CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-903/S-008, S-011, S-012, S-016

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Consumer Safety Officer Labeling Review

NDA: 20-903/S-008, S-011, S-012, S-016

Date submitted: November 7, 2000 (S-008), February 26, 2001(S-011), February 28, 2001(S-012), May11, 2001(S-016)

Sponsor: The Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Products: REBETRON COMBINATION THERAPY™, SCH 30500 - Intron® A (Interferon alfa-2b, recombinant) for Injection/ SCH 18908 - Ribavirin. (REBETOL®)

Materials Reviewed: Draft Labeling dated July 20, 2001, for all four supplements under consideration

Appendices:
1. REBETOL® label
2. REBETOL® Medication Guide
3. REBETRON COMBINATION THERAPY™ pen Medication Guide
4. REBETRON COMBINATION THERAPY™ vial Medication Guide

Background:

From June, 1998 until present time, REBETRON COMBINATION THERAPY™ has been marketed in various combinations of ribavirin plus Interferon alfa-2b. During the initial NDA review, the Schering Corporation (the Sponsor) cited various safety concerns for not providing ribavirin in a stand alone packaging configuration. On November 7, 2000, the Sponsor submitted a labeling supplement (S-008 for NDA 20-903), submitted as a prior approval supplement, that proposed to allow the marketing of a stand alone 84 capsule container of REBETOL® (ribavirin), accompanied by appropriate labeling.

On February 26, 2001, the Sponsor submitted a special supplement, changes being effected (CBE) (S-011 for NDA 20-903), that revised the medication guide for REBETRON COMBINATION THERAPY™ to provide information to patients on how to avoid a "pen discoloration" observed in post-marketing reports for the injection pen included in some marketing configurations of REBETRON COMBINATION THERAPY™.

On February 28, 2001, the Sponsor submitted "General Correspondence, Chemistry," providing for the implementation of a "Safety-Lok Syringe" to replace the syringe previously marketed with REBETRON COMBINATION THERAPY™. This request for replacement was made because the manufacturer of the syringe originally marketed with REBETRON COMBINATION THERAPY™ discontinued this item. On March 7, 2001, the Sponsor requested that the February 28, 2001 "General Correspondence, Chemistry," be coded as a special supplement, changes being effected (S-012 for NDA 20-903).

On May 11, 2001, the Sponsor submitted a labeling supplement (S-016 for NDA 20-903), submitted as a prior approval supplement, pursuant to 21 CFR Part 208, allowing for the inclusion of an official Medication Guide for REBETRON COMBINATION THERAPY™.

Label Revisions, S-008:

1. The addition of a separate label for REBETOL (see Appendix 1, REBETOL label).

Label Revisions, S-011 (instructions for use section, Medication Guide Pen):

1. Add instructions to pinch a 2-inch fold of skin prior to injection (see below, step 14).
2. Revision of Diagram P for a SC injection from a 90° angle of insertion to an approximately 45° angle of insertion, to include a new step in the instructions for use section, Medication Guide Pen, as follows:

    14. To give the injection, remove the pen cap from the needle. With one hand, pinch a 2-inch fold of loose skin.

    15. With your other hand, pick up the pen and hold it as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45° (see Diagram P) **then press the push button down fully.**

    If blood comes into the pen, do not inject. Withdraw the needle and consult your physician or pharmacist.

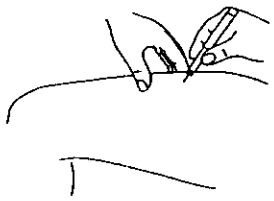


Diagram P

3. Addition of instructions for patients to hold down push button after injection (step 16), as follows:

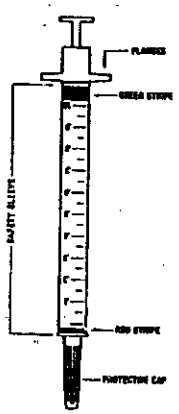
    16. Leave the needle in place for a few seconds, while holding down the push button, to allow the INTRON A Solution to distribute under the skin.

4. Addition of instruction to release the push button slowly after injection (step 17), as follows:

    17. Slowly release the push button, then remove the needle.

Label Revisions, S-012:

1. Addition of Figure A for Safey-Lok syringe, below:



2. Addition of instruction number 5 in "Preparing the INTRON A dose" for instructions for the Safey-Lok syringe, as follows:

   5. Remove the protective cap from the syringe needle. Ensure safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Fill the syringe with air by pulling the plunger to the level that represents your correct dose. **(Figure B)**.

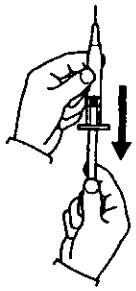


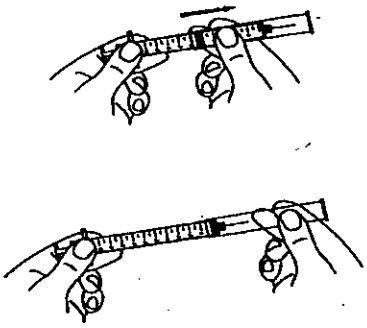
Figure B

3. Information about the Safey-Lok syringe included in the "Subcutaneous (under the skin) Injection" section as follows:

   2. Remove the cap from the needle. Ensure the safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Hold the syringe with one hand, as you would hold a pencil. With the other hand, pinch approximately a 2-inch fold of loose skin.

4. Addition of instructions (inclusion of a new point number 6) on how to lock the Safey-Lok syringe and two figures depicting such, as follows:

   6. After use, firmly grasp the safety sleeve and pull over the exposed needle until you hear a click, and the green stripe on the safety sleeve covers the red stripe on the needle.



Label Revisions, S-016: (Where not otherwise noted, changes **bolded** and in **italics**)

1. Addition of a Medication Guide for REBETOL® (See Appendix 2)

2. New instructions for injection of Intron A, as follows:

How do I Inject INTRON A?

- When you have been trained to do it properly. If you have any questions, contact your health care provider before injecting INTRON A.
- Use the sterile technique taught by your health care provider. Use disposable needles after each use, and throw them away properly as directed by your health care provider, nurse, or pharmacist.
- If someone else gives you your injection, that person should be trained in the use of sterile technique and how to avoid an accidental needle stick.

3. New instructions for the preparation of the Intron A dose, as follows:

1. ***Check the date printed on the INTRON A carton to make sure that the expiration date has not passed.***

3. Remove the protective plastic wrapper from the syringe provided (Figure A). ***The safety sleeve should be tight against the flange for use and moved over the needle only when ready for disposal, as instructed in step 6.***

5. ***Remove the protective cap from the syringe needle. Ensure safety sleeve is pushed firmly against the syringe flange so that the needle is fully exposed. Fill the syringe with air by pulling the plunger to the level that represents your correct dose.*** **(Figure B).**

(see Labeling revision, S-012 for Safey-Lok syringe changes)

8. Turn vial and syringe upside down in one hand. Be sure tip of needle is in the INTRON A solution. Your other hand will be free to move the plunger. Pull back on plunger slowly to draw the ***correct dose into syringe*** **(Figure E).** (Change **bolded** and in ***italics***)

9. Remove the needle from the vial **(Figure F)** and check for air bubbles in the syringe. If you see any bubbles, tap the syringe gently. ***Then, with the needle pointing up, push the plunger slowly until the bubbles disappear.***

10. Replace the needle cap. ***If the solution is cold, warm the syringe between your hands. Lay the syringe down on a flat surface so that needle does not touch anything.***

4. The section entitled, " ——————————— ' has been renamed "**Subcutaneous (under the skin) Injection.**"

5. In the Subcutaneous (under the skin) Injection section, point number 1, second sub-bullet, the words " ——————— have been replaced with the following:

   "If you are very thin, use only"

6. In the Subcutaneous (under the skin) Injection section, point number 3, the following wording has been incorporated:

   With a quick dart-like motion, push the needle about 1/4 inch into the pinched skin at an angle of 45° to 90°.

7. In the Subcutaneous (under the skin) Injection section, point number 4, the following wording has been incorporated:

   If blood does not appear in the syringe, gently push the plunger all the way down.

8. In the Subcutaneous (under the skin) Injection section, point number 7 (previously point number 6), the following wording has been incorporated for paragraphs two and three of this section:

   Your health care professional should tell you about the proper handling and disposal of all syringes and needles and the importance of not reusing any syringes or needles.

   Your health care professional should give you a container for throwing away used needles and syringes. Throw away the full container according to directions provided by your doctor.

Conclusions/Recommendations:

It should be conveyed to the applicant that the Draft Labeling is acceptable, and an approval letter should be sent.

Destry M. Sillivan, MS
Regulatory Project Manager

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/s/

Destry Sillivan
7/27/01 11:45:14 AM
CSO

This is the CSO review for S-008, S-011, S-012, S-016, NDA- 20-903

Therese Cvetkovich
8/7/01 02:03:35 PM
MEDICAL OFFICER

Tony DeCicco
8/24/01 12:34:34 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-903/S-016

CBE 0 Supplement

Schering Corporation
Attention: Joseph F. Lamendola
Senior Director, Marketed Products, Support and Training
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Rebetron™ Combination Therapy (Interferon alfa-2b, recombinant/ribavirin)

NDA Number: 20-903

Supplement number: S-016

Date of supplement: May 11, 2001

Date of receipt: May 14, 2001

This supplemental application, submitted as a "Special Supplement-Changes Being Effected," provides for the inclusion of a new WARNING in the package insert for Rebetron™ Combination Therapy. This WARNING outlines lactic acidosis as a potential adverse event when other purine nucleoside analogues are used in combination with ribavirin.

In order to qualify this submission as a "Changes Being Effected," you must submit the following:

1. A full explanation of the basis for the change.

2. The data on which the change is based.

3. Twenty copies of the final printed labeling. In addition, you are required to revise promptly all promotional labeling and drug advertising to make it consistent with changes in the labeling.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 13, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room # N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Destry M. Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tony DeCicco
6/4/01 09:49:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 6, 2001

To: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

From: Karen Young, RN, BSN, Regulatory Project Manager, DAVDP

Through: Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 20-903

Subject: SLR 008, Proposed Draft Labeling for Rebetol® Capsules

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The following comment is being conveyed on behalf of the medical review team and is in reference to SLR 008.

Our review of your proposal to unbundle an 84 capsule package of Rebetol is ongoing. Once we receive your draft Medication Guide we should be able to complete our review within a fairly short time period. At this point, however, we would like to make sure that your plans to market this package of Rebetol have not changed. Please provide a timeline for submission of the Medication Guide as well as your plans for marketing of the unbundled package of Rebetol once approval is given.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Destry Sillivan
6/20/01 11:10:08 AM
CSO

Dr. Cvetkovicht, this is the facsimile that requests timeline for Medguide and marking configuration plans

Therese Cvetkovich
7/6/01 03:17:10 PM
MEDICAL OFFICER

Appears This Way
On Original

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:**
May 4, 2001	June 15, 2001	01-0103

TO: Debra B. Birnkrant, M.D.
Acting Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Destry M. Sullivan, Project Manager
HFD-530

PRODUCT NAME:	**MANUFACTURED BY**: Schering Corporation
Rebetol (Ribavirin Capsules) 200 mg **NDA #:** 20-903/SL-008	

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), OPDRA conducted a review of the proposed proprietary name "Rebetol" to determine the potential for confusion with approved proprietary and established names as well as unapproved pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name Rebetol.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 14, 2001

NDA NUMBER: 20-903/SL-008

NAME OF DRUG: Rebetol
(Ribavirin Capsules) 200 mg

NDA HOLDER: Schering Corporation

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530), for assessment of the proposed proprietary drug name, Rebetol, regarding potential name confusion with other proprietary/established drug names as well as unapproved pending names.

BACKGROUND

Ribavirin Capsules were approved on June 3, 1998 under NDA 20-903 with the proprietary name Rebetol. However, this application was not for the approval of ribavirin capsules alone but for the combination therapy known as Rebetron. This combination therapy contains Rebetol (Ribavirin) and Intron A (interferon alfa-2b, recombinant). Intron A is Schering Corporation's proprietary name for alfa 2-b, recombinant, a purified sterile recombinant interferon product. This product was approved by the Center for Biologics Evaluation and Research (CBER). Rebetol is Schering Corporation's proprietary name for ribavirin, a nucleoside analog with antiviral activity. Rebetol Capsules are indicated in combination with Intron A Injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alfa interferon or who have relapsed following alfa interferon therapy. The mechanism of inhibition of hepatitis C virus by this combination therapy has not been established.

CDER's Labeling and Nomenclature Committee (LNC) reviewed both proprietary names (Rebetol and Rebetron). The LNC found *Rebetol unacceptable* because it looked and sounded to similar to Regonal, Mebral, Regutal, Resinol, Felbatol, Roxanol and Tegretol. The LNC did *not* object to the use of the proprietary name *Rebetron* for the combination pack. The Division overturned LNC's decision on Rebetol and thus the ribavirin component of the combination therapy was labeled as Rebetol. Although, the Orange Book lists the proprietary name Rebetol, according to the sponsor, Rebetol has never been marketed individually and has only been sold as the combination pack know as Rebetron. According to the manufacturer, the combination pack will still be available for commercial distribution.

II. RISK ASSESSMENT

Although the proprietary name Rebetol was approved for use in June of 1998, to date it has never been sold individually under this name. Practitioners could only purchase the product as part of the combination pack known as Rebetron. Therefore, practitioners would probably prescribed the combination therapy with the proprietary name Rebetron rather than Rebetol. The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Rebetol to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Two products were identified in the Expert Panel Discussion that was thought to have potential for confusion with Rebetol. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns about the name with regard to promotional claims.

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2001, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

TABLE 1

Tegretol	Carbamazepine Tablets 100 mg and 200 mg and Suspension 100 mg/5 mL	200 mg twice daily or 1 teaspoonful QID	S/A, L/A per OPDRA
Carbatrol	Carbamazepine Extended-release Capsules 200 mg and 300 mg	200 mg twice daily	S/A, L/A per OPDRA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

Three separate studies were conducted within FDA, to determine the degree of confusion of Rebetol with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 85 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Rebetol (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Rebetol 200 mg ii po qam & 3 qpm #60 No refills	*Outpatient:* Rebetol 200 mg, two every morning and 3 every evening. Dispense 60 with no refills.
Inpatient: Rebetol 400 mg qam and 600 mg qpm	

2. Results

Results of these exercises are summarized below:

	[illegible] participants	[illegible] (%)	"Rebetol" response	Other response
Written: Outpatient	27	19 (70 %)	2 (11 %)	17 (89 %)
Inpatient	28	20 (72 %)	12 (60 %)	8 (40 %)
Verbal: Outpatient	30	10 (33 %)	3 (30 %)	7 (70 %)
Total:	85	49 (58 %)	17 (35 %)	32 (65%)

Among participants in the written prescription studies for Rebetol, 25 of 39 respondents (64 %) interpreted the name incorrectly. All participants in the outpatient study provided the same incorrect response, Rebitol, misinterpreting the "a" as an "i". The majority of participants in the inpatient study misinterpreted the "b" as an "l". For example: Relstol Reletol and Relatol.

Among participants in the verbal prescription study for Rebetol, 7 of 10 (70 %) participants interpreted the name incorrectly. *One* respondent interpreted the name as *"Brevital", two* as *"Revitol",* and *one* as *"Revital"* only one of which is marketed in the United States. The remaining incorrect interpretations were misspelled and/or phonetic variations of Rebetol (Revital, Rebatol, and Rebitol). " Several heard the prefix "Reb" as "Rev".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Rebetol", the primary concerns raised by the Expert Panel were related to two sound-alike, look-alike names that already exist in the U.S. marketplace. *Tegretol* and *Carbatrol* were considered to be the most problematic in terms of their potential for medication errors.

OPDRA conducted prescription studies to simulate the prescription ordering process in order to detect potential medication errors. In this case, there was no confirmation that *Rebetol* could be confused with *Tegretol* and/or *Carbatrol.* However, a negative finding does not discount the potential for name confusion given the small sample size. One participant interpreted *Rebetol* as *Brevital* in the verbal study. In addition, two other products were identified Revitol and Revital; however, neither of these are marketed in the United States. The remaining incorrect interpretations of the written studies were misspelled/phonetic variations of the proposed name, *Rebetol.*

Tegretol and *Carbatrol* are proprietary names for carbamazepine, an anticonvulsant and specific analgesic for trigeminal neuralgia. Tegretol is available as a 200 mg tablet and Carbatrol is available as 200 mg and 300 mg extended-release capsules. Rebetol, Tegretol and Carbatrol share overlapping strengths, dosage forms and dosing intervals. We concur with LNC's decision that *Rebetol* sounds to similar to *Tegretol*. Confusion between these two products has the potential to cause serious patient harm, as the primary toxicity of ribavirin is hemolytic anemia.

Brevital contains the active ingredient methohexital sodium. Brevital is indicated for intravenous induction of anesthesia prior to the use of other general anesthetic agents; intravenous induction of anesthesia and as an adjunct to subpotent inhalational anesthetic agents (such as nitrous oxide in oxygen) for short surgical procedures; use along with other parenteral agents, usually narcotic analgesics, to supplement subpotent inhalational anesthetic agents (such as nitrous oxide in oxygen) for longer surgical procedures; as intravenous anesthesia for short surgical, diagnostic, or therapeutic procedures associated with minimal painful stimuli and as an agent for inducing a hypnotic state.

Rebetol and *Brevital* differ in their route of administration, dosage forms, indications for use and dosing intervals. In addition, the two products will not be stored in the same area. *Brevital* will be available in the OR and/or anesthesia carts. Although a positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population, given these differences between these two products we believe the potential for confusion is relatively low.

Since the proprietary name Rebetol is currently utilized by Schering in the marketplace, OPDRA searched the FDA Adverse Event Reporting System *(AERS)* database for all post-marketing safety reports of medication errors reported for the active ingredient "ribavirin%" and the trade name "rebetol%", and verbatim for both using the Meddra Preferred Term, DRUG MALADMINISTRATION. In addition, OPDRA completed the same search only this time utilizing the active ingredient "ribavirin%" and the trade name "rebetron". This search strategy retrieved twelve reports utilizing the proprietary name Rebetol and three utilizing Rebetron. None of these reports were related to proprietary name confusion. However, one report was related to similar appearance of the labeling for Rebetron's 70 and 84 count combination kits.

OPDRA also searched MedLine and some commonly utilized online drug references to determine which proprietary name (Rebetol or Rebetron) is recognized in the literature. The results varied dependent on the reference text that was searched. When searching under the proprietary name Rebetol, the majority of references queried produced results that referred to both Ribavirin and the combination of ribivirin and alfa interferon. Databases and reference texts such as Clinical Pharmacology online, American Drug Index, and the Monthly Prescribing Reference only listed the combination pak's proprietary name, Rebetron.

OPDRA questions the rational behind the unbundling of these products because the current insert states that Rebetol capsule monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication. Moreover, the insert states there is no information regarding the use of Rebetol capsules with other interferons. The insert also states the safety and efficacy of Rebetol capsule monotherapy for the treatment of HIV infection, adenovirus, early RSV infection, parainfluenza, or influenza have not been established and Rebetol capsules should not be used for these indications. The Division has not supplied a revised insert that would explain the indications of use and dosage for Rebetol Capsules monotherapy other than off label use.

OPDRA is also concerned that the unbundling of these products may cause confusion among health care providers who are routinely used to prescribing Rebetron. The sponsor would need to educate health care providers on this issue and commit to revising the literature that links Rebetol to the combination therapy pak of Rebetrol.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

OPDRA has reviewed the draft container label provided recommends the following label revisions, which might minimize potential user error.

A. Revise the established name to read as "Ribavirin Capsules, USP".

B. Relocate the product strength, 200 mg, so appears immediately following the proprietary and established name as follows:

REBETOL
(Ribavirin Capsules, USP)
200 mg

C. Relocate the "Each capsule contains..." statement to appear on the side panel.

D. Revise the net quantity statement so that it includes only the number of capsules. In addition, unbox and unbold this statement as well.

E. Revise to read "Usual Dosage" rather than "Usual Dose".

IV. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name Rebetol.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph., at 301-827-3231.

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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/s/

Carol Holquist
6/4/01 09:09:24 AM
PHARMACIST

Jerry Phillips
6/4/01 09:12:29 AM
DIRECTOR

Martin Himmel
6/5/01 11:24:58 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-903/S-011

CBE-0 SUPPLEMENT

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products, Support and Training
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Rebetron™ Combination Therapy (Interferon alfa-2b, recombinant/ribavirin)

NDA Number: 20-903

Supplement number: S-011

Date of supplement: February 26, 2001

Date of receipt: February 27, 2001

This supplemental application, submitted as a "Special Supplement-Changes Being Effected", proposes to revise the medguide section ("pen" medguide section)of the Rebetron™ Combination Therapy patient package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 28, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room # N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Destry M. Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug

Approved This Way
On Original

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/s/

Tony DeCicco
5/11/01 03:11:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-903/S-012

CBE-0 SUPPLEMENT

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products, Support and Training
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Rebetron™ Combination Therapy (Interferon alfa-2b, recombinant/ribavirin)

NDA Number: 20-903

Supplement number: S-012

Date of supplement: February 28, 2001

Date of receipt: March 1, 2001

This supplemental application, submitted as a "Special Supplement-Changes Being Effected", provides for the inclusion of a safety lock syringe, marketed with Rebetron™ Combination Therapy, with corresponding changes to the package insert and patient package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 30, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room # N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Destry M. Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug

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/s/

Tony DeCicco
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*)			FROM:	
HFD-400 Sammie Beam			Destry M. Sillivan, RPM, HFD-530	
DATE April 27, 2001	IND NO.	NDA NO. 20-903	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT November 8, 2000
NAME OF DRUG Ribavirin (Rebetol)		PRIORITY CONSIDERATION accelerated	CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE June 15, 2001

NAME OF FIRM
The Schering Corporation

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	X OTHER *(SPECIFY BELOW)*
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS*(List below)*	
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	
	☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Request for Name Consult (Trademark consult):

Schering has requested that each component of Rebetron Combination Therapy be made available separately. The two components of this therapy are ribavirin and Interferon alpha 2b. Schering has long referred to ribavirin as "Rebetol," but as the combination therapy has a name of its own (Rebetron Combination Therapy), and was only available as a "bundled" package, this name was never an issue. As Schering now wants to "unbundle" the two components, DAVDP believes that a name consult should be completed by OPDRA for the name "Rebetol."

DAVDP hopes to approve this labeling supplement by June 15.

Please contact Destry Sillivan at (301) 827-2379 should you have any questions.

CC:

SIGNATURE OF REQUESTER Destry Sillivan	METHOD OF DELIVERY *(Check one)* ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Destry Sillivan
5/8/01 11:06:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-903, S-008

INFORMATION REQUEST LETTER

Schering Corporation
Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your November 7, 2000 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rebetron Combination Therapy, Capsules and Intron A (Interferon Alfa-2b, recombinant) for injection for the treatment of Hepatitis C infection.

We also refer to your submission dated September 25, 1998.

We are in the process of reviewing of your submission dated November 7, 2000, which requests the unbundling of Rebetron Combination Therapy, and have the following comments and information requests. Your prompt written response will allow us to continue our evaluation of your supplemental NDA.

In a position paper submitted to NDA 20-903 on September 25, 1998, you enumerated the scientific, ethical, and legal issues supporting your position that Rebetol and Intron A should not be marketed separately.

Your current supplemental NDA requests the unbundling of Rebetol and Intron A. This indicates to us that you have altered your position on the aforementioned issues. Therefore, we request that you submit your rationale for unbundling Rebetol and Intron A. In your response, please include a detailed discussion why the issues outlined in your September 25, 1998 position paper are no longer applicable. We ask that you respond to this request by January 4, 2001.

If you have any questions, call Destry M. Sillivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

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

/s/

Debra Birnkrant
12/19/00 02:58:12 PM

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