CENTER FOR DRUG EVALUATION AND RESEARCH

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

Table of Contents

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:

Submission(s) Reviewed	Document Date
Original	29/Jan/2003
Amendment N-000/C	11/Apr/2003
Amendment	22/Apr/2003
Amendment BC	30/Jun/2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Schering Corporation
Address:	2000 Galloping Hill Road Kenilworth, NJ 07033
Representative:	Isidoro J. Perez Vice President, Worldwide Regulatory Affairs 908-740-4290
Telephone:	908-740-3583

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):

- Chem. Type: 3
- Submission Priority: P

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

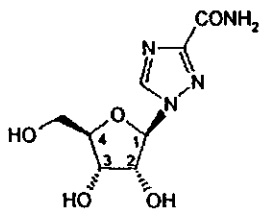
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

__SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Name: 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide
CAS Reg. No.: 36791-04-5
Molecular Formula: $C_8H_{12}N_4O_5$
Molecular Weight: 244.2
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			1	Acceptable	1/12/01	None
	III			4	Not Applicable	Not Applicable	None
	III			4	Not Applicable	Not Applicable	None
	III			4	Not Applicable	Not Applicable	None

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-903	Intron A® (interferon alfa-2a) Injection and Rebetol (ribavirin) Tablets for —

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Pending	7/11/03	DMPQ (HFD-324), OC
EA	Acceptable based on categorical exclusion	7/11/03	Rao Kambhampati, Ph.D. (HFD-530)
Methods Validation	Pending	7/11/03	Philadelphia District Laboratory (HFR-MA160)

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) for 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

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 ( ) that 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/RKambhampati
HFD-830/DD/CChen
HFD-530/Chem Team Leader/SMiller
HFD-530/PM/DSillivan

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ON ORIGINAL

56 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/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

Sponsor: SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 070335030

Stamp Date : 30-JAN-2003
PDUFA Date : 30-JUL-2003
Action Goal :
District Goal: 31-MAY-2003

Brand Name : REBETOL [redacted]
(RIBAVIRIN) 40 MG/ML
Estab. Name:
Generic Name: RIBAVIRIN
Dosage Form: (SOLUTION)
Strength : 40 MG/ML

FDA Contacts: D. SILLIVAN Project Manager (HFD-530) 301-827-2335
R. KAMBHAMPATI Review Chemist (HFD-530) 301-827-2423
S. MILLER Team Leader (HFD-530) 301-827-2392

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

Establishment : [redacted] FEI : [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE
Last Milestone: OC 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

OAI

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

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ON ORIGINAL

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DUPLICATE MILESTONE FROM FACTS

Establishment : CFN : 2211256 FEI : 2211256
SCHERING CORP
1011 MORRIS AVE
UNION, NJ 07083

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: POTENTIAL OAI

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

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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 OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-JUL-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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/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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