

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125196

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW

Chemistry Review Data Sheet

BLA 125196

**PegIntron™ /REBETOL® Combo Pack
Containing
PegIntron™ REDIPEN® Single-dose Delivery System
(peginterferon alfa-2b)
And
REBETOL® (ribavirin, USP) capsules**

Schering Corporation

**Ko-Yu Lo, Ph.D.
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment**



Chemistry Review Data Sheet

1. BLA: 125196
2. REVIEW #: 1
3. REVIEW DATE: 04/02/2008
4. REVIEWER: Ko-Yu Lo
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	26/JUN/2006
Amendment 001	11/AUG/2006
Amendment 002	23/AUG/2006
Amendment 003	16/OCT/2006
Amendment 005	08/FEB/2007
Amendment 008	03/OCT/2007
Amendment	31/MAR/2008

7. NAME & ADDRESS OF APPLICANT:

Name	Schering Corporation
Address	2000 Galloping Hill Road, Kenilworth, NJ 07033
Representative	Rachael Steiner, Associate Director and Liaison, Global Regulatory Affairs
Telephone	908-740-2525

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Peginterferon alfa-2b/Ribavirin
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Ribavirin: Antiviral

11. DOSAGE FORM: Lyophilized powder/Capsule

12. STRENGTH/POTENCY: 50, 80, 120, 150 mcg/0.5 mL/200 mg



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13. ROUTE OF ADMINISTRATION: Subcutaneous/Oral
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 X Not a SPOTS product (for ribavirin)
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR
FORMULA, MOLECULAR WEIGHT:

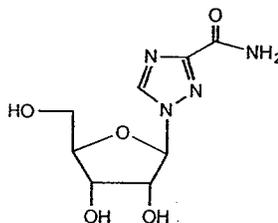
USAN Ribavirin

Chemical Name 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide

Molecular Formula C₈H₁₂N₄O₅

Molecular Weight 244.21

Structure Formula



17. RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	BLA 103949	PegIntron™
	NDA 20-903	Rebetol®



The Chemistry Review for BLA 125196

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the BLA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

PegIntron™/REBETOL® Combo Pack contains PegIntron™ REDIPEN® Single-dose Delivery System (peginterferon alfa-2b) and REBETOL® (ribavirin) Capsules. The PegIntron Redipen product is approved in BLA 103949 and the Rebetol product is approved in NDA 20-903. All CMC information for the combo pack is crossed referenced to the two cited applications. The combo pack will be available in following configurations:

- A box containing four 50 mcg per 0.5 mL PegIntron™ REDIPEN units, each containing 1 BD® needle and 2 alcohol swabs, and two bottles of 56 REBETOL Capsules, 200 mg.
- A box containing four 80 mcg per 0.5 mL PegIntron™ REDIPEN units, each containing 1 BD® needle and 2 alcohol swabs, and two bottles of 56 REBETOL Capsules, 200 mg
- A box containing four 120 mcg per 0.5 mL PegIntron™ REDIPEN units, each containing 1 BD® needle and 2 alcohol swabs, and two bottles of 70 REBETOL Capsules, 200 mg
- A box containing four 150 mcg per 0.5 mL PegIntron™ REDIPEN units, each containing 1 BD® needle and 2 alcohol swabs, and two bottles of 84 REBETOL Capsules, 200 mg
- A box containing four 150 mcg per 0.5 mL PegIntron™ REDIPEN units, each containing 1 BD® needle and 2 alcohol swabs, and two bottles of 98 REBETOL



Chemistry Assessment Section

Capsules, 200 mg

Description of Individual Components**PegIntron™**

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

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

REDIPEN®

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

REBETOL®

REBETOL® is Schering Corporation's brand name for ribavirin, a nucleoside analog. Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol.

REBETOL® Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

PegIntron™/REBETOL® Combo Pack therapy is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

Dosage and Administration

The recommended dose of PegIntron™ is 1.5 mcg/kg/week in combination with 800-1400 mg REBETOL® based on patient body weight. The volume of PegIntron™ to be injected depends on the strength of PegIntron™ and patient's body weight. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

C. Basis for Approvability or Not-Approval Recommendation

This review addresses CMC related issues for the Rebetol component of the combo pack.

- The manufacture of Rebetol capsules and sites of manufacture, packaging, and control operations remain the same as provided in the approved NDA 20-903. The NDA 20-903 allows for secondary packaging operations at Schering Corporation in Kenilworth, New Jersey. The proposed secondary package of Rebetol Capsules and PegIntron Redipen into the combo pack cartons at the Kenilworth facility is acceptable.
- Container labels for Rebetol bottles to be packaged into the combo packs (Amendment 005, 2/8/2007) are acceptable. The label state "This package should be dispensed with PegIntron (Peginterferon alfa-2b), and is not intended for individual sale" (see Attachment 1).
- Container labels for the combo packs are acceptable (see Attachment 1).
- A statement of Categorical Exclusion from environmental assessment (EA) has been provided (Amendment 002) and is acceptable.
- Description, Storage and How Supplied sections of the revised Package Insert (Amendment dated 3/31/08) are acceptable.

The BLA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for PegIntron/REBETOL Combo Pack.

Ko-yu Lo 4/3/08
Ko-Yu Lo, Ph.D. Review Chemist

Norman R. Schuff 6/18/2008
Norman R. Schuff, Ph.D. Branch Chief
Branch IV, Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

1 Page(s) Withheld

 Trade Secret / Confidential

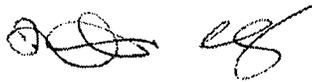
 ✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry- 1

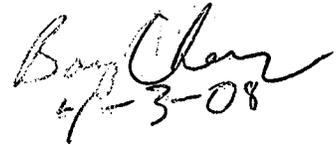
March 26, 2008

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4-3-08

Approved by: Barry Cherney, Ph.D., Deputy Director, DTP, HFD-122
Re: Review of Labeling of BLA 125196/0
Cc: Victoria TysonMedlock, RPM
Sponsor: Schering Corporation
The first action due date: **April 5, 2008.**



Recommendation: I recommend approving the labeling of the combo packers for PegIntron and Rebetol.

Review: The labels of four strengths (50, 80, 120, 150 mcg) of PegIntron all have drug name, route of injection, storage condition, lot# and expiration written clearly, and each strength was high-lighted with distinct color.

The labeling of the five combo packers (PegIntron/REBETOL Combo Pack: 150 mcg 84 Combo Packer, 150 mcg 98 Combo Packer, 120 mcg Combo Packer, 80 mcg Combo Packer, and 50 mcg Combo Packer) all have drug name, contents, route of injection, storage condition, and barcode written clearly, and each strength was high-lighted with distinct color. Expiration date will be stamped on the Combo Packers.

PI contains the approved strengths and condition of storage and is acceptable.