy measurements.

The placebo containing pens were assembled using production equipment and procedures identical to those for the finished product containing commercial PegIntron drug product.

### ***Reviewer's comment:***

***Table 7, section 8.1.1.1 , Comparative pre-filled pen dose accuracy using Pegintron 50 µg cartridges versus PegIntron placebo cartridges was reviewed. Both placebo and drug cartridges met the ISO 11608 dose accuracy limit and there appeared to be no significant difference between the cartridges. Therefore, dose accuracy testing using the placebo cartridges is acceptable.***

### **Performance- Dose Accuracy, Environmental Testing**

Three dose volume settings (0.20 mL, 0.35 mL and 0.50 mL) that cover the entire range of volumes dispensed by the PegIntron pre-filled pen were tested by (b)(4) under the following conditions in accordance with ISO 11608-1:

- Dose accuracy when subjected to standard atmosphere 23  $\pm$  2°C/ 25% to 75% RH
- Dose accuracy when subjected to cool atmosphere 5  $\pm$  3°C
- Dose accuracy when subjected to hot atmosphere 40  $\pm$  2 °C / 50  $\pm$  10% RH
- Dose accuracy after being subjected to dry heat storage preconditioning
- Dose accuracy after being subjected to cold storage preconditioning
- Dose accuracy after being subjected to free fall

Results were summarized in Tables 8 through 13.

**Reviewer's comment:**

**Tables 8 through 13 were reviewed. All tested pens met upper and lower limit specification for the three dose volume settings (0.20mL, 0.35mL and 0.5.0mL) when subjected to environmental conditions as prescribed by ISO 11608.**

**Biocompatibility**

PegIntron pre-filled pen patient contact components as identified in **Table 14** have been evaluated to demonstrate the biological safety of the PegIntron pre-filled pen.

**Reviewer's comment:**

**Materials safety data sheets (MSDS) are provided in the master file. However, it is not clear which colorants are used in the PegIntron pen. The master file holder should clarify which colorants are used in the pen.**

**Performance- Sharps Injury Protection Features**

Testing was performed to assure the consistent actuation of the needle shield. Twenty one hundred (2100) PegIntron pre-filled pens were tested for the needle shield lock feature during PegIntron pre-filled pen design verification and no failures were observed. All PegIntron pre-filled pen needle shields extended automatically, covered the needle and were locked after the injections were completed.

**Reviewer's comment:**

**The performance testing requirements for the sharps injury prevention feature, the needle shield lock, have been satisfied. The number of 2100 units tested exceeds the 500 unit recommendation detailed in the guidance...**

**Accelerated Aging/**

Two (2) accelerated aging studies have been initiated in accordance with ASTM D3045 Aging Testing and (b)(4). The PegIntron pre-filled pen components were pre-conditioned at  $40 \pm 2$  °C at 70% RH for up to 55 weeks. According to ASTM D3045, each 11 weeks of storage under these accelerated conditions can be extrapolated to one (1) year aging equivalent under 23°C ambient storage conditions. Therefore the study is designed to support up to five (5) years of retainer and sub-assembly storage under ambient conditions.

The PegIntron pre-filled pen was tested and evaluated according to the International Standard ISO 11608-1. At each time point, fifty (50) injectors were tested, ten (10) injectors per each of the five (5) dose settings.

**Reviewer's comment:**

**The data is acceptable to confirm a five year shelf life for the pen injector subassemblies.**

**Real Time Stability**

A real time stability study was conducted using a development batch of PegIntron

placebo pre-filled pens to support storage of the pen components at the approved drug product storage conditions ( $5 \pm 3^{\circ}\text{C}$ / ambient RH). Testing focused on mechanical function and physical appearance of the PegIntron pre-filled pen.

PegIntron pre-filled pens were staged at the  $5 \pm 3^{\circ}\text{C}$ / ambient RH storage condition for a total of 538 days which is equivalent to eighteen (18) months. Visual inspection and device function tests were performed on one hundred and twenty-five (125) test samples at the initial and 18 month time points. All of the results met the acceptance criteria. This stability study is ongoing and samples at the 36 month time point will also be evaluated.

***Reviewer's comment:***  
***CDER will review ongoing stability studies.***

### **Shipping and Transport**

Shipping studies were conducted in accordance with the International Safe Transport Association (ISTA) General - Simulation Performance Test Procedure 3A and 3E for Standard packaged products. After simulated ship testing, dose accuracy testing and container closure integrity testing of the cartridges were performed to demonstrate that the packaging provides sufficient protection of the product during shipment. The applied test conditions simulate worst case shipment conditions. Shipping presentations with maximum and minimum loads were packaged and shipped from Schering-Plough Labo NV operations (Heist) (b)(4) for testing.

***Reviewer's comment:***  
***Simulated and real-time shipping studies indicate that the secondary and outer packaging are sufficient to maintain functionality and dose accuracy of the pen injector.***

## **5. CDRH Recommendations**

Based on our review the following deficiencies should be conveyed to the Master File Holder:



1. You have provided MSDS for materials of composition of the pen injector. Please specify which MSDS are specific to the PegIntron Pre-filled pen.
2. Your amended master file indicates that there were injector failures during testing that were attributed to needle blockages. You state that corrective actions were

taken and performance qualification of the new needle (b)(4)  
(b)(4) would be performed. Please submit your performance qualification documentation.

3. Please provide the test report for internal test (b)(4) to verify that performance of the DCI pen injector and new push-on needles meets the requirements of ISO 11608.

| Digital Signature Concurrence Table              |   |
|--|---|
| Reviewer Sign-Off<br>Jacqueline Ryan             | <br>Digitally signed by Jacqueline S. Ryan<br>DN: c=US, o=U.S. Government,<br>ou=HHS, ou=FDA, ou=People,<br>0.9.2342.19200300.100.1.1=200057029<br>3, cn=Jacqueline S. Ryan<br>Date: 2013.07.19 10:24:30 -04'00' |
| Branch Chief Sign-Off<br><br>For Richard Chapman | <br>Date: 2013.07.19<br>11:21:10 -04'00'   |
|  |   |

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/s/  
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VICTORIA L TYSON  
07/30/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

DATE: June 27, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Victoria Tyson, Regulatory Project Manager, CDER/OND/OAP/DAVP

SUBJECT: BLA 103949/5259  
Applicant: Schering Corp (Merck & Co, Inc.)  
Drug: PegIntron (peginterferon alfa-2b)  
Device: Peninjector  
Intended Use: for treatment of Chronic Hepatitis C in patients with compensated liver disease  
CDRH CTS Tracking: ICC1200241/CON1222

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Digitally signed by Quynhnhu T. Nguyen -S  
Date: 2013.06.28 14:57:23 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

**Martha F. Story**  
2013.06.28 15:00:07 -04'00'

Molly Story, Human Factors and Accessible Medical Technology Specialist for  
Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Overview and Recommendations*

The Office of Antimicrobial Products, Office of New Drugs, Center for Drugs Evaluation and Research requested a human factors consultative review of human factors validation study report submitted under BLA 103949/5259 for the PegIntron Dual Chamber Injector. This product is intended to replace the currently marketed product called REDIPEN.

The human factors validation study with at least 15 participants representing each of the three major groups: healthcare providers, patients with treatment experience, patients and caregivers naïve to treatment. The study consisted of two arms: a training arm and an IFU only arm. To be consistent with CDRH Human Factors draft guidance in evaluating realistic and expected product use scenario, this reviewer focused on the results of the training arm. The reviewer found that the results of the validation study included reports of multiple failures and close calls when users were performing critical tasks under simulated use conditions. Some of the errors could result in mis-dosing or performance that is not in accordance with the Instructions for Use (IFU).

As a result, an information request was issued to have the Sponsor address the above concerns, or to modify the design of the dual-chamber pre-filled syringe and the corresponding labeling, including the Package Insert and the IFU, and conduct an additional human use factors/usability validation study that demonstrates that they have effectively reduced the prevalence of use error. The Sponsor provided a response to FDA request On April 19, 2013. The Sponsor clarified that some of the use errors could be addressed by seeking guidance from the patient's healthcare provider or from calling the toll-free customer service number. The other use errors were due to study artifacts: participants not reading the prescription, or misinterpreting that the dose pictured in the IFU as the dose that they should dial. And in some instances, the user did administer a full dose but did not hold the device at the injection site for a full 15 seconds. Review of this response indicated that the observed use errors did not result serious harm to the patient or the user. Additionally, the Sponsor has agreed to modify the IFU as recommend by FDA in providing additional emphasis on (1) the consequences of seeing "wet injections," (2) what to do about scenarios in which they inadvertently dialed past the 1 & 2 markings and activated the needle shield, or when they failed to attach the needle prior to dialing etc. Furthermore, the Sponsor also stated that they will ensure [REDACTED] (b)(4)

[REDACTED] Therefore, this reviewer finds that the Sponsor's response acceptable and does not have any further concerns with regards to the Human Factors component for this submission.

**CDRH Human Factors Review**

**Combination Product Device Information**

Submission Number: sBLA 103949/5259  
Applicant: Schering Corp (Merck and Co. Inc.)  
Drug Constituent: PegIntron (peginterferon alfa-2b)  
Device Constituent: Peninjector  
Intended Use: for treatment of Chronic Hepatitis C in patients with compensated liver disease  
Review Materials:  
<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6810e9d4e>

**CDRH Human Factors Involvement History**

| Date      | Involvements  |
|-----------|---|
| 11/8/2012 | CDRH HF was requested to provide a review of the human factors validation study report. |

**Summary of Review Materials and Reviewer Discussion**

Schering Corp has conducted a human factors validation study with at least 15 participants representing each of the three major groups: healthcare providers, patients with treatment experience, patients and caregivers naïve to treatment. The study consisted of two arms: a training arm and an IFU only arm. The training arm was conducted in two rounds: round 1 focused on training and round 2 focused on unassisted simulated-use testing (one week later). Of the 85 users participating in round 1 training, only 1 user failed to complete a successful injection. Per the protocol, this user was excluded from round 2 based on the rationale that such an individual would not be a candidate for self-injection. In the IFU only segment, users relied on the IFU, with no additional training to demonstrate that patients can use the injector without training. This represents a use scenario where the patient may not receive training from a healthcare provider, which the Sponsor indicated this scenario is not consistent with the approach recommended in the product labeling. To be consistent with CDRH HF guidance in evaluating realistic and expected product use scenario, this reviewer focused on the results of the training arm.

Based on use-related risk analysis and formative studies, the following tasks were identified as critical for successful dose delivery:

1. Turn Dial to number 1
2. Dial yellow paper from the needle cap
3. Support device in upright position and push needle straight down firmly
4. Turn dial to your prescribed dose
5. Press device against the skin
6. Hold injector at the injection site for 15 seconds

The study results showed that there were 8 failures and 19 instances of confusion or difficulty in the training arm. The Sponsor provided their analysis of the study results in following tables:

| Failure # | Observed Failure (user cohort)                                   | User assessment  | Critical Task associated with failure  | Step | Task priority | Consequence           | Severity | Probability* | Status (Acceptable / Actionable) |
|-----------|--|--|--|------|---------------|-----------------------|----------|--------------|----------------------------------|
| TA-1      | Loses liquid and does not recognize mistake, Step 20 (HCP)       | Assumed liquid streaming from the device was the result of a pressure differential | Hold injector in place for 15 seconds  | 20   | 1             | repeat partial dose   | Low      | Low          | Acceptable                       |
| TA-2      | Fails to fully attach needle, Step (Experienced)                 | Thought device was broken / defective - user recognized problem                    | Support device in upright position and Push needle straight down firmly.     | 9    | 1             | one time missed dose  | Very Low | Very Low     | Acceptable                       |
| TA-3      | Dials past 2 and activates the needle shield (HCP)               | Confused by markings on device / thought 0.2 was 2                                 | User unable to continue  | 1    | 1             | one time missed dose  | Very Low | Very Low     | Acceptable                       |
| TA-4      | Attaches needle before dialing, Step 1 (Experienced)             | Overconfident - did not read IFU or watch video                                    | Out of sequence error for needle attachment - attached needle before mixing. | 1    | 2             | one time partial dose | Very Low | Very Low     | Acceptable                       |
| TA-5      | Holds upside down while turning, Step 1 (Experienced)            | Nervous because was being watched  | Turn dial to number 1 with device in upright position.                       | 1    | 2             | repeat partial dose   | Very Low | Low          | Acceptable                       |
| TA-6      | Does not attempt to dial at all / doesn't realize, Step 12 (HCP) | Respondent was nervous   | Turn dial to your prescribed dose  | 12   | 2             | repeat missed dose    | Moderate | Low          | Acceptable                       |
| TA-7      | Sets and injects wrong dose, Step 12 (HCP)                       | Thought click and shield indicated to stop dialing                                 | Turn dial to your prescribed dose  | 12   | 2             | Repeat under dose     | Very low | Low          | Acceptable                       |
| TA-8      | Sets and injects wrong dose, Step 12 (Experienced)               | Dials to 0.5 based off visual in IFU   | Turn dial to your prescribed dose  | 12   | 2             | one time over dose    | Moderate | Very Low     | Acceptable                       |

| # | Segment                          | Observed Close Call   | Subjective Feedback  | Related Critical Task  | Process Step | Task Priority |
|---|----------------------------------|---|--|--|--------------|---------------|
| 1 | HCP (1)<br>Naïve (1)<br>Exp. (2) | Tries to attach needle upside down, then turns to attach correctly                        | a) Confused / forgot<br>b) Couldn't tell which way needle points by looking at it  | Support device in upright position and Push Needle straight down firmly. | 9            | 1             |
| 2 | HCP (1)                          | Tries to twist needle on, then pushes   | a) Forgot is was push on<br>b) Used to different injection device that requires twist  | Support device in upright position and Push Needle straight down firmly. | 9            | 1             |
| 3 | Naïve (1)<br>Exp. (1)            | Tries to attach needle with paper on, then removes  | a) Confused by figures 6 & 7 on IFU<br>b) Forgot   | Remove yellow paper from the needle cap                                  | 8            | 1             |
| 4 | HCP (1)<br>Naïve (6)<br>Exp. (3) | Performs dial to mix out of IFU sequence with no consequence but before needle attachment | a) Did not read IFU properly<br>b) Forgot / rushing through steps<br>c) Text (see figure 2 in step 1) made respondent think to got to step 2 | Turn Dial to number 1  | 1            | 2             |
| 5 | Naïve (1)<br>Exp. (1)            | Tries to inject without setting dose, then sets dose                                      | a) Did not read IFU properly<br>b) Did not watch video close enough  | Turn dial to your prescribed dose  | 12           | 2             |

The reviewer found that the results of the validation study included reports of multiple failures and close calls when users were performing critical tasks under simulated use conditions. Some of the errors could result in mis-dosing or performance that is not in accordance with the Instructions for Use (IFU). When users were interviewed regarding the errors committed, it is clear that they were not aware of having made the errors or what to do to prevent future errors and did not understand device user interface features, including the markings on the device and audible feedback “click” which are intended to facilitate correct use. The report stated that the severity or harm of a missed dose or over- or under dosing could range from low to moderate

depending on whether the error occurs once or multiple times. The reviewer was concerned that the test results could indicate that the proposed device, including its packaging and IFU, have not been optimized to minimize errors as observed during testing. The reviewer was particularly concerned that users are not sure how to use the device correctly and are not aware when they are making errors. The Sponsor indicate that the user could seek further support by calling an 800 customer service number, but it is not clear how that would help given that users are often unaware of the errors they are committing.

In addition, the review of the IFU indicates that additional information and emphasis should be considered to more adequately communicate to the user (1) the consequences of seeing “wet injections,” (2) what to do about scenarios in which they inadvertently dialed past the 1 & 2 markings and activated the needle shield, or when they failed to attach the needle prior to dialing etc.

As a result, this reviewer recommended that an information request be transmitted to the Sponsor to address the above concerns, or to modify the design of the dual-chamber pre-filled syringe and the corresponding labeling, including the Package Insert and the IFU, and conduct an additional human use factors/usability validation study that demonstrates that they have effectively reduced the prevalence of use error.

On April 19, 2013, the Sponsor provided a response to FDA request. The Sponsor stated that they acknowledge FDA’s concerns regarding the potential of use errors. The Sponsor clarified that subtlety and interpretation of the results were not adequately described in the application. In this response, the Sponsor would like to provide more details of the observed use errors. There were thirteen participants (eight in Round 2 of the Training Arm and five in the IFU Only-Arm) were observed making use errors. Six of these participants (three in the Training Arm and three in IFU Only Arm) recognized an error had occurred and it is our expectation that these people would seek guidance from their HCP or our toll-free customer service number. During the exit interview, some of the study participants mentioned that they would seek additional help should they experience an issue during use of the device. The remaining seven participants did not detect that a use error has occurred. The following list provides further discussion of the nature and root cause analysis performed on the errors that the seven participants experienced focusing on trained participants:

- 1) 1 trained participant, who dialed 0.50 and injected the wrong dose, indicated that they followed the dose pictured in the IFU. However, in real life, they indicated that they would only dial the dose prescribed by the doctor and not what was in the IFU. This indicated that this error was the result of a study artifact. However, the IFU was modified to clarify that the dose displayed in the IFU is for illustrative purposes.
- 2) 1 trained participant, who did not dial dose, yet attempted to inject, indicated that the use error was a result of being nervous and he also admitted to not reading or following the IFU.
- 3) 1 trained participant, who did not hold the injection for less than 15 seconds, did deliver a complete dose. This participant waited for the clicking and tactile feedback during dose delivery.



## Appendix 1: Device Descriptions

The PegIntron pre-filled pen is a single use, variable dose, auto injector intended for use by adult patients with Hepatitis C, healthcare professionals, and caregivers. This PegIntron pre-filled pen, like the current RediPen® injector, is designed to deliver an adjustable, subcutaneous dose from the same dual chamber PegIntron® cartridges with automatic reconstitution of drug product from the cartridge. The first chamber of the cartridge contains the lyophilized drug product and the second contains sterile water for injection. The PegIntron pre-filled pen includes a separate sterile needle to be attached to the injector prior to administration; and a mechanism that allows the user to dial the prescribed dose prior to administration.

Figure 1: DCI (front) and Push On needle (image), diagram:



Figure 2: DCI (front) in blister tray with Push On needle (image), diagram: English labeling will be used in the validation study.

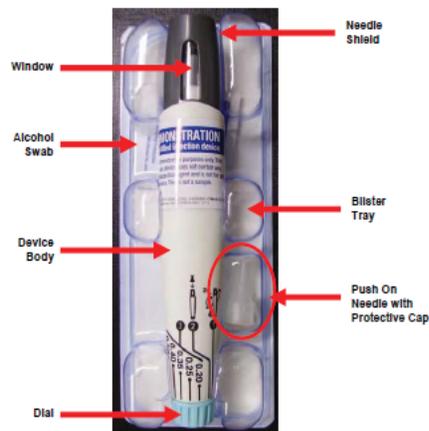


Figure 3: Open carton with blister tray and IFU partially inserted:



Figure 4: DCI (back):

Labeling on this device is for the demonstration device (for demonstration purposes only).



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VICTORIA L TYSON  
07/30/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Design Validation Summary, Label, Labeling and Packaging Review**

Date: July 12, 2013

Reviewer: Morgan Walker, PharmD, MBA  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh.  
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): PegIntron Selectdose (Peginterferon alfa 2b) Powder for Injection  
50 mcg per 0.5 mL, 80 mcg per 0.5 mL,  
120 mcg per 0.5 mL, and 150 mcg per 0.5 mL

Application Type/Number: BLA 103949

Applicant/sponsor: Merck and Co.

OSE RCM #: 2013-2393

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the Design Validation Summary, proposed Instructions for Use (IFU), Medication Guide (MG), container labels, and carton and insert labeling for PegIntron Selectdose, BLA 103949, for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND

The Applicant submitted supplement 5259 to BLA 103949 which provides a new pen injector device for the drug product PegIntron. The Applicant also submitted a request for proprietary name review for the new pen injector device, PegIntron Selectdose. The Applicant has a currently marketed pen device, PegIntron Redipen, which will eventually be phased out.

The Applicant stated in the Design Validation Summary that the decision to replace the RediPen injector currently used for subcutaneous injection of PegIntron by the PegIntron pre-filled pen (b)(4). User needs were identified, with priority given to patient complaints and errors, most of which were associated with performing injection steps out of sequence. In addition, current PegIntron Redipen users have experienced documented product quality issues such as errors with the dose button, dose dialing, medication leakages, bent needles, and mixing issues (see OSE Review # 2012-277 and Appendix G).

CDRH sent an IR and advice to the Applicant on April 19, 2013 regarding the results of the Human Use Factors/Usability Validation Study. CDRH stated their concerns for the multiple failures and close calls when users were performing critical tasks under simulated use conditions. In addition, CDRH stated that the IFU should include additional information and emphasis to more adequately communicate to the user (1) the consequences of seeing “wet injections,” (2) what to do about scenarios in which they inadvertently dialed past the 1 & 2 markings and activated the needle shield, or when they failed to attach the needle prior to dialing etc.

The Applicant submitted an updated IFU in response to the above IR on May 23, 2013. Thus, our recommendations for the IFU will be based on the updated submission.

Additionally, an information request (IR) was sent to the Applicant on June 14, 2013 requesting details of plans to phase-in the proposed PegIntron Selectdose and to phase-out PegIntron Redipen. The Applicant responded to the IR on June 21, 2013 stating that they intend to begin marketing and distribution of PegIntron Selectdose shortly after FDA approval. Remaining inventory of Redipen components will be assembled and packaged as needed to ensure continuity of PegIntron Redipen supply (b)(4).

Distribution of the PegIntron Selectdose is (b)(4), (b)(4).

The Applicant

(b)(4)

(b)(4)

## 1.2 REGULATORY HISTORY

PegIntron was approved by the Agency on January 19, 2001. This approval included the vial (50 mcg/0.5 mL, 80 mcg/0.5 mL, 120 mcg/0.5 mL, 150 mcg/0.5 mL) and the Redipen (50 mcg/0.5 mL, 80 mcg/0.5 mL, 120 mcg/0.5 mL, 150 mcg/0.5 mL).

## 1.3 PRODUCT INFORMATION

The following product information is provided in the October 10, 2012 submission.

- Active Ingredient: Peginterferon alfa-2b Powder for Injection
- Indication of Use: For the treatment of Chronic Hepatitis C with compensated liver disease
- Route of Administration: Subcutaneous injection
- Dosage Form: Powder for injection
- Strength: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL
- Dose and Frequency: Combination with ribavirin: 1.5 mcg/kg/week; monotherapy: 1 mcg/kg/week
- How Supplied: Single-use prefilled pen (package contains one pen, one push-on needle, and 2 alcohol swabs)
- Storage: 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)

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for PegIntron Redipen medication error reports to identify any issues that may be pertinent to the proposed pen device. In addition, DMEPA has a pending consult from DAVP regarding review of PegIntron Redipen medication error reports (OSE Review # 2012-277) (All issues specifically inherent to PegIntron Redipen will be described in OSE RCM # 2012-277.)

A FAERS search was conducted for consult OSE Review #2012-277. Therefore, we conducted a gap search for this review using the FAERS database using the strategy

listed in Table 1. We also reviewed the PegIntron Selectdose Design Validation Summary, proposed IFU, MG, container labels, carton and insert labeling submitted by the Applicant.

## 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

| <b>Table 1: FAERS Search Strategy</b> |  |
|---------------------------------------|--|
| Date                                  | January 31, 2012 – April 7, 2013   |
| Drug Names                            | PegIntron (trade name)<br>PegIntron Redipen (verbatim term)  |
| MedDRA Search Strategy                | Medication Errors (HLGT)<br>Product Packaging Issues HLT<br>Product Label Issues HLT<br>Product Quality Issues (NEC) HLT |

The FAERS database search identified 165 cases. Each case was reviewed for relevancy and duplication. After individual review, 162 cases were not included in the final analysis for the following reasons:

- Adverse drug reaction unrelated to medication error
- Dose omission
- Improper storage
- Medication error with a medication other than PegIntron Redipen (PegIntron Redipen was reported as a concomitant medication)
- Product quality issues with PegIntron Redipen
- Wrong technique errors

## 2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Design Validation Summary submitted October 10, 2012
- Insert Labeling submitted October 10, 2012
- Sample Pen device submitted October 10, 2012
- IFU submitted October 10, 2012, May 3, 2013
- MG submitted October 10, 2012

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted October 10, 2012 (Appendix A)
- Carton Labeling submitted October 10, 2012 (Appendix B)

### 2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed combined proprietary name, label and labeling reviews for PegIntron in OSE Review #'s 06-0214 and 2006-744. We also completed an additional labeling review for PegIntron in OSE Review # 2009-1762. We completed a proprietary name review for [REDACTED] (b)(4) in OSE Review # 2012-2392 which was found unacceptable by OPDP. Recently, we complete a proprietary name review for PegIntron Selectdose in OSE Review # 2013-450 and the proprietary name was found acceptable at this time. Thus, we reviewed them to ensure all of our recommendations were considered or implemented. We also reviewed our previous reviews for any issues that may be relevant to this review. Our evaluation found that all of our recommendations were implemented.

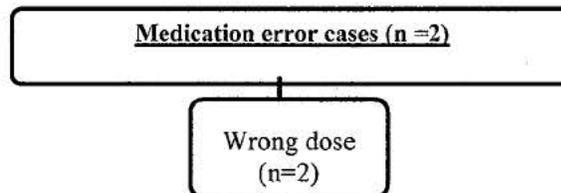
## 3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the PegIntron Selectdose Design Validation Summary as well as the associated label and labeling.

### 3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, two PegIntron Redipen medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Figure 1 provides a stratification of the number of cases included in the review by type of error.

Figure 1: PegIntron Redipen medication errors (n = 2) categorized by type of error



#### Wrong dose errors:

Case # [REDACTED] (b)(6) v1 reported a patient who was taking the 0.5 mL instead of 0.4 mL by mistake. Cause and patient outcomes not reported.

Case # [REDACTED] (b)(6) v2 reported a patient had injected himself with the incorrect dose due to user issue. It was reported that when the patient has injected himself without dialing the

<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Redipen to the correct dose, he had gotten a taste in the back of his throat making him feel that he had gotten a dose.

### 3.2 DESIGN VALIDATION SUMMARY ASSESSMENT

DMEPA reviewed the Design Validation Summary submitted to the Agency and identified the following vulnerabilities:

#### A. Protocol Assessment and Design Validation Summary Results

- Appendix A. Design Validation Protocol: Attachment C. Alternate practices (acceptable and unacceptable use scenarios) page 67
  1. The column that is titled “Pass, Prompt Training in R1” illustrates scenarios in which the Applicant considers these “passes” because the test article still worked. However, these “passes” are still failures because the actual task was not completed correctly.
- Appendix B. U.S. Dual Chamber Injection Design Validation Summary Report (See Appendix F)
  1. Sections 2.1.1 and 2.2.2 present what the Applicant calls “Close Calls” which is defined as instances in which the user experiences confusion, misinterpretation, difficulty or an error that would result in mistreatment or harm, but the user “recovers” and no actual performance failure is recorded in the study documentation. All of these should be treated as failures instead of close calls despite the fact that the device was not compromised. These close calls still presented scenarios of performance error within the critical steps and could potentially lead to dose omission medication errors.
  2. Section 2.2 of the IFU Only Arm had less than 15 participants for each user group (i.e. 10 patients with treatment experience and 5 patients and caregivers naïve to treatment). This may not be enough participants to accurately present if using the IFU only will provide enough information for the patient to use the new pen correctly.
  3. The Applicant defined critical steps as the following:
    - a. Step 1 Turn Dial to number 1
    - b. Step 8 Remove yellow paper from the needle cap
    - c. Step 9 Support device in upright position and Push Needle straight down firmly.
    - d. Step 12 Turn dial to your prescribed dose
    - e. Step 17 Press device against the skin
    - f. Step 20 Hold injector in place for 15 seconds

Several study participants either failed or experienced “close calls” at these critical steps (See Appendix F).

The study participants in the Design Validation Summary did not report any device functionality issues with the dose knob, dialing a dose, bent needles, or mixing issues which were frequently reported with PegIntron Redipen. However, the study still identified user errors associated with the use of the proposed PegIntron Selectdose. However, with improved device functionality with the proposed PegIntron Selectdose, the risk of future user errors may be mitigated with labeling changes to the Instructions for Use (IFU) as well as user interface changes on the actual pen. Based upon our review of the Design Validation Summary, we conclude the proposed PegIntron Selectdose provides better device functionality over the PegIntron Redipen.

### 3.3 INSERT LABELING ASSESSMENT

A review of the proposed insert labeling did not identify any vulnerabilities that may pose a risk for medication error to occur at this time.

### 3.4 IFU ASSESSMENT

A review of the proposed IFU as well as outcomes from the Design Validation Summary testing identified the following vulnerabilities that may pose a risk for medication errors to occur:

1. There is no statement at the beginning of the IFU alerting patients of the new pen. In addition, patients should be informed that this device is different from the Redipen and the steps to deliver a dose will be different.
2. The pictures in the IFU are in black and white and therefore make it difficult to identify steps where the directions focus on color. For example, it is difficult to identify the yellow paper that covers the needle cap if the picture is in black and white.
3. There is no emphasis on the following critical process steps identified in Table 3: DCI Critical Task Analysis of the Design Validation Protocol in the IFU which had related failures identified in the Design Validation Summary:

-  (b)(4)
- 
- 
- 
- 
- 
- 

Based on the user errors observed in the Design Validation Summary, DMEPA met with Patient Labeling to discuss the user errors and recommendations for the IFU to help mitigate these errors. Both DMEPA and Patient Labeling concurred with each other's recommendations. Patient Labeling incorporated recommendations from Patient Labeling and DMEPA in their review. In addition to the recommendations incorporated into the Patient Labeling review, DMEPA will provide additional recommendations for the IFU that should be conveyed to the Applicant in Section 5.

We also recommend additional testing of the IFU as a Post-Marketing Requirement (PMR) so a revised IFU can be developed to help mitigate user errors observed in the Design Validation Summary.

### **3.5 MEDICATION GUIDE ASSESSMENT**

A review of the proposed MG did not identify any vulnerabilities that may pose a risk for medication error to occur at this time.

### **3.6 CONTAINER LABEL AND CARTON LABELING ASSESSMENT**

A review of the proposed container label and carton labeling identified the following vulnerabilities:

1.  (b)(4)

DMEPA will provide recommendations for the container label and carton labeling in Section 5.

### **3.7 PEN DEVICE ASSESSMENT**

A review of the proposed pen identified the following vulnerabilities to the pen label:

1. The doses printed on the pen contain trailing zeros.
2. There are no units of measure next to the doses on the pen.

DMEPA will provide recommendations for the label of the pen device in Section 5.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

DMEPA concludes that the proposed MG and insert labeling are acceptable from a medication error perspective. However, the pen device, IFU, container labels, and carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and may mitigate any confusion.

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA supplement:

- A. Comments to the Division
  1. The Applicant should participate in a Post-Marketing Requirement (PMR) to conduct additional testing of the Instructions for Use (IFU) after the recommendations from this review (B. Comments to the Applicant 2. IFU Recommendations) and the July 2013 Patient Labeling Review for this Supplement. The goal of the PMR should be to revise the IFU based upon the additional testing as part of the PMR to help mitigate user errors and failures identified in the initial Design Validation Study. Additionally, we would like to review the Instructions for Use re-validation Study Protocol prior to the Applicant conducting the study and also review the results

after the study is completed. The study should be completed within 6 months after approval.

B. Comments to the Applicant

1. Pen Device Label Recommendations

- a. Remove all trailing zeros from the device
- b. Provide units of measure next to the numerical dose (i.e. 0.2 mL versus 0.2)

2. IFU Recommendations

- a. During all printings in the marketing (b)(4) the Redipen and Selectdose until all lots of the Redipen expire, place a statement at the beginning of the IFU alerting patients, healthcare practitioners, and caregivers that this is a new pen device that is different from the Redipen and the steps to deliver a dose will be different.
- b. Emphasize the importance of critical steps (b)(4), and (b)(4) identified in the Design Validation Summary with bold text.
- c. Upon removal of the trailing zeros from the pen device, replace all current pictures with new pictures of the pen device without trailing zeros.
- d. Secondary to multiple errors identified in the Design Validation Summary, in Figures (b)(4) expand the picture to show the entire pen and in Figure (b)(4) add language that the pen is in an upright position.
- e. Secondary to multiple errors identified in the Design Validation Summary such as failure to remove the yellow paper from the push-on needle and placing the needle at the wrong end of the pen device, ensure that all pictures are presented in color instead black and white to clearly illustrate the supplies needed to administer a dose of PegIntron.

3. Carton labeling and Container Label Recommendations

- a. Ensure the Selectdose carton labeling and container labels are well differentiated from the Redipen carton labeling and container labels. We recommend changing the primary trade dress color from blue to another color, to avoid dispensing errors because both the Selectdose and Redipen products will coexist in the marketplace.
- b. For ease of readability, use title case instead (b)(4) letters for the trademark 'PegIntron Selectdose'.
- c. Flag all the carton labeling with a phrase similar to: "New Pen Device", to alert patients and pharmacists the Selectdose is a new device and not the same as the Redipen. This flag label may help prevent selection use errors (b)(4).

The carton labeling should contain this flag for approximately 6 months during the launch of the new device.

- d. On the Professional Samples, delete the space “Place Pharmacy Label Here” as the samples will not be dispensed from a pharmacy, thus do not require this section for labeling.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**Appendix F: Design Validation Summary Results**

- Summary of findings from the Design Validation Summary Report page 178

**Section 2.1: Training Arm Failures (n=8):**

**Table 4: Risk Analysis of Critical Task Failures – Training Arm**

| Failure # | Observed Failure (user cohort)                                   | User assessment  | Critical Task associated with failure  | Step | Task priority | Consequence           | Severity | Probability* | Status (Acceptable / Actionable) |
|-----------|--|--|--|------|---------------|-----------------------|----------|--------------|----------------------------------|
| TA-1      | Loses liquid and does not recognize mistake, Step 20 (HCP)       | Assumed liquid streaming from the device was the result of a pressure differential | Hold injector in place for 15 seconds  | 20   | 1             | repeat partial dose   | Low      | Low          | Acceptable                       |
| TA-2      | Fails to fully attach needle, Step (Experienced)                 | Thought device was broken / defective - user recognized problem                    | Support device in upright position and Push needle straight down firmly.     | 9    | 1             | one time missed dose  | Very Low | Very Low     | Acceptable                       |
| TA-3      | Dials past 2 and activates the needle shield (HCP)               | Confused by markings on device / thought 0.2 was 2                                 | User unable to continue  | 1    | 1             | one time missed dose  | Very Low | Very Low     | Acceptable                       |
| TA-4      | Attaches needle before dialing, Step 1 (Experienced)             | Overconfident - did not read IFU or watch video                                    | Out of sequence error for needle attachment - attached needle before mixing. | 1    | 2             | one time partial dose | Very Low | Very Low     | Acceptable                       |
| TA-5      | Holds upside down while turning, Step 1 (Experienced)            | Nervous because was being watched  | Turn dial to number 1 with device in upright position.                       | 1    | 2             | repeat partial dose   | Very Low | Low          | Acceptable                       |
| TA-6      | Does not attempt to dial at all / doesn't realize, Step 12 (HCP) | Respondent was nervous   | Turn dial to your prescribed dose  | 12   | 2             | repeat missed dose    | Moderate | Low          | Acceptable                       |
| TA-7      | Sets and injects wrong dose, Step 12 (HCP)                       | Thought click and shield indicated to stop dialing                                 | Turn dial to your prescribed dose  | 12   | 2             | Repeat under dose     | Very low | Low          | Acceptable                       |
| TA-8      | Sets and injects wrong dose, Step 12 (Experienced)               | Dials to 0.5 based off visual in IFU   | Turn dial to your prescribed dose  | 12   | 2             | one time over dose    | Moderate | Very Low     | Acceptable                       |

\* see Table 10 for Risk Classification Criteria

**Section 2.1.2 is titled “Training Arm Close Calls”. All of these should be treated as failures instead of close calls. (n=19)**

**Table 5: Summary of Close calls - Training Arm**

| # | Segment                          | Observed Close Call   | Subjective Feedback  | Related Critical Task  | Process Step | Task Priority |
|---|----------------------------------|---|--|--|--------------|---------------|
| 1 | HCP (1)<br>Naïve (1)<br>Exp. (2) | Tries to attach needle upside down, then turns to attach correctly                        | a) Confused / forgot<br>b) Couldn't tell which way needle points by looking at it  | Support device in upright position and Push Needle straight down firmly. | 9            | 1             |
| 2 | HCP (1)                          | Tries to twist needle on, then pushes   | a) Forgot is was push on<br>b) Used to different injection device that requires twist  | Support device in upright position and Push Needle straight down firmly. | 9            | 1             |
| 3 | Naïve (1)<br>Exp. (1)            | Tries to attach needle with paper on, then removes  | a) Confused by figures 6 & 7 on IFU<br>b) Forgot   | Remove yellow paper from the needle cap                                  | 8            | 1             |
| 4 | HCP (1)<br>Naïve (6)<br>Exp. (3) | Performs dial to mix out of IFU sequence with no consequence but before needle attachment | a) Did not read IFU properly<br>b) Forgot / rushing through steps<br>c) Text (see figure 2 in step 1) made respondent think to got to step 2 | Turn Dial to number 1  | 1            | 2             |
| 5 | Naïve (1)<br>Exp. (1)            | Tries to inject without setting dose, then sets dose                                      | a) Did not read IFU properly<br>b) Did not watch video close enough  | Turn dial to your prescribed dose  | 12           | 2             |

**Section 2.2: IFU only Arm**

- There were less than 15 subjects for each user group (15 total instead of 15 per user group)
- 5 failures in this arm

| Failure # | Observed Failure (user cohort)   | User assessment  | Critical Task associated with failure    | Step | Task priority | Consequence           | Severity | Probability* | Status (Acceptable/ Actionable) |
|-----------|--|--|--|------|---------------|-----------------------|----------|--------------|---------------------------------|
| IFU-1     | Forces dial past 1 & 2 / activates needle shield, Step 1 (Naïve)       | Recognized problem, indicated during home use would seek support (HCP or manufacturer) | User unable to continue to attach needle | 9    | 1             | one time missed dose  | Very Low | Very Low     | Acceptable                      |
| IFU-2     | Forces dial past 1 & 2 / activates needle shield, Step 1 (Experienced) | Recognized problem and indicated would seek HCP support to correct.                    | User unable to continue to attach needle | 9    | 1             | one time missed dose  | Very Low | Very Low     | Acceptable                      |
| IFU-3     | Loses liquid and does not recognize mistake, Step 20 (Experienced)     | Respondent counted in his head, but not long enough                                    | Hold injector in place for 15 seconds    | 20   | 1             | repeated partial dose | Low      | Low          | Acceptable                      |
| IFU-4     | Activates needle guard and injects into air (Experienced)              | Recognized problem, would expect training before initial use.                          | Press device against skin                | 17   | 2             | one time missed dose  | Very Low | Very Low     | Acceptable                      |
| IFU-5     | Sets and injects wrong dose, Step 12 (Naïve)                           | Did not recognize problem, would not use a device without being instructed.            | Turn dial to your prescribed dose        | 2    | 2             | Repeated overdose     | Moderate | Low          | Acceptable                      |

\* See Table 10 for Risk Classification Criteria

### 2.2.2 IFU Only Arm Close Calls. All of these should be treated as failures instead of close calls. (n=12)

| # | Segment               | Observed Close Call   | Subjective Feedback  | Related Critical Task   | Step | Task Priority |
|---|-----------------------|---|--|---|------|---------------|
| 1 | Exp. (2)              | Fails to hold for 15 seconds; loses liquid but recognizes mistake                         | a) Forgot to hold for 15 seconds<br>b) Didn't think 4ml injection would take 15 seconds                    | Hold injector in place for 15 seconds                                   | 20   | 1             |
| 2 | Exp. (1)              | Confused and initially cannot locate needle   | a) Assumed needle would be pre-attached  | Remove yellow paper from the needle cap                                 | 8    | 2             |
| 3 | Exp. (1)              | Tries to attach needle with paper on, then removes  | a) Did not read IFU properly   | Remove yellow paper from the needle cap                                 | 8    | 2             |
| 4 | Exp. (1)              | Other, tries to attach needle to wrong end of device                                      | a) Needle looks like it should attach to dose dial end because of shape/size                               | Support device in upright position and Push Needle straight down firmly | 9    | 1             |
| 5 | Exp. (1)              | Tries to attach by needle upside down, then turns to attach correctly                     | a) Couldn't tell which way needle points by looking at it  | Support device in upright position and Push Needle straight down firmly | 9    | 1             |
| 6 | Exp. (1)              | Confused on how to turn dial or position to hold device                                   | a) Initially unsure how much force to use  | Turn Dial to number 1   | 1    | 2             |
| 7 | Naive (1)<br>Exp. (1) | Tries to dial dose but stops/corrects before turning past 2 prior to attaching the needle | a) Nervous<br>b) Forgot/rushing though steps<br>c) Did not read IFU properly                               | Turn dial to prescribed dose  | 1    | 1             |
| 8 | Exp. (3)              | Confusion or hesitation with dialing the dose, but dials                                  | a) Confusion between 0.4ml on card and 0.40 on device; the number on the device do not match the dose card | Turn dial to your prescribed dose                                       | 12   | 2             |

**Appendix G:** Medication Errors submitted to the Agency from the Applicant (October 16, 2012) regarding PegIntron Redipen

The FDA requested that Merck provide "the medication errors reported" in relation to its PegIntron Redipen. To provide a summary of the data available to us, Merck reviewed all US post-marketing reports of adverse events within our safety surveillance information system regarding PegIntron cumulatively to 30JUN2012.

**MEDICATION ERRORS and COMPLICATIONS ASSOCIATED with DEVICE**

The search was initially conducted on reports with a reported adverse event encompassed with the MedDRA high level group term of *Medication Errors or Complications Associated with Device*. This search returned 1,125 medically confirmed reports and 1,975 consumer reports. These reports were reviewed and assessed for the source of the medication error or complication associated with device; the results of which follow.

***Medically Confirmed Reports***

Of the 1,125 medically confirmed cases (see Table 1), 356 reports described an adverse event of interest that was not related to use with the Redipen. Instead, these 356 cases involved a medication error or complication associated with device adverse event that stems from another co-suspect product or the vial formulation of PegIntron.

Of the remaining 769 reports regarding a medication error or complication associated with Redipen, most did not describe a concern with the functionality of the pre-filled pen including: 90 reports of storage issues including lack of refrigeration, 27 reports of an indirect exposure by another person such as a sexual partner, 24 reports of an accidental exposure such as accidental needle sticks, 14 reports of a product dispensing error including instances of the wrong drug being dispensed, and 9 reports of problems with the kit/packaging contents such as missing components.

An additional 191 reports identified the medication error to be the result of patient or user failure or misuse of the Redipen. There were 110 reports where the patient or user used the pre-filled pen inappropriately: 35 reports of administering more medication than prescribed, 30 of missing a dose, 17 noting an incorrect dose being selected and administered, 11 having problems with the administration such as intravenous or intramuscular injections, 7 using a demonstration pen instead of one with the medication, 3 using an expired pen, 3 being administered on an incorrect schedule, 2 with delays in administering a dose, 1 of use in an unapproved age group, and 1 that was not otherwise specified beyond improper use. The other 81 reports of failure or misuse by the patient or user noted errors in their operation of the pen: 23 reports of operating the pre-filled pen out of sequence, 15 of not following the instructions for use for the pre-filled pen, 15 of leaving the needle cap on during the injection, 11 of an accidental release of the medication prior to the subcutaneous injection, 6 of dropping or damaging the pre-filled pen, 6 not otherwise specified beyond misuse, 3 reports where the user error was determined by a quality analysis of the malfunctioning pen, and 2 of mixing incorrectly. A number of reports noted a suspected problem with the operation of the pre-filled pen without a clear failure in the pen. There were 27 reports of an unexpected release of the medication without clear evidence of a pen malfunction and high risk for a user error to

be involved. 16 reports noted a patient or user's concern that the dose received was inappropriate without clear evidence of an incorrect dose due to subjective elements such as liquid left in the pen or not experiencing side effects. 19 reports noted some leakage of fluid from various segments of the pre-filled pen but most regarding the needle attachment point. An additional 11 reports noted liquid leaking after completion of the injection from the needle or injection site. In these cases, no evidence of a malfunction was clearly evident. More likely, these reports result from a patient or user's unfamiliarity with the various doses available from the same pre-filled pen with differing medication remaining after injection, confusion about the priming process resulting in some leakage of fluid, or some patient/user difficulty in operating the pre-filled pen resulting in concerns.

The remaining 341 reports noted a malfunction in the operation of the pen. These stem from problems with the dialing, releasing the dose button, injection, mixing/diluting the medication, priming, or the needle. Most reports noted a single pen malfunction ("single report"), but 22 reports noted different malfunctions in more than one pen ("multiple report"). Within these 341 reports, a malfunction was reported: in dialing in 128 reports (118 single and 10 multiple), in releasing the dosing button in 72 (61 in single and 11 in multiple), in injecting in 66 reports (59 single and 7 multiple), in mixing/diluting in 43 reports (34 single and 9 multiple), with the needle in 8 reports (8 single and 0 multiple), with priming in 5 single reports, and not otherwise specified in 34 single cases. None of these 341 reports had a returned pen that showed a defect in the pen. In fact, with all cases, all those that were returned for quality analysis, the malfunction was determined to be a result of patient or user error in operating the pre-filled pen and not an inherent defect in the product.

*Table 1: Healthcare Provider Reports of Medication Errors & Complications Associated with Device*

|      |  |  |
|------|--|--|
| 356  | Reports Not Involve Redipen                                  |  |
| 90   | Storage Issue  |  |
| 27   | Indirect Exposure by Other Person                            |  |
| 24   | Accidental Exposure  |  |
| 14   | Product Dispensing Errors                                    |  |
| 9    | Incomplete or Contaminated Packaging                         |  |
| 191  | Patient/User Identified Errors:                              |  |
|      | 110  | in Use of the Medication:                      |
|      | 35   | Over Dose                                      |
|      | 30   | Missed Dose                                    |
|      | 17   | Wrong Dose Given                               |
|      | 11   | Incorrect Administration                       |
|      | 7  | Demonstration Injected                         |
|      | 3  | Used Expired Medication                        |
|      | 3  | Wrong Schedule                                 |
|      | 2  | Dose Delayed                                   |
|      | 1  | Improper                                       |
|      | 1  | Incorrect for Age                              |
|      | 81   | in Operating the Device:                       |
|      | 15   | Not Following the Instructions for Use         |
|      | 15   | Left Cap on Needle During Injection            |
|      | 23   | Operating Out of Sequence                      |
|      | 11   | Accidental Released Medication                 |
|      | 3  | User Error Determined by Product Analysis      |
|      | 6  | Dropped or Damaged                             |
|      | 2  | Mixing Done Incorrectly                        |
|      | 6  | Not Otherwise Specified (NOS)                  |
| 27   | Unexplained Release of Medication Prior to Injection         |  |
| 16   | Patient Unsure of Amount of Medication Received/Administered |  |
| 19   | Medication Leaking from Device                               |  |
| 11   | Leak of Medication Reported After/During Injection           |  |
| 341  | Reported Malfunction with Operation                          |  |
|      | 118  | Problems in Dialing of Redipen                 |
|      | 61   | Problems with Release of Dose Button           |
|      | 59   | Problems with Injection Button or Stage        |
|      | 34   | Problems in Mixing/Diluting Medication         |
|      | 8  | Needle Related Problem                         |
|      | 5  | Priming Problem                                |
|      | 34   | Malfunction of Redipen Not Otherwise Specified |
|      | 22   | Multiple Device Problems                       |
|      | 10 of 22   | Noting a Dialing Problem                       |
|      | 11 of 22   | Noting a Release of Dose Button Problem        |
|      | 7 of 22  | Noting an Injection Stage Problem              |
|      | 9 of 22  | Noting a Mixing/Diluting Stage Problem         |
| 1125 | Total of Medically Confirmed Reports                         |  |

**Consumer Reports**

Of the 1,975 non-medically confirmed cases (See Table 2), 243 reports described an adverse event of interest that was not related to use with the Redipen. Instead, these 243 cases involved a medication error or complication associated with device adverse event

that stems from another co-suspect product or the vial formulation of PegIntron. Of the remaining 1,732 reports regarding a medication error or complication associated with Redipen, most did not describe a concern with the functionality of the pre-filled pen including: 133 reports of storage issues including lack of refrigeration, 51 reports of problems with the kit/packaging contents such as missing components, 22 reports of an indirect exposure by another person such as a sexual partner, 20 reports of a product dispensing error including instances of the wrong drug being dispensed, and 17 reports of an accidental exposure such as accidental needle sticks.

An additional 313 reports identified the medication error to be the result of patient or user failure or misuse of the Redipen. There were 108 reports where the patient or user used the pre-filled pen inappropriately: 46 of missing a dose, 26 reports of administering more medication than prescribed, 15 having problems with the administration such as intravenous or intramuscular injections, 13 noting an incorrect dose being selected and administered, 3 with delays in administering a dose, 2 using an expired pen, 1 using a demonstration pen instead of one with the medication, 1 with the wrong drug injected, and 1 that was not otherwise specified beyond non-compliant use. The other 205 reports of failure or misuse by the patient or user noted errors in their operation of the pen: 63 of not following the instructions for use for the pre-filled pen, 38 of leaving the needle cap on during the injection, 34 reports of operating the pre-filled pen out of sequence, 24 of an accidental release of the medication prior to the subcutaneous injection, 18 reports where the user error was determined by a quality analysis of the malfunctioning pen, 17 of dropping or damaging the pre-filled pen, 7 of forgetting to attach the needle, 3 not otherwise specified beyond misuse, and 1 of forgetting to prime the pen.

A number of reports noted a suspected problem with the operation of the pre-filled pen without a clear failure in the pen. There were 78 reports of an unexpected release of the medication without clear evidence of a pen malfunction and high risk for a user error to be involved. 61 reports noted a patient or user's concern that the dose received was inappropriate without clear evidence of an incorrect dose due to subjective elements such as liquid left in the pen or not experiencing side effects. 43 reports noted some leakage of fluid from various segments of the pre-filled pen but most regarding the needle attachment point. An additional 30 reports noted liquid leaking after completion of the injection from the needle or injection site. In these cases, no evidence of a malfunction was clearly evident. More likely, these reports result from a patient or user's unfamiliarity with the various doses available from the same pre-filled pen with differing medication remaining after injection, confusion about the priming process resulting in some leakage of fluid, or some patient/user difficulty in operating the pre-filled pen resulting in concerns.

The remaining 964 reports noted a malfunction in the operation of the pen. These stem from problems with the dialing, releasing the dose button, injection, mixing/diluting the medication, priming, or the needle. Most reports noted a single pen malfunction ("single report"), but 67 reports noted different malfunctions in more than one pen ("multiple report"). Within these 964 reports, a malfunction was reported: in dialing in 390 reports (352 single and 38 multiple), in releasing the dosing button in 224 (201 in single and 23 in multiple), in injecting in 150 reports (130 single and 20 multiple), in mixing/diluting in

134 reports (104 single and 30 multiple), with the needle in 17 reports (14 single and 3 multiple), and not otherwise specified in 96 single cases. None of these 964 reports had a returned pen that showed a defect in the pen. In fact, in regards to all 1,975 cases wherein a pen was returned for quality analysis, the malfunction was determined to be a result of patient or user error in operating the pre-filled pen and not a defect in the product.

*Table 2: Consumer Reports of Medication Errors & Complications Associated with Device*

|      |  |   |
|------|--|---|
| 243  | Reports Not Involve Redipen                                  |   |
| 133  | Storage Issue  |   |
| 51   | Incomplete or Contaminated Packaging                         |   |
| 22   | Indirect Exposure by Other Person                            |   |
| 20   | Product Dispensing Errors                                    |   |
| 17   | Accidental Exposure  |   |
| 313  | Patient/User Identified Errors:                              |   |
| 108  | in Use of the Medication:                                    |   |
| 46   | Missed Dose  |   |
| 26   | Over Dose  |   |
| 15   | Incorrect Administration                                     |   |
| 13   | Wrong Dose Given   |   |
| 3    | Dose Delayed   |   |
| 2    | Used Expired Medication                                      |   |
| 1    | Wrong Drug Injected  |   |
| 1    | Demonstration Injected                                       |   |
| 1    | Non-compliant Use  |   |
| 205  | in Operating the Device:                                     |   |
| 63   | Not Following the Instructions for Use                       |   |
| 38   | Left Cap on Needle During Injection                          |   |
| 34   | Operating Out of Sequence                                    |   |
| 24   | Accidental Released Medication                               |   |
| 18   | User Error Determined by Product Analysis                    |   |
| 17   | Dropped or Damaged   |   |
| 7    | Not Attaching the Needle                                     |   |
| 3    | Not Otherwise Specified (NOS))                               |   |
| 1    | Forgot to Prime  |   |
| 78   | Unexplained Release of Medication Prior to Injection         |   |
| 61   | Patient Unsure of Amount of Medication Received/Administered |   |
| 43   | Medication Leaking from Device                               |   |
| 30   | Leak of Medication Reported After/During Injection           |   |
| 964  | Reported Malfunction with Operation                          |   |
| 352  | Problems in Dialing of Redipen                               |   |
| 201  | Problems with Release of Dose Button                         |   |
| 130  | Problems with Injection Button or Stage                      |   |
| 104  | Problems in Mixing/Diluting Medication                       |   |
| 14   | Needle Related Problem                                       |   |
| 96   | Malfunction of Redipen Not Otherwise Specified               |   |
| 67   | Multiple Device Problems                                     |   |
|      | 38 of 67   | Noting a Dialing Problem                |
|      | 23 of 67   | Noting a Release of Dose Button Problem |
|      | 20 of 67   | Noting an Injection Stage Problem       |
|      | 30 of 67   | Noting a Mixing/Diluting Stage Problem  |
|      | 3 of 67  | Noting a Needle Problem                 |
| 1975 | Total Consumer Reports                                       |   |

**Summary & Conclusion**

Based on this review of adverse event reports regarding medication errors and complications associated with the device since the launch of PegIntron on 25 MAY 2000

to 30 JUN 2012, the MAH provides a summary and conclusion of its findings. The MAH has estimated that the US patient exposure for this period is at least (b)(4) patient treatment years for PegIntron.

The rate of an adverse event relating to a medication error or a complication associated with device for PegIntron is uncommon at a rate of 8.99 adverse events per (b)(4) patient treatment years (b)(4) patient treatment years). 30.3% (b)(4) of the medically confirmed and 48.8% (b)(4) of the consumer reports with a medication error noted a malfunction with the functionality of the prefilled pen. 7.2% (b)(4) of the medically confirmed and 10.4% (b)(4) of the consumer reports with a medication error noted a patient error in operating the pre-filled pen.

Most of the reports could not verify the nature or extent of the malfunction and are reported based on user complaint information. In those few instances where the product was available for quality analysis, all revealed that the malfunction was a result of an error in the operation of the pre-filled pen by the user and not one of a manufacturing or design defect. This supports the conclusion that the vast majority of reports involving a malfunction with the operation of the device are more likely a result of a use error. This review and analysis shows that the occurrence of a medication error for PegIntron is infrequent (<1 event per 100 patient treatment years). This reporting rate of a medication errors related to the operation of the pre-filled pen is even less frequent by the fact that only about half of the reports of a medication error are associated with either an error in operation of the pre-filled pen or a reported malfunction, which is again most likely related to an error in operation. In any case, these reports are infrequent. The reports of a medication error or complication associated with the device did not indicate any factors relating to the safety of the medication, and therefore, the MAH concludes that no new safety issues with medication errors or complications associated with device are identified. The MAH will continue to monitor the safety profile of PegIntron on a continuous basis.

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/s/  
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JAMIE C WILKINS PARKER on behalf of MORGAN A WALKER  
07/12/2013

JAMIE C WILKINS PARKER  
07/12/2013

SCOTT M DALLAS  
07/12/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103949Orig1s5259**

**PROPRIETARY NAME REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Division of Medication Error Prevention and Analysis**

**Proprietary Name Review**

Date: November 29, 2012

Reviewer: Morgan Walker, Pharm.D., M.B.A.  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: PegIntron <sup>(b)(4)</sup> (Peginterferon alfa – 2b)  
50 mcg per 0.5 mL, 80 mcg per 0.5 mL,  
120 mcg per 0.5 mL, 150 mcg per 0.5 mL

Application Type/Number: BLA 103949/5259

Sponsor: Merck and Co.

OSE RCM #: 2012-2392

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the proposed proprietary name PegIntron (b)(4) (Peginterferon alfa – 2b), 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, and 150 mcg per 0.5 mL for BLA 103949/5259. The proposed proprietary name was submitted by Merck and Co. for evaluation on October 10, 2012.

### 1.1 PRODUCT INFORMATION

- Established Name: Peginterferon alfa – 2b
- Indication of Use: For treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease
- Route of Administration: Subcutaneous injection
- Dosage Form: Powder for injection
- Strengths: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL
- Dose and Frequency: Combination with ribavirin: 1.5 mcg/kg/week; monotherapy: 1 mcg/kg/week
- How Supplied: Single-use prefilled pen (package contains one pen, one push-on need, and 2 alcohol swabs)
- Storage: 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)

## 2 DISCUSSION

During the initial steps of the proprietary name review process, the Office of Prescription Drug Promotion (OPDP) did not recommend the use of the proposed proprietary name PegIntron (b)(4) because it implies that certain characteristics of the device offer ease of use for patients. OPDP provided the following statement:

*“OPDP objects to the proposed trade name “Pegintron (b)(4) because it implies that certain characteristics of the device offer ease of use for patients. The term*

(b)(4)  
” prefilled pen is proposed to provide delivery of the drug Peginterferon, which is indicated, as part of a combination regimen, for the treatment of Chronic Hepatitis C in patients with compensated liver disease. The proposed trade name suggests that attributes of the injection device makes it easy for a patient to use. However, the proper use of the device involves several important steps and considerations. OPDP notes that there are some instructions that are imprinted on the device itself; however, these instructions are in small type and are not necessarily intuitive to patients. Therefore, it is not self-evident that the device is easy to use. Adequate evidence is necessary to support

*any suggestions that the Pegintron injection device is easy to use. In the absence of adequate evidence, the proposed proprietary name is misleading.”*

This concern was shared with the Division of Anti-Viral Products (DAVP). In email correspondence dated November 26, 2012, DAVP concurred with OPDP’s assessment. DMEPA also concurs with this finding and will not perform a safety assessment of the proposed proprietary name.

### 3 CONCLUSIONS AND RECOMMENDATIONS

The proposed proprietary name, PegIntron (b)(4) is unacceptable from a promotional perspective. The Applicant will be notified of FDA’s decision to object to the name based on promotional concerns via letter.

#### 3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, PegIntron (b)(4) and have concluded that this name is unacceptable for the following reason:

Pegintron (b)(4)k implies that certain characteristics of the device offer ease of use for patients. The term (b)(4)” can be (b)(4)

(b)(4) The (b)(4) prefilled pen is proposed to provide delivery of the drug Pegintron, which is indicated, as part of a combination regimen, for the treatment of Chronic Hepatitis C in patients with compensated liver disease. The proposed trade name suggests that attributes of the injection device makes it easy for a patient to use. However, the proper use of the device involves several important steps and considerations. OPDP notes that there are some instructions that are imprinted on the device itself; however, these instructions are in small type and are not necessarily intuitive to patients. Therefore, it is not self-evident that the device is easy to use. Adequate evidence is necessary to support any suggestions that the Pegintron injection device is easy to use. In the absence of adequate evidence, the proposed proprietary name is misleading.

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

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/s/

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MORGAN A WALKER  
11/29/2012

JAMIE C WILKINS PARKER  
11/29/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Proprietary Name Review**

Date: May 7, 2013

Reviewer: Morgan Walker, PharmD, MBA  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh.  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: PegIntron Selectdose (Peginterferon alfa 2b) Powder for Injection  
50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, and 150 mcg per 0.5 mL

Application Type/Number: BLA 103949

Applicant/Sponsor: Merck and Co.

OSE RCM #: 2013-450

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## **1 INTRODUCTION**

This review evaluates the proposed proprietary name, PegIntron Selectdose, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

### **1.1 REGULATORY HISTORY**

PegIntron Selectdose is the second proposed proprietary name for this product. DMEPA previously reviewed the name PegIntron (b)(4) that was submitted by the Applicant for this product in OSE Review # 2012-2392. This name was turned down by OPDP because the name implied that certain characteristics of the device offer ease of use for patients.

In addition, the PegIntron Selectdose is a new device and will eventually replace PegIntron Redipen.

### **1.2 PRODUCT INFORMATION**

The following product information is provided in the February 7, 2013 proprietary name submission.

- Active Ingredient: Peginterferon alfa-2b Powder for Injection
- Indication of Use: For the treatment of Chronic Hepatitis C with compensated liver disease
- Route of Administration: Subcutaneous injection
- Dosage Form: Powder for injection
- Strength: 50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, 150 mcg per 0.5 mL
- Dose and Frequency: Combination with ribavirin: 1.5 mcg/kg/week; monotherapy: 1 mcg/kg/week
- How Supplied: Single-use prefilled pen (package contains one pen, one push-on needle, and 2 alcohol swabs)
- Storage: 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)

## **2. RESULTS**

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

### **2.1 PROMOTIONAL ASSESSMENT**

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Anti-Viral Products concurred with the findings of OPDP's promotional assessment of the proposed name.

## **2.2 SAFETY ASSESSMENT**

The following aspects were considered in the safety evaluation of the name.

### ***2.2.1 United States Adopted Names (USAN) SEARCH***

We acknowledge that the root name, PegIntron, contains the USAN Stem 'Peg-'. However, PegIntron was approved prior to DMEPA having signatory authority for proprietary names. The USAN Stem 'Peg-' aligns with the established name of this product and is used appropriately to refer to the product. PegIntron is currently marketed without any medication errors with the root name having the USAN Stem. Changing the root name secondary to a USAN stem at this point would likely cause more errors than prevent them.

The March 1, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the modifier, Selectdose.

### ***2.2.2 Components of the Proposed Proprietary Name***

The proprietary name is comprised of two words, the root name 'PegIntron' and the modifier 'Selectdose'. The Applicant indicated in their submission that the proposed name, PegIntron Selectdose, is derived from the existing (approved) drug name PegIntron. The Applicant also stated that the modifier, Selectdose, is primarily intended to provide limited differentiation between the current PegIntron pre-filled pen, Redipen, and the new PegIntron pre-filled pen. See section 2.2.7 for the analysis of the proposed modifier.

### ***2.2.3 Medication Error Data Selection of Cases***

DMEPA searched FDA Adverse Event Reporting System (FAERS) database on March 22, 2013 for medication errors involving name confusion with the root name, PegIntron, and names found during the Expert Panel Discussion (EPD) searches using a Drug Interactions Quick Query.

The FAERS search did not retrieve any relevant cases.

### ***2.2.4 FDA Name Simulation Studies***

Seventy-one practitioners participated in DMEPA's prescription studies. There were no other misinterpretations, sound or orthographic similarities to any currently marketed products or any proposed products. There were several misinterpretations in the inpatient study where participants interpreted 'P' in PegIntron as an 'R'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

### ***2.2.5 Comments from Other Review Disciplines at Initial Review***

In response to the OSE, February 27, 2013 e-mail, the Division of Anti-viral Products (DAVP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

### 2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, PegIntron Selectdose. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, PegIntron Selectdose identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, and External Name Study)

| <b>Look Similar</b>           |               |                               |                   |                       |               |
|-------------------------------|---------------|-------------------------------|-------------------|-----------------------|---------------|
| <i>Name</i>                   | <i>Source</i> | <i>Name</i>                   | <i>Source</i>     | <i>Name</i>           | <i>Source</i> |
| USAN: Peg-                    | FDA           | PEG-3350                      | FDA               | Pagitane              | FDA           |
| Select One***                 | FDA           | PEG-Interleukin-2             | FDA (Orphan drug) | Peganone              | FDA           |
| Select-OB                     | FDA           | Regroton                      | FDA               | Pagoclone             | FDA           |
| <b>Look and Sound Similar</b> |               |                               |                   |                       |               |
| <i>Name</i>                   | <i>Source</i> | <i>Name</i>                   | <i>Source</i>     | <i>Name</i>           | <i>Source</i> |
| PegIntron Clearclick***       | FDA           | Pegintron/Rebetrol Combo Pack | FDA               | Peganone              | FDA           |
| PegIntron                     | FDA           | Pegintron Redipen             | FDA               | PegIntron Redipen Pak | FDA           |

Our analysis of the fourteen names and one USAN stem contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined none of the names will pose a risk for confusion as described in Appendix D.

### 2.2.7 Evaluation of Modifier 'Selectdose'

The actual drug product, PegIntron, is not being changed at this time (i.e. same active ingredient and concentrations). Instead, PegIntron Selectdose provides a new pen device to support the regular dosing as well as dose reductions of PegIntron that the currently marketed PegIntron Redipen does not. PegIntron Selectdose provides a smaller dosing volume (i.e. 0.2 mL) that PegIntron Redipen does not provide. Current patients using PegIntron Redipen have to use both a vial and a pen for dose reductions. Both products will (b)(4) and eventually, PegIntron Redipen will be phased out and patients (b)(4). The proposed proprietary name reflects the fact that the new pre-filled pen has a dial that allows for proper dose selection.

The Applicant did not provide data to support that the modifier is not error prone or a source of confusion. We have evaluated whether or not the proposed proprietary name requires the modifier, evaluated the appropriateness of the chosen modifier 'Selectdose', and considered if this product should utilize a different proprietary name to help differentiate between the new product and the currently marketed PegIntron Redipen.

The differences between the two products are highlighted in yellow in the dose reduction guidelines listed below:

**TABLE 6<sup>1</sup>:  
Reduced PegIntron Dose (0.5 mcg/kg) for (1 mcg/kg) Monotherapy in Adults**

| Body wWeight<br>kg (lbs) | PegIntron<br>REDIPEN <sup>2</sup> Pre-filled Pen/<br>Vial Strength to<br>Use | Amount of PegIntron (mcg) to<br>Administer<br>(mcg) | Volume (mL) <sup>**</sup> of PegIntron to<br>Administer<br>(mL) |
|--------------------------|--|---|---|
| ≤45<br>(≤100)            | 50 mcg per 0.5 mL <sup>‡</sup>   | 20  | 0.2   |
| 46–56<br>(101–124)       | 50 mcg per 0.5 mL <sup>‡</sup>   | 25  | 0.25  |
| 57–72<br>(125–159)       | 50 <del>80</del> mcg per 0.5 mL  | 30<br>32  | 0.30 <del>0.2</del>   |
| 73–88<br>(160–195)       | 50 mcg per 0.5 mL  | 40  | 0.4   |
| 89–106<br>(196–234)      | 50 mcg per 0.5 mL  | 50  | 0.5   |
| 107–136<br>(235–300)     | 80 mcg per 0.5 mL  | 64  | 0.4   |
| ≥137<br>(≥301)           | 80 mcg per 0.5 mL  | 80  | 0.5   |

<sup>‡</sup> Must use vial. Minimum delivery for REDIPEN 0.3 mL.

<sup>\*\*</sup> When reconstituted as directed.

**TABLE 7<sup>1</sup>:  
Two-Step Dose Reduction of PegIntron in Combination Therapy in Adults**

| First Dose Reduction to PegIntron 1 mcg/kg |   |   |   | Second Dose Reduction to PegIntron 0.6 mcg/kg |  |   |  |
|--|---|---|---|---|--|---|--|
| Body wWeight<br>kg (lbs)                   | PegIntron<br>REDIPEN <sup>2</sup> Pre-filled<br>Pen/Vial Strength<br>to Use | Amount of<br>PegIntron<br>(mcg) to<br>Administer<br>(mcg) | Volume<br>(mL) <sup>**</sup> of<br>PegIntron to<br>Administer<br>(mL) | Body wWeight<br>kg (lbs)                      | PegIntron<br>REDIPEN <sup>2</sup> Pre-filled<br>Pen/<br>Vial Strength to Use | Amount of<br>PegIntron<br>(mcg) to<br>Administer<br>(mcg) | Volume<br>(mL) <sup>**</sup><br>of PegIntron<br>to<br>Administer<br>(mL) |
| <40<br>(<88)                               | 50 mcg per 0.5 mL   | 35  | 0.35  | <40<br>(<88)                                  | 50 mcg per 0.5 mL <sup>‡</sup>   | 20  | 0.2  |
| 40–50<br>(88–111)                          | 50 <del>120</del> mcg per 0.5<br>mL   | 45<br>48  | 0.45<br>0.2   | 40–50<br>(88–111)                             | 50 mcg per 0.5 mL <sup>‡</sup>   | 25  | 0.25   |
| 51–60<br>(112–<br>133)                     | 50 mcg per 0.5 mL   | 50  | 0.5   | 51–60<br>(112–<br>133)                        | 50 <del>80</del> mcg per 0.5 mL  | 30<br>32  | 0.3<br>0.2   |
| 61–75<br>(134–<br>166)                     | 80 mcg per 0.5 mL   | 64  | 0.4   | 61–75<br>(134–<br>166)                        | 50 mcg per 0.5 mL  | 35  | 0.35   |
| 76–85<br>(167–<br>187)                     | 80 mcg per 0.5 mL   | 80  | 0.5   | 76–85<br>(167–<br>187)                        | 50 <del>120</del> mcg per 0.5<br>mL  | 45<br>48  | 0.45<br>0.2  |
| 86-104<br>(188-230)                        | 120 mcg per 0.5 mL  | 96  | 0.4   | 86-104<br>(188-230)                           | 50 mcg per 0.5 mL  | 50  | 0.5  |
| 105-125<br>(231-275)                       | 420 <del>150</del> mcg per 0.5<br>mL  | 408<br>105  | 0.35  | 105-125<br>(231-275)                          | 80 mcg per 0.5 mL  | 64  | 0.4  |
| >125<br>(>275)                             | 450 mcg per 0.5 mL <sup>‡</sup>   | 435 <sup>‡</sup>  | 0.45 <sup>‡</sup>   | >125<br>(>275)                                | 80 mcg per 0.5 mL <sup>‡</sup>   | 72 <sup>‡</sup>   | 0.45 <sup>‡</sup>  |

<sup>‡</sup> Must use vial. Minimum delivery for REDIPEN 0.3 mL.

<sup>\*\*</sup> When reconstituted as directed.

<sup>1</sup> For patients weighing greater than 125 kg (>275 pounds), the PegIntron dose should be calculated based on the individual patient weight. This may require combinations of various PegIntron dose strengths and volumes.

### ***2.2.7.1 Safety assessment of the modifier ‘Selectdose’***

The Applicant proposes to use the modifier ‘Selectdose’ to differentiate between the proposed product and the currently marketed PegIntron Redipen. The modifier “Selectdose” is a novel modifier that has no established meaning. Selectdose is not a medical abbreviation, does not contain a USAN stem, and does not appear to present any overt safety concerns from a look or sound alike perspective.

Despite the fact that there was no data was submitted by the Applicant to support that the modifier communicates the different dosing properties that the currently marketed pen does not have, the modifier ‘Selectdose’ does appear to imply that a patient has to select a dose in order to administer the medication in the pen. It is not a false claim or misleading. Additionally, there is no modifier in current use that conveys these types of product differences so it is reasonable that a novel modifier would be developed.

There are currently marketed products that use novel modifiers to denote a specific formulation or packaging configuration (e.g., Zyprexa Relprevv and Nicoderm CQ,) that differentiate these products from the existing product line. In some circumstances, these modifiers do not have any intended meaning or derivation and may not explicitly communicate or relate to the difference between the products. In other words, these modifiers serve only to indicate there is a difference between two products (e.g. Zyprexa Relprevv differs in some way from Zyprexa) but does not communicate the nature of the difference. The modifier “Selectdose” is similar to the aforementioned examples in that “Selectdose” describes a different device and is being used to differentiate the two PegIntron products.

We also evaluated the potential risk of confusion within the PegIntron product line. Although there are several differences in the product characteristics, omission and oversight of the modifier was still evident in our name simulation studies in which three participants omitted the modifier. We considered the potential safety implications of this error. Given that the drug product itself is not changing, this will not impact the patient clinically, since the patient will be receiving the same drug, just via a different device. If patients need a dosage adjustment and does not receive PegIntron Selectdose, patients would have to use PegIntron Redipen (until market supply is depleted) and a vial of PegIntron.

### ***2.2.7.2 Safety of using a unique name to market this product***

An alternative to using a modifier to distinguish this product from the currently marketed products is to use a totally different root name. Thus, we considered the risk of introducing a total new proprietary name for this product. The introduction of a new name also carries a risk of medication errors. Specifically, marketing the new product under a unique name may lead to additional medication errors such as therapeutic duplication and overdoses. These errors may have greater associated safety risks than the omission or oversight of the modifier as discussed in Section 2.2.7.1. Therefore, for the aforementioned reasons listed in Sections 2.2.7.1, and 2.2.7.2. DMEPA finds that the proprietary

name 'PegIntron Selectdose,' although not free from the risk of error, offers a safer approach to naming this product.

#### **2.2.8      *Communication of DMEPA's Analysis at Midpoint of Review***

DMEPA communicated our findings to DAVP via e-mail on April 10, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from DAVP on April 15, 2013, they stated no additional concerns with the proposed proprietary name, PegIntron Selectdose.

### **3      CONCLUSIONS**

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Danyal Chaudhry, OSE project manager, at 301-796-3813.

#### **3.1      COMMENTS TO THE APPLICANT**

We have completed our review of the proposed proprietary name, PegIntron Selectdose, and have concluded that this name is acceptable.

The proposed proprietary name must be re-reviewed 90 days prior to approval of the BLA. The results are subject to change. If any of the proposed product characteristics as stated in your February 7, 2013 submission are altered, the name must be resubmitted for review.

#### 4 REFERENCES

1. ***Micromedex Integrated Index (<http://csi.micromedex.com>)***

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (<http://factsandcomparisons.com>)***

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)***

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (<http://www.uspto.gov>)***

USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online ([www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com))***

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

**9. *Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at ([www.thomson-thomson.com](http://www.thomson-thomson.com))***

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

**10. *Natural Medicines Comprehensive Databases ([www.naturaldatabase.com](http://www.naturaldatabase.com))***

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

**11. *Access Medicine ([www.accessmedicine.com](http://www.accessmedicine.com))***

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

**12. *USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)***

USAN Stems List contains all the recognized USAN stems.

**13. *Red Book ([www.thomsonhc.com/home/dispatch](http://www.thomsonhc.com/home/dispatch))***

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

**14. *Lexi-Comp ([www.lexi.com](http://www.lexi.com))***

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

**15. *Medical Abbreviations ([www.medilexicon.com](http://www.medilexicon.com))***

Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

**16. *CVS/Pharmacy ([www.CVS.com](http://www.CVS.com))***

This database contains commonly used over the counter products not usually identified in other databases.

**17. *Walgreens ([www.walgreens.com](http://www.walgreens.com))***

This database contains commonly used over the counter products not usually identified in other databases.

**18. *Rx List* ([www.rxlist.com](http://www.rxlist.com))**

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

**19. *Dogpile* ([www.dogpile.com](http://www.dogpile.com))**

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

**20. *Natural Standard* (<http://www.naturalstandard.com>)**

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

## APPENDICES

### Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.<sup>2</sup>

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

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<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

**Table 1.** Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

| <b>Type of Similarity</b> | <b>Considerations when Searching the Databases</b> |  |   |
|---------------------------|--|--|---|
|                           | <i>Potential Causes of Drug Name Similarity</i>    | <i>Attributes Examined to Identify Similar Drug Names</i>  | <i>Potential Effects</i>  |
| Look-alike                | Similar spelling                                   | Identical prefix<br>Identical infix<br>Identical suffix<br>Length of the name<br>Overlapping product characteristics   | <ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul> |
|                           | Orthographic similarity                            | Similar spelling<br>Length of the name/Similar shape<br>Upstrokes<br>Down strokes<br>Cross-strokes<br>Dotted letters<br>Ambiguity introduced by scripting letters<br>Overlapping product characteristics | <ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>  |
| Sound-alike               | Phonetic similarity                                | Identical prefix<br>Identical infix<br>Identical suffix<br>Number of syllables<br>Stresses<br>Placement of vowel sounds<br>Placement of consonant sounds<br>Overlapping product characteristics          | <ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>   |

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

### **1. Database and Information Sources**

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

### **2. Expert Panel Discussion**

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

### **3. FDA Prescription Simulation Studies**

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

#### **4. Comments from Other Review Disciplines**

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

#### **5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name**

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>3</sup> When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

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<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

***“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?”***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

***“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”***

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

**Appendix B:** Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

| Letters in Name,<br>PegIntron Selectode | Scripted May Appear<br>as | Spoken May Be<br>Interpreted as |
|---|---------------------------|---------------------------------|
| P                                       | R                         | B                               |
| p                                       | yn, ys, g, j, l, q        | b                               |
| e                                       | a, i, l, o, u, p          | Any vowel                       |
| g                                       | q, j, s                   | k, j                            |
| i                                       | L                         | Any vowel                       |
| I                                       | e, l                      | Any vowel                       |
| n                                       | m, u, x, r, h, s          | dn, gn, kn, mn, pn              |
| t                                       | r, f, x, A                | d                               |
| r                                       | s, n, e, v                | N/A                             |
| o                                       | a, c, e, u                | Oh                              |
| n                                       | m, u, x, r, h, s          | dn, gn, kn, mn, pn              |
|   |                           |                                 |
| S                                       | G, L, Z, 5                | X or C                          |
| s                                       | G, 5, g, n                | x                               |
| e                                       | a, i, l, o, u, p          | Any vowel                       |
| l                                       | b, e, s, A, P, i          |                                 |
| e                                       | a, i, l, o, u, p          | Any vowel                       |
| c                                       | a, e, i, l                | k                               |
| t                                       | r, f, x, A                | d                               |
| d                                       | cl, ci                    | b, t                            |

|                      |                  |           |
|----------------------|------------------|-----------|
| o                    | a, c, e, u       | Oh        |
| s                    | G, 5, g, n       | x         |
| e                    | a, i, l, o, u, p | Any vowel |
| <b>Letter String</b> |                  |           |
| ele                  | ili, eie, icl,   |           |

**Appendix C: Prescription Simulation Samples and Results**

**Figure 1. PegIntron Selectdose Study (Conducted on March 1, 2013)**

| Handwritten Requisition Medication Order   | Verbal Prescription  |
|--|--|
| <p><u>Medication Order:</u></p> <p><i>PegIntron selectdose 120mcg/0.5mL</i></p> <hr/> <p><i>96 mcg (0.4 mL) subcutaneously weekly</i></p>                      | <p>PegIntron Selectdose</p> <p>80mcg/0.5 mL</p> <p>Inject 64 mcg (0.4 mL) subcutaneously every week</p> <p>Disp.: #4</p> |
| <p><u>Outpatient Prescription:</u></p> <p><i>PegIntron Selectdose <math>\frac{80mcg}{0.5mL}</math></i></p> <p><i>Inject 64 mcg (0.4 mL) subQ weekly #4</i></p> |  |

**FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)**

191 People Received Study

71 People Responded

Study Name: PegIntron Selectdose

| Total                                  | 27        | 23    | 21         |       |
|--|-----------|-------|------------|-------|
| INTERPRETATION                         | INPATIENT | VOICE | OUTPATIENT | TOTAL |
| ?                                      | 0         | 1     | 0          | 1     |
| ???                                    | 1         | 0     | 0          | 1     |
| PEG INTRON                             | 0         | 2     | 0          | 2     |
| PEG INTRON SELECT                      | 0         | 1     | 0          | 1     |
| PEG INTRON SELECT DOSE                 | 0         | 3     | 9          | 12    |
| PEG INTRON SELECTDOSE                  | 0         | 0     | 1          | 1     |
| PEG INTRON SELECTIVE                   | 0         | 2     | 0          | 2     |
| PEGINTRON                              | 0         | 0     | 1          | 1     |
| PEG-INTRON CELACTOSE                   | 0         | 1     | 0          | 1     |
| PEGINTRON ELECTIVE                     | 0         | 1     | 0          | 1     |
| PEG-INTRON LITE DOSE                   | 0         | 1     | 0          | 1     |
| PEGINTRON SELECT DOSE                  | 1         | 2     | 5          | 8     |
| PEG-INTRON SELECT DOSE                 | 0         | 2     | 0          | 2     |
| PEGINTRON SELECT DOSE<br>80 MCG/0.5 ML | 0         | 0     | 1          | 1     |
| PEGINTRON SELECTDOSE                   | 0         | 3     | 4          | 7     |
| PEG-INTRON SELECTIVE                   | 0         | 1     | 0          | 1     |
| PEG-INTRON SELECTOS                    | 0         | 1     | 0          | 1     |
| PEG-INTRONON<br>SELECTIVE              | 0         | 1     | 0          | 1     |
| PEGLATIMSELEETDOSE                     | 1         | 0     | 0          | 1     |

|                       |   |   |   |   |
|-----------------------|---|---|---|---|
| PEGLATINSELECTDOSE    | 1 | 0 | 0 | 1 |
| PEGLATONSELECTDSE     | 1 | 0 | 0 | 1 |
| PEGLATRON SELECT DOSE | 3 | 0 | 0 | 3 |
| PEGLATRON SELECTDOSE  | 2 | 0 | 0 | 2 |
| PEGLATRONSELECTDOSE   | 1 | 0 | 0 | 1 |
| PEGLATUMSELECTDOSE    | 1 | 0 | 0 | 1 |
| PEGLATURNSELEETDOSE   | 1 | 0 | 0 | 1 |
| PEGLOTION SELECTDOSE  | 1 | 0 | 0 | 1 |
| PEGLUTAM SELECTDOSE   | 1 | 0 | 0 | 1 |
| PEGLUTURN SELECTDOSE  | 1 | 0 | 0 | 1 |
| REGLARTRONSELECTDOSE  | 1 | 0 | 0 | 1 |
| REGLATIM SELECT DOSE  | 2 | 0 | 0 | 2 |
| REGLATIMSELECTDOSE    | 2 | 0 | 0 | 2 |
| REGLATON SELECT DOSE  | 1 | 0 | 0 | 1 |
| REGLATORN SELECT DOSE | 1 | 0 | 0 | 1 |
| REGLATRIM SELECTDOSE  | 1 | 0 | 0 | 1 |
| REGLATRIMSELECTDORE   | 1 | 0 | 0 | 1 |
| REGLATRON SELECT DOSE | 1 | 0 | 0 | 1 |
| REGLATRON SELECTDOSE  | 1 | 0 | 0 | 1 |
| TAGINTRON             | 0 | 1 | 0 | 1 |

**Appendix D:** Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

| No. | Proprietary Name             | Active Ingredient               | Similarity to PegIntron Selectdose | Failure preventions  |
|-----|------------------------------|---------------------------------|------------------------------------|--|
| 1.  | (b)(4)                       | Levonorgestrel                  | Look Similar                       | (b)(4)   |
| 2.  | Select Ob                    | Prenatal vitamins               | Look similar                       | Lacks orthographic similarity with modifier  |
| 3.  | PEG-3350                     | NA                              | Look similar                       | Lacks orthographic similarity with root name   |
| 4.  | PEG-Interleukin-2            | NA                              | Look similar                       | (b)(4)   |
| 5.  | Regroton                     | Chlorthalidone Reserpine        | Look similar                       | Lacks orthographic similarity with root name   |
| 6.  | Pagitane                     | Cycrimine Hydrochloride         | Look similar                       | Withdrawn FR Effective August 5, 1996  |
| 7.  | Peganone                     | Ethotoin                        | Look/sound similar                 | Lacks orthographic and phonetic similarity with root name  |
| 8.  | Pagoclone                    | NA                              | Look similar                       | (b)(4)   |
| 9.  | (b)(4)                       | Pegintron alfa-2b               | Look/sound similar                 | (b)(4)   |
| 10. | PegIntron                    | Pegintron alfa-2b               | Look/sound similar                 | The same root name as the proposed proprietary name  |
| 11. | Pegintron/Rebetol Combo Pack | Pegintron alfa-2b and Ribavirin | Look/sound similar                 | There will be market overlap for a limited amount of time, however, the modifier provides orthographic differentiation |
| 12. | Pegintron Redipen            | Pegintron alfa                  | Look/sound similar                 | There will be market overlap for a limited amount of time, however, the modifier provides orthographic differentiation |
| 13. | Pegintron Redipen Pak        | Pegintron alfa                  | Look/sound similar                 | There will be market overlap for a limited amount of time, however, the modifier provides orthographic differentiation |

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/s/  
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MORGAN A WALKER  
05/07/2013

JAMIE C WILKINS PARKER  
05/07/2013

CAROL A HOLQUIST  
05/07/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Proprietary Name Review--Final**

Date: June 3, 2013

Reviewer: Morgan Walker, Pharm.D., MBA  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: PegIntron Selectdose (Peginterferon alfa 2b) Powder for Injection  
50 mcg per 0.5 mL, 80 mcg per 0.5 mL, 120 mcg per 0.5 mL, and  
150 mcg per 0.5 mL

Application Type/Number: BLA 103949

Applicant/Sponsor: Merck and Co.

OSE RCM #: 2013-1086

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## **1 INTRODUCTION**

This re-assessment of the proposed proprietary name, PegIntron Selectdose is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, PegIntron Selectdose, acceptable in OSE Review #2013-450 (BLA 103949).

## **2 METHODS AND DISCUSSION**

For re-assessments of proposed proprietary names, DMEPA searches a standard set of databases and information sources (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. For this review we used the same search criteria described in OSE Review #2013-450. We did not search the USAN stems list as the root name, PegIntron, contains a USAN stem and has been evaluated in OSE Review #2013-450. We note that none of the proposed product characteristics were altered. However, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. The searches of the databases yielded no new names thought to look or sound similar to PegIntron Selectdose and do not represent a potential source of drug name confusion.

## **3 CONCLUSIONS**

The re-evaluation of the proposed proprietary name, PegIntron Selectdose, did not identify any vulnerabilities that would result in medication errors with any additional name(s) noted in this review. Thus, DMEPA has no objection to the proprietary name, PegIntron Selectdose, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Anti-Viral Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

#### 4 REFERENCES

1. **OSE Reviews.** #2013-450 (BLA 103949)

2. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved **brand name**, **generic drugs**, **therapeutic biological products**, **prescription** and **over-the-counter** human drugs and **discontinued drugs** and “**Chemical Type 6**” approvals.

3. **Division of Medication Error Prevention and Analysis Proprietary Name Consultation Request**

Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis for review. The list is generated on a weekly basis from the Access database/tracking system.

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/s/

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MORGAN A WALKER

06/03/2013

JAMIE C WILKINS PARKER

06/03/2013