

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-546**

**ADMINISTRATIVE DOCUMENTS**  
**CORRESPONDENCE**

– **Patent Information Pursuant to 21 CFR§314.59(Section 13)**

RE: REBETOL® ( Brand of Ribavirin) — in combination with Intron A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with 3 years of age and older.

Trade Name: REBETOL®  
Active Ingredient: Ribavirin  
Strength: 40 mg/mL.  
Dosage Form: —

Pursuant to the provisions of 21 CFR§ 314.53, we hereby supply the patent information for the captioned Schering Corporation NDA:

1. U.S. Patent No. 6,472,373  
Expiration Date: September 21, 2017  
Pediatric Exclusivity Date: March 21, 2018  
Type of Patent: Method of Use  
Patent Owner: Schering Corporation.
2. U.S. Patent No. 6,461,605  
Expiration Date: November 1, 2016  
Pediatric Exclusivity Date: May 1, 2017  
Type of Patent: Method of Use  
Patent Owner: Schering Corporation.



3. U.S. Patent No. 6,172,046  
Expiration Date: September 21, 2017  
Pediatric Exclusivity Date: March 21, 2018  
Type of Patent: Method of Use  
Patent Owner: Schering Corporation.
4. U.S. Patent No. 6,063,772  
Expiration Date: January 23, 2016  
Pediatric Exclusivity Date: July 23, 2017  
Type of Patent: Method of Use  
Patent Owner: ICN Pharmaceuticals, Inc.
5. U.S. Patent No. 5,767,097  
Expiration Date: January 23, 2016  
Pediatric Exclusivity Date: July 23, 2017  
Type of Patent: Method of Use  
Patent Owner: ICN Pharmaceuticals, Inc.

The undersigned declares (a) that each of U.S. Patent Nos. 6,472,373; 6,461,605; 6,172,046; 6,063,772; and 5,767,097 covers, among other things, methods of using REBETOL® (ribavirin) in combination with INTRON A® (interferon alfa-2b recombinant) injection to treat patients with chronic hepatitis C, (b) that a method of using REBETOL® (ribavirin) in combination with INTRON A® (interferon alfa-2b recombinant) injection to treat chronic hepatitis C in patients 3 years of age and older is the indication for which approval is being sought under section 505 of the Federal Food, Drug and Cosmetic Act, 21 USC§355.



**EXCLUSIVITY SUMMARY for NDA # 21-546**

Trade Name: **REBETOL®** (ribavirin, USP) Oral Solution Generic Name: **ribavirin**  
Applicant Name The Schering Corp. HFD-530  
Approval Date

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES/  / NO /  /
- b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type(SE1, SE2, etc.)?

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

- d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /  / NO /  /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

Not applicable

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a

previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?  
YES /  / NO /  /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # \_P00321 SCH 18908:

Investigation #2, Study # \_P00018 SCH 18908 Cohorts 1 and 2

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not re-demonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1            YES /  /            NO /  /

Investigation #2            YES /  /            NO /  /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1            YES /  /            NO /  /

Investigation #2

YES /  /

NO /  /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # \_P00321 SCH 18908:

Investigation #2, Study # \_P00018 SCH 18908 Cohorts 1 and 2

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND 49,923 YES /  / NO /  / Explain:

Investigation #2

IND 49,923 YES /  / NO /  / Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / \_\_\_ / Explain \_\_\_\_\_ NO / \_\_\_ / Explain \_\_\_\_\_

\_\_\_\_\_

Investigation #2

YES / \_\_\_ / Explain \_\_\_\_\_ NO / \_\_\_ / Explain \_\_\_\_\_

\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / \_\_\_ / NO /  /

If yes, explain: \_\_\_\_\_

Destry M. Sullivan  
Signature of Preparer  
Title: Regulatory Project Manager

Date :July 22, 2003

Signature of Office or Division Director      Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/  
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Debra Birnkrant  
8/6/03 10:00:16 AM

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**16. DEBARMENT CERTIFICATION**

Schering Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

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ON ORIGINAL**



SCHERING-PLOUGH RESEARCH INSTITUTE



If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy):

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 3 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 16 Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Health Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi  
HFD-960/ Grace Carmouze  
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

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Destry Sullivan  
8/5/03 04:20:42 PM

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# SCHERING CORPORATION

2000 GALLOPING HILL ROAD



KENILWORTH, N.J. 07033

TELEPHONE: (908) 298-4000

July 29, 2003

Debra Birnkrant, M.D., Director  
Division of Antiviral Drug Products, HFD-530  
Food and Drug Administration  
Center of Drug Evaluation and Research  
Office of Drug Evaluation IV  
Document Control Room N-414  
9201 Corporate Blvd.  
Rockville, MD 20850

NDA 21-546  
SCH 18908  
REBETOL® (ribavirin, USP)  
Oral Solution

**SUBJECT: GENERAL CORRESPONDENCE**

Dear Dr. Birnkrant:

Schering agrees to the following Phase 4 commitment:

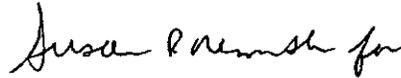
1. Long-Term Follow-Up: Patients who completed 24 weeks of follow-up in Protocols P00018 or P00321 are eligible to enroll in Protocol P01906, "Long-Term Follow-Up Protocol to Assess Pediatric Subjects After Completing 24 weeks of Follow-Up in a SPRI Clinical Trial for the Treatment of Chronic Hepatitis C." This protocol was amended to IND 49,923 on March 20, 2001 (Serial No.: 397) and enrollment began in July 2001. Patients will be evaluated yearly for five years beginning 12 months after the last visit (i.e., follow-up week 24) on study P00018 or P00321.

Final Report Submission: December 2008

Please contact Dr. Susan Nemeth at 908-740-4892 or Dr. Penelope Giles at 908-740-2340 if you have any questions.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,



Isidoro J. Perez  
Vice President  
Worldwide Regulatory Affairs

SN/lh  
Attachments

:\OP\SUBMIT\USA\NDA\1546\Letter\072903.doc

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**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN  
SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**DATE:** 7-28-03

**FROM:** Debra Birnkrant, M.D.  
Director, Division of Antiviral Drug Products, HFD-530

**TO:** Division File for NDA 21-546

**SUBJECT:** Division Director's Memorandum for NDA 21-546  
for Rebetol<sup>®</sup> Oral Solution

This memorandum is written in support of the approval of Rebetol<sup>®</sup> Oral Solution (ribavirin, USP), a nucleoside analog for use in combination with Intron A<sup>®</sup> (interferon-alfa-2b) for the treatment of compensated, chronic hepatitis C infection in pediatric subjects between the ages of 3 -16 who are naïve to previous therapy. This regulatory action is based on the favorable risk/benefit profile of the drug as determined by a multidisciplinary review of the totality of the data contained in NDA 21-546. This memorandum will focus on the clinical trials containing data to determine a sustained viral response rate in pediatric subjects and an overall risk/benefit assessment addressing safety issues related to laboratory parameters and psychiatric side effects.

**BACKGROUND:**

Please see review by Russell Fleischer, Senior Clinical Reviewer, for information related to the regulatory history of this application. Additionally, this application was granted a 6-month priority review because it contains data in a pediatric population for which there are no other approved therapies.

**TRIAL RESULTS: EFFICACY**

Two clinical studies were provided in this application in support of marketing approval. As outlined in Mr. Fleischer's review, sustained viral response (SVR), defined as HCV RNA below the level of quantification of an assay, as determined 24 weeks after completion of therapy, is the standard for assessing treatment response to antiviral agents for hepatitis C. A total of 125 pediatric patients received Rebetol<sup>®</sup> Oral Solution or Capsules 15 mg/kg/day plus Intron A 3 MIU/m<sup>2</sup> TIW for 48 weeks followed by 24 weeks of off therapy follow-up (assessment of efficacy was based on 118/125 subjects because 7 subjects were removed from the analysis for site specific problems - see statistical and biopharmaceutics reviews). The overall response rate was 46%. The response-

rate was higher in Genotype non-1 subjects, 81%, compared to 36% in Genotype-1 subjects, regardless of baseline viral load. These findings are consistent with results in the adult population and confirm the efficacy of Rebetol® Oral Solution in combination with Intron A® for this indication in the pediatric population. Also see review by Russell Fleischer, Senior Clinical Reviewer, Rafia Bhore, Statistical Reviewer and Derek Zheng, Biopharmaceutics Reviewer.

#### TRIAL RESULTS: SAFETY

The safety database contains data on 166 pediatric subjects who received combination therapy with Rebetol® Oral Solution or Capsules and Intron A®, of whom 125 received the to-be marketed dose. The most important safety finding identified in the Senior Clinical Reviewer's review was that adolescents appear to be at greater risk of suicidal ideation/attempt compared to adult subjects (2.4% vs 1%). Four patients out of a database of 166 patients had suicidal ideation or attempt, three of whom were adolescents between 13 and 14 years of age. Psychiatric adverse events are known to be associated with interferon therapy. Perhaps the higher rate in the adolescent population also relates to the stresses associated with this stage of development in combination with having a serious chronic disease such as hepatitis C. The higher frequency of this behavior is being added to the Warnings Section of the label; it already appears in the Precautions Section as preliminary data from these trials had previously been reviewed as part of efficacy supplement, NDA 20-903 SE8/S-013.

The primary toxicity associated with ribavirin is hemolytic anemia. The overall mean reduction in hemoglobin in pediatric patients was 1.5 g/dL compared to 2.6 g/dL in adults. Five percent of subjects who received the Oral Solution required dose reduction for anemia and the schedule for dose reduction is provided in the Dosage and Administration Section of the label.

Common adverse events included flu-like symptoms, and gastrointestinal complaints of nausea, vomiting, abdominal pain and anorexia, all of which are associated with interferon. Treatment-related decreases in weight and growth parameters were observed and found to reverse upon discontinuation of therapy; this finding was previously noted in the efficacy supplement and already appears in the label.

#### RISK/BENEFIT ASSESMENT:

To date, there are no approved therapies for the treatment of pediatric subjects with chronic compensated hepatitis C infection. Although we previously reviewed data from the clinical trials contained in this marketing application, it was preliminary data and only resulted in labeling with regard to dosage and

administration with the Capsule for treatment of hepatitis C in subjects older than 5 years of age. Although the data contained in this NDA support the marketing approval of ribavirin Oral Solution to be used in combination with interferon alfa-2b, health care practitioners must use their clinical judgement as to when to initiate therapy because little is known about the natural history of this infection in children. Given the toxicity of this combination, wording will be provided in the label to address the duration of treatment and will be similar to that for adults. This will limit unnecessary exposure to this combination if patients are not responding by 24 weeks.

In sum, I am in full support of the approval of Rebetol<sup>®</sup> Oral Solution and Capsules at a dose of 15 mg/kg/day to be used in combination with Intron A<sup>®</sup> 3 MIU/m<sup>2</sup> TIW for the treatment of pediatric subjects between the ages of 3-16 who have compensated hepatitis C infection. A medication guide will also be part of the labeling.

PROPOSED PHASE 4 COMMITMENTS:

A clinical post-marketing commitment will be requested and will be finalized prior to approval. See below:

Pediatric patients will be followed for five years to assess longterm effects of Rebetol<sup>®</sup> Oral Solution in combination with Intron A<sup>®</sup> on growth and development, antiviral response and safety.

**APPEARS THIS WAY  
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/s/  
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Debra Birnkrant  
7/29/03 09:36:55 AM  
MEDICAL OFFICER

Please sign my memo to file egarding the Rebetol  
Oral Solution NDA(PDUFA) date 7/30/03

Mark Goldberger  
7/31/03 01:42:24 PM  
MEDICAL OFFICER

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**DATE:** July 23, 2003

**TO:** NDA 21-546  
Rebetol® (ribavirin) Oral Solution

**FROM:** Russell Fleischer, PA-C, MPH  
Senior Clinical Analyst, Acting Medical Team Leader  
DAVDP (HFD-530)

**TROUGH:** Debra Birnkrant, MD  
Director, DAVDP

**RE:** Team Leader Memorandum

Pursuant to a Pediatric Written Request (WR), Schering Plough (the applicant) submitted an NDA containing safety, pharmacokinetic and antiviral activity of Rebetol Oral Solution in pediatric patients with chronic HCV infection. Data from two studies were submitted in support of this application. The first study (P00018) was conducted in two cohorts. In Cohort 1, 61 pediatric patients with chronic HCV infection were randomized to receive Rebetol Capsules 8, 12, or 15 mg/kg/day with Intron® A 3 MIU/m<sup>2</sup> SC thrice weekly for 48 weeks. Assessments of antiviral activity and safety occurred at weeks 4 and 12. The 15 mg/kg/day dose was determined to provide the best balance between efficacy (reduction of HCV RNA) and safety (change from baseline in hemoglobin). Cohort 2 enrolled an additional 35 children at the 15 mg/kg/day dose of ribavirin who also received 48 weeks of combination treatment. A separate study, P00321, enrolled 70 patients who received either the Capsule or Oral Solution formulations. In total, 125 patients received the ribavirin dose proposed for marketing: 15 mg/kg/day for 48 weeks.

In March 2001, the applicant submitted safety and pharmacokinetic data from the two above described studies, which were ongoing, in order to meet certain requirements of the WR (see Dr. Kassa Ayalew's Medical Review of NDA \_\_\_\_\_). At that time, all patients had completed the 48-week treatment period but only one-half had completed the required 24 week off therapy follow up period. This application contained the final sustained virologic response (SVR) data for all children, and one new bioavailability study. No new safety data was included.

Dr. Ayalew initiated the review of this new NDA in February 2003 with significant oversight by me. Dr. Ayalew left DAVDP in July 2003, and I completed the review in his absence. Dr. Ayalew's initial safety and efficacy conclusions were confirmed, and this application is approvable.



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** June 10, 2003

**To:** Kathy Maglaras, Associate Manager,  
WRA, Marketed Products Support  
Schering Corporation

**Address:** Galloping Hill Road  
Kenilworth, NJ 07033

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Steve Miller, Ph.D., Chemistry Team Leader, HFD-530  
Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530

**NDA** NDA 21-546, REBETOL® (ribavirin) ←

**Subject:** CMC comments for NDA 21-546

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With reference to your NDA# 21-546 for Rebetol (ribavirin, USP) Oral Solution, please address the following chemistry, manufacturing, and controls (CMC) comments and recommendations:

2

Bottle and Carton Labels (dated 5/22/03):

\_\_\_\_\_  
\_\_\_\_\_

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.

\_\_\_\_\_  
Destry M. Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products

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/s/  
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Destry Sullivan  
6/12/03 01:59:09 PM  
CSO

Steve this is the CMC fax for Rebetol oral  
soln for June 10, 2003

Stephen Paul Miller  
6/12/03 04:41:34 PM  
CHEMIST

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Food and Drug Administration  
Rockville, MD 20857

**FILING REVIEW LETTER**

**NDA 21-546**

The Schering Corporation  
Attention: Isodoro J. Perez  
Vice President, U.S. Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

Dear Mr. Perez,

Please refer to your January 29, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for REBETOL® (ribavirin, USP).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 30, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Please consider the following comment, as your response will aid us in our review of your application.

**CHEMISTRY:**

- Please consider changing the name of the dosage form in the new drug name to: "Rebetol® (ribavirin, USP) Oral Solution".

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

Sincerely,

*{See appended electronic signature page}*

Anthony DeCicco, RPh.  
Chief, Regulatory Project Management  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV

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/s/

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Tony DeCicco  
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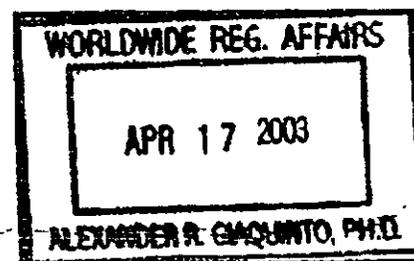
## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

April 9, 2003

Schering-Plough Research Institute  
2000 Galloping Hill Road  
Kenilworth, New Jersey 07033



Attention: Alexander Giaquinto  
Senior Vice President, Worldwide Regulatory Affairs

Re: Designation Request # 02-1624

Dear Mr. Giaquinto:

Reference is made to your request for orphan-drug designation dated September 16, 2002, of ribavirin (in combination with recombinant interferon alpha-2b (INTRON® A) for the treatment of chronic hepatitis C in pediatric patients aged 3 -16 years and your amendment of February 11, 2003. Please also refer to our acknowledgement letter dated September 26, 2002, and our letter of notification dated January 13, 2003.

We have completed the review of the information submitted in your original request and amendment and we have determined that ribavirin qualifies for orphan-drug designation for the *treatment of chronic hepatitis C in pediatric patients*. Please note that it is ribavirin and not its formulation that has received orphan-drug designation. You have notified us that you are currently developing ribavirin under the trade name Rebetol®.

Please be advised that if ribavirin is approved for an indication broader than the orphan-drug designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA (21 USC 360cc). Therefore, prior to final marketing approval, we request that you compare the designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of ribavirin as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the

development of your product for marketing, please feel free to contact Tan Nguyen, MD, PhD, at (301) 827-3666.

Please refer to this letter as official notification and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

/s/

Marlene E. Haffner, MD, MPH  
- Rear-Admiral, United States Public Health Service -  
Director, Office of Orphan Products Development

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/s/

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Destry Sullivan  
3/17/03 02:48:51 PM  
CSO

Dr. Miller, this is the facsimile for Rebetol ~~\_\_\_\_\_~~  
name change

Stephen Paul Miller  
3/28/03 02:18:50 PM  
CHEMIST

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**45 DAY FILING MEETING MINUTES**

**NDA:** 21-546

**DATE:** March 11, 2003

**DRUG:** NDA 21-546 Rebetol (ribavirin).

**SPONSOR:** The Schering Corp

**PARTICIPANTS:** Debra Birnkrant, M.D., Division Director  
Jeffrey Murray, M.D., Deputy Division Director  
Steven Gitterman, M.D., Medical Team Leader  
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst  
Kassa Ayalew, M.D., Medical Officer  
Rafia Bhore, Ph.D., Statistical Reviewer  
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader  
Hao Zhang, M.D., Pharmacology/Toxicology Reviewer  
Kellie Reynolds, Pharm.D., Clinical Pharmacology/Biopharmaceutics  
Team Leader  
Derek Zhang, Pharm.D., Clinical Pharmacology/Biopharmaceutics Reviewer  
Jules O'Rear, Ph.D., Microbiology Team Leader  
Narayana Battula, Ph.D., Microbiology Reviewer  
Stephen Miller, Ph.D., Chemistry Team Leader  
Rao Kambhampati, Ph.D., Chemistry Reviewer  
Destry Sullivan, M.S., Regulatory Project Manager  
Anthony DeCicco, R.Ph., Chief, Project Management  
Antione El Hage, Ph.D., Director, DSI

**BACKGROUND:** This new drug application (NDA) has been submitted to supply a Rebetol pediatric oral solution for use in the treatment of HCV-infected children.

Submission date is January 29, 2003, and date of receipt is January 30, 2003. Schering has submitted this NDA entirely in electronic format. It will be a priority review for this application, as it is a pediatric submission. Therefore, the review goal date is July 30, 2003.

**CHEMISTRY (CMC):**

This submission is fileable from the CMC perspective.

CMC notes that the submitted name "Rebetol" is not consistent with the USP Guidelines and will have to be amended.

**PHARMACOLOGY/TOXICOLOGY:**

This submission is fileable from the Pharm/Tox perspective.

**MICROBIOLOGY:**

This submission is fileable from the Microbiology perspective.

**BIOPHARMACEUTICS:**

This submission is fileable from the Biopharmaceutics perspective.

**CLINICAL:**

This submission is fileable from the Clinical perspective.

**STATISTICS:**

This submission is fileable from the statistical perspective.

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/s/

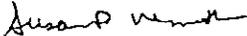
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Russell Fleischer  
6/19/03 10:29:26 AM

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I certify that there was no safety update included in this application, NDA 21-546.

Destry M. Sullivan, M.S.  
LT, USFHS  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0297 Expiration Date: February 29, 2004.	
		<b>USER FEE COVER SHEET</b>	
<b>See Instructions on Reverse Side Before Completing This Form</b>			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <a href="http://www.fda.gov/cder/pdula/default.htm">http://www.fda.gov/cder/pdula/default.htm</a>			
1. APPLICANT'S NAME AND ADDRESS  Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033  Attn: Mr. Isidoro Perez		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21,546	
2. TELEPHONE NUMBER (Include Area Code)  ( 908 ) 740-4290		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).	
3. PRODUCT NAME Rebetol (ribavirin, USP)		6. USER FEE I.D. NUMBER 4395	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)			
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)			
<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)			
<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)			
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See item 8, reverse side if answered YES)			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:			
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448		Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  /for Mr. Perez		TITLE Vice President Worldwide Regulatory Affairs	DATE 1/29/03

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-546	Efficacy Supplement Type -	Supplement Number
Drug: REBETOL® (ribavirin, USP) Oral Solution		Applicant: The Schering Corp.
RPM: Destry M. Sullivan		HFD-530 Phone # (301) 827-2335
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		Type 3
• Other (e.g., orphan, OTC)		Type V (Orphan)
❖ User Fee Goal Dates		July 30, 2003
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception (The sponsor has paid a fee, but requested an exception due to Orphan Drug status. This request is pending.)		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		N/A
N/A, since only applicable to 505(b)(2)		
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified N/A

Exclusivity (approvals only)	
• Exclusivity summary	Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	<input checked="" type="checkbox"/> Yes, Application # 02-1624 <input type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
<b>Chemistry Information</b>	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	<input checked="" type="checkbox"/>
• Original applicant-proposed labeling	Not necessary
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews)	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	<input checked="" type="checkbox"/>
• Reviews	See Chemistry Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	<input checked="" type="checkbox"/>
• Documentation of agreements relating to post-marketing commitments	<input checked="" type="checkbox"/>
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	<input checked="" type="checkbox"/>
❖ Memoranda and Telecons	<input checked="" type="checkbox"/>
❖ Minutes of Meetings	
• EOP2 meeting-	
• Pre-NDA meeting	
• Pre-Approval Safety Conference	
• Other (45 day filing meeting minutes)	<input checked="" type="checkbox"/>

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
<b>Summary Application Review</b>	
❖ Summary Reviews (Division Director, Medical Team Leader)	✓
<b>Clinical Information</b>	
❖ Clinical reviews	✓
❖ Microbiology (efficacy) review	✓
❖ Safety Update review	N/A See Medical Officer's review
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	✓
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review	✓
❖ Biopharmaceutical review	✓
❖ Controlled Substance Staff review(s) and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review	✓
❖ Environmental Assessment	
• Categorical Exclusion	✓
• Review & FONSI	N/A
• Review & Environmental Impact Statement	See Chemistry Review
❖ Micro (validation of sterilization & product sterility) review	N/A
❖ Facilities inspection (provide EER report) See Chemistry Review PENDING	Date completed: (✓) Acceptable ( ) Withhold recommendation
❖ Methods validation PENDING	( ) Completed (✓) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review, including referenced IND reviews	✓
❖ Nonclinical inspection review summary	N/A
❖ Statistical review of carcinogenicity studies	N/A
❖ CAC/ECAC report	N/A

722/03 DMS