Application Number 21-546

CHEMISTRY REVIEW(S)
NDA #21-546

Rebetol®
(ribavirin, USP)
Oral Solution

Schering Corporation

Rao Kambhampati, Ph.D.
Division of Antiviral Drug Products
HFD-530
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Chemistry Review Data Sheet

1. NDA# 21-546

2. REVIEW #: 1

3. REVIEW DATE: 7/11/2003

4. REVIEWER: Rao Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
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<tbody>
<tr>
<td>Original</td>
<td>29/Jan/2003</td>
</tr>
<tr>
<td>Amendment N-000/C</td>
<td>11/Apr/2003</td>
</tr>
<tr>
<td>Amendment</td>
<td>22/Apr/2003</td>
</tr>
<tr>
<td>Amendment BC</td>
<td>30/Jun/2003</td>
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7. NAME & ADDRESS OF APPLICANT:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Schering Corporation</th>
</tr>
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<tbody>
<tr>
<td>Address:</td>
<td>2000 Galloping Hill Road</td>
</tr>
<tr>
<td></td>
<td>Kenilworth, NJ 07033</td>
</tr>
<tr>
<td>Representative:</td>
<td>Isidoro J. Perez</td>
</tr>
<tr>
<td></td>
<td>Vice President, Worldwide Regulatory Affairs</td>
</tr>
<tr>
<td></td>
<td>908-740-4290</td>
</tr>
<tr>
<td>Telephone:</td>
<td>908-740-3583</td>
</tr>
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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Rebetol® Oral Solution
b) Non-Proprietary Name (USAN): ribavirin oral solution
c) Code Name/#: Rebetol ; ribavirin —
d) Chem. Type/Submission Priority (ONDC only):
9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL CATEGORY: Antiviral

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 40 mg of ribavirin/1 mL (each bottle contains 100 mL of solution)

13. ROUTE OF ADMINISTRATION: 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

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

   Chemical Name: 1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide
   CAS Reg. No.: 36791-04-5
   Molecular Formula: C₁₃H₁₂N₄O₃
   Molecular Weight: 244.2
   Structural Formula:

17. RELATED/SUPPORTING DOCUMENTS:

   A. DMFs:
### CHEMISTRY REVIEW

Chemistry Review Data Sheet

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<th>TYPE</th>
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<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
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Action codes for DMF Table:
1. DMF Reviewed.
2. Type 1 DMF
3. Reviewed previously and no revision since last review
4. Sufficient information in application
5. Authority to reference not granted
6. DMF not available
7. Other (explain under "Comments")

Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>NDA</td>
<td>20-903</td>
<td>Intron A® (interferon alfa-2a) Injection and Rebetol (ribavirin) Tablets for</td>
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18. STATUS:

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<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
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<td>DMPQ (HFD-324), OC</td>
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<tr>
<td>EA</td>
<td>Acceptable based on categorical exclusion</td>
<td>7/11/03</td>
<td>Rao Kambhampati, Ph.D. (HFD-530)</td>
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<tr>
<td>Methods Validation</td>
<td>Pending</td>
<td>7/11/03</td>
<td>Philadelphia District Laboratory (HFR-MA160)</td>
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The Chemistry Review for NDA 21-546

The Executive Summary

I. Recommendations
   • A. Recommendation and Conclusion on Approvability
      Once CDER's Office of Compliance determines that the overall facility recommendation is
      acceptable, NDA #21-546 is recommended for approval from the chemistry, manufacturing, and
      controls (CMC) standpoint. All other CMC issues have been resolved satisfactorily.
   • B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
     Management Steps, if Approval: None

II. Summary of Chemistry Assessments
   • A. Description of the Drug Substance(s) and Drug Product(s)
      The Applicant, Schering Corporation (Schering), intends to seek approval of the FDA for Rebetol®
      (ribavirin, USP) Oral Solution to be used as part of combination therapy with Intron A® for the
      treatment of chronic hepatitis C among previously untreated pediatric patients at least three years of
      age or older. Since chronic hepatitis C is a serious disease for which there are currently no other
      approved treatments in the pediatric population, the applicant requested a priority review for this
      application and the DAVDP granted priority review status to this NDA. The applicant also requested
      for Orphan Drug Designation to the Office of Orphan Drug Products Development on the basis of the
      epidemiological data, which indicate that the total prevalence in the US of chronic hepatitis C in
      pediatric patients is less than 200,000. The FDA also granted Orphan Drug Designation to this NDA.

      The ribavirin drug substance is manufactured and it is currently used by Schering for the manufacturing of Rebetol (ribavirin, USP) capsules, 200 mg. Schering proposed of Rebetol Oral Solution, 40
      mg/mL. (ribavirin drug substance to ) for the manufacturing of Inhalation Solution, a FDA approved drug for
      the treatment of RSV infection in infants. The CMC for the ribavirin drug substance was cross
      referenced to the Schering’s NDA #20-903 for Rebetol Capsules.

      The drug product, Rebetol® (ribavirin, USP) Oral Solution, is a clear, colorless to pale or light yellow
      liquid. It is packaged in 4 oz. amber glass bottles with child resistant plastic caps. Each bottle contains
      approximately 100 mL of the solution containing a total of 4 g of ribavirin. Each 1 mL of the solution
      contains 40 mg of ribavirin drug substance as the active ingredient and the following excipients:
      sucrose , sorbitol solution ( glycerin ), propylene glycol , sodium citrate , citric acid , sodium benzoate ,
      natural and artificial flavor for bubble gum #15864 , and purified water . The intended
      commercial batch size is All excipients are of USP or NF grade except bubble gum flavor for
      which specifications were provided in the NDA and a for the cross-reference of the composition and other CMC information. The drug product is manufactured
      and packaged at the applicant’s facility in Kenilworth, NJ. The process involves conventional
      The release specifications included description, color, identity for ribavirin (HPLC, TLC) and sodium benzoate (HPLC), assay for ribavirin and sodium benzoate and
Executive Summary Section

degradation products content by HPLC, deliverable volume (USP <698>), pH, and microbial limits (USP <61>). Antimicrobial effectiveness testing (USP <51>) is conducted on stability samples. The in-process controls included. Letters of Authorization were provided for the cross-reference of the CMC information in appropriate DMFs for the. Batch analysis data were provided for batches (commercial scale). The stability data were provided for primary stability batches (and one commercial scale batch). The conditions studied were refrigerated.

Maximum data were provided for the commercial scale batch. The proposed expiration dating period of 36 months for Rebetol oral solution bottles that are stored at 2-8°C or 25°C is acceptable.

B. Description of How the Drug Product is Intended to be Used
Rebetol® (ribavirin, USP) Oral Solution is indicated in combination with Intron A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy. Rebetol Oral Solution (40 mg/mL) is packaged in 4 oz size amber glass bottles (100 mL/bottle) with child resistant closures. The Rebetol Oral Solution bottles should be stored at 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) and they have an expiration dating period of 36 months.

C. Basis for Approvability or Not-Approval Recommendation
The drug substance is Schering for the manufacturing of approved Rebetol capsules. The manufacturing and packaging processes and in-process controls used for the drug product are acceptable. Adequate batch analysis data were provided for the drug product. The specifications for drug product contain adequate tests and the proposed methods are acceptable. The submitted long-term stability data supports the proposed expiration dating period of 36 months for Rebetol Oral Solution bottles that are stored at 2-8°C or 25°C. The trade name, Rebetol®, is already in use for the marketing of capsules. The established name for the drug substance, ribavirin, is same as the USAN name. Some changes were recommended to the package insert and bottle and carton labels and these changes will be incorporated by the applicant in the final printed documents. Three of the four facilities that are involved in the manufacturing, packaging, and/or testing of the drug substance and drug product were found to be acceptable by DMPQ (HFD-324). The fourth facility, Schering, Las Piedras, Puerto Rico, is a drug substance release testing facility and it is still pending. This facility currently releases the drug substance for approved Rebetol (ribavirin) capsules. The analytical methods validation is pending, and as is normally the case, completion of the validation study by the FDA laboratory is not anticipated prior to approval. The Applicant’s request for an exemption from the EA requirement under categorical exclusion is acceptable.

III. Administrative
• A. Reviewer’s Signature
  Signed electronically in DFS by Rao Kambhampati, Ph.D., Senior Regulatory Review Scientist
• B. Endorsement Block
  Signed electronically in DFS by Stephen P. Miller, Ph.D., Chemistry Team Leader
C. CC Block
HFD-530/Chem Reviewer/R.Kambhampati
HFD-830/DD/CChen

HFD-530/Chem Team Leader/SMiller
HFD-530/PM/DSullivan
Page(s) Withheld

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☐ § 552(b)(5) Deliberative Process
☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-----------------------
Rao Kambhampati
7/11/03 05:52:16 PM
CHEMIST

Please sign off and file into DFS.

Stephen Paul Miller
7/28/03 03:39:04 PM
CHEMIST

An overall recommendation of "Acceptable" was issued by CDER’s Office of Compliance on July 28, 2003, for all facilities involved in the manufacture and testing of ribavirin oral solution. NDA 21-546 is recommended for approval from the CMC perspective.
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21546/000
Org Code: 530
Priority: 3P
Stamp Date: 30-JAN-2003
Action Goal: 30-JUL-2003
District Goal: 31-MAY-2003

FDA Contacts:
D. SILLIVAN 301-827-2335
R. KAMBHAMPATI 301-827-2423
S. MILLER 301-827-2392

Sponsor: SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033-5030

Brand Name: REBETOL
MG/ML

Generic Name: RIBAVIRIN
Dosage Form: SOLUTION
Strength: 40 MG/ML

Project Manager (HPD-530)
Review Chemist (HPD-530)
Team Leader (HPD-530)

Overall Recommendation: ACCEPTABLE on 28-JUL-2003 by J. D AMBROGIO (HPD-322) 301-827-9049

Establishment: FEI:

DMF No: AADA:

Responsibilities:
Profile: CSN
Last Milestone: RC RECOMMENDATION
Milestone Date: 24-MAR-03
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: 2210048
FEI: 2210048
SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: LIQ
OAI Status: POTENTIAL

Last Milestone: OC RECOMMENDATION
Milestone Date: 25-JUN-03
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Establishment: CFN: 2211256
SCHERING CORP
1011 MORRIS AVE
UNION, NJ 07083

FEI: 2211256

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL

OAI Status: POTENTIAL

Last Milestone: CC RECOMMENDATION
Milestone Date: 25-JUN-03
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

APPEARS THIS WAY ON ORIGINAL
DUPLICATE MILESTONE FROM FACTS

Establishment: CFN: 2650155 FEI: 2650155
SCHERING CORP
PRIDCO INDUSTRIAL PARK SR 83
LAS PIEDRAS, PR 00671
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CTL
Last Milestone: QC RECOMMENDATION
Milestone Date: 24-JUL-03
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

APPEARS THIS WAY ON ORIGINAL
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Rao Kambhampati
7/11/03 05:52:16 PM
CHEMIST

Please sign off and file into DFS.

Stephen Paul Miller
7/28/03 03:39:04 PM
CHEMIST

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