

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-511

CHEMISTRY REVIEW(S)

DRAFT**NDA #21-511****Copegus™
(ribavirin, USP)
Tablets****Hoffmann-La Roche Inc.****Rao Kambhampati, Ph.D.
Division of Antiviral Drug Products
HFD-530**

**APPEARS THIS WAY
ON ORIGINAL**

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA# 21-511
2. REVIEW #: 1
3. REVIEW DATE: 11/26/2002
4. REVIEWER: Rao Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
BB-IND# 7823	
IND# 58,827	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	31/May/2002
Amendment (BC)	29/Jul/2002
Amendment (BC)	04/Sep/2002
Amendment (BC)	17/Oct/2002
Amendment	24/Oct/2002
Amendment	31/Oct/02
Amendment	11/Nov/2002
Amendment	12/Nov/2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Hoffmann-La Roche Inc.
Address:	340 Kingsland Street Nutley, NJ 07110
Representative:	Jennifer A. Dudinak, Pharm. D. Program Director
Telephone:	973-562-2930

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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Copegus™
- b) Non-Proprietary Name (USAN): Ribavirin
- c) Code Name/#: Ro 20-9963
- d) Chem: Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P and Fast-Track

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL CATEGORY: Antiviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 200 mg/tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

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.: 36791-04-05

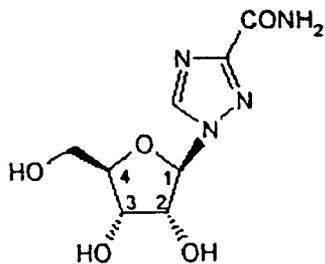
Molecular Formula: C₁₃H₁₂N₄O₅

Molecular Weight: 244.2

Structural Formula:

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	I			2	Not Applicable	Not Applicable	None
	I			2	Not Applicable	Not Applicable	None
	I			2	Not Applicable	Not Applicable	This facility was withdrawn by the Applicant
	II			1	Acceptable	6/17/02	None
	III			4	N/A	Not Applicable	None
	III			4	N/A	Not Applicable	None
	III			4	N/A	Not Applicable	None
	III			1	Acceptable		<i>Check acceptable</i>
	III						
	III						
	III						
	III						
	III			4	N/A		
	III			4	N/A		

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	IV					
	IV					

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
BLA	125061/0	Pegasys (peginterferon alfa-2a) Injection and Copegus (ribavirin) Tablets combination therapy for the treatment of Hepatitis C
BLA	103964/0	Pegasys monotherapy for the treatment of Hepatitis C
IND	58,827	Ribavirin Tablets for combination therapy
BB-IND	7823	Peginterferon alfa-2a and ribavirin tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	10/21/02	J.D. Ambrogio (HFD-324), OC
Trademark Review	Acceptable	7/31/02	Jennifer Fan, Pharm. D., DMETS (HFD-420), ODS
EA	Categorical Exclusion Acceptable	N/A	N/A
Biopharm for Dissolution Method including acceptance criteria	Acceptable	11/19/02	Kellie Reynolds (HFD-530)

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Methods Validation	Pending		
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**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for NDA 21-511

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA #21-511 is recommended for approval.

B. *Post-Marketing* (Phase 4) Commitments, Agreements, and/or Risk Management Steps, if recommendation is for *Approval*.

N/A

II. Summary of Chemistry Assessments

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

The Applicant, Hoffmann La-Roche, intends to seek approval of the FDA for a combination therapy involving Pegasys[®] (peginterferon alfa-2a) Injection and Copegus[™] (ribavirin) Tablets for the treatment of patients with chronic hepatitis C infection. Since this combination therapy involves a biologic and a drug, a BLA #125061/0 was filed to CBER for seeking approval of Pegasys to be used in combination with Copegus and a NDA #21-511 was filed to CDER for seeking approval of Copegus to be used in combination with Pegasys. Both CBER and CDER are expected to take action on their respective applications on the same date.

The drug substance, ribavirin, is an USP compound (USP 25, 2002, pp 1526). Ribavirin is a nucleoside analog with antiviral activity. It was previously approved by the FDA for use in the formulation of Virazole Aerosol (ribavirin for inhalation solution) for the treatment of respiratory syncytial virus (RSV) infection in infants and for use in Rebetol Capsules, 200mg, for a combination therapy with Intron A (interferon alfa-2b) injection or PEG-Intron (peginterferon alfa-2b) Injection for the treatment of patients with chronic hepatitis C infection.

The _____ is manufactured and supplied to the Applicant by _____ as according to the process and controls described in their DMF _____ and a Letter of Authorization was provided for cross-reference. This DMF was reviewed by Edwin Ramos (Chemistry Reviewer, OGD) when it was cross-referenced in an ANDA #76,203 by Three Rivers Pharmaceuticals. The DMF was found to be adequate (6/17/02). The Applicant provided the remaining CMC information (except container/closure information) directly in the NDA. Ribavirin is a

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white to off-white powder and has a melting point of 166-168°C. It has a pKa value of _____ and partition coefficient (log P) of _____. Ribavirin is _____ and is not light sensitive, and is very stable in the solid state. Ribavirin is freely soluble in water, _____ slightly soluble in _____ and very slightly soluble in _____. The ribavirin molecule has four chiral centers at C-1, C-2, C-3 and C-4 of the furanose ring. The structural characteristics of ribavirin were elucidated by means of _____ and _____ techniques, which included _____

_____ The thermal properties have been investigated by _____ and _____. The data were compared to the USP reference standard to confirm the chemical structure and polymorphic form of ribavirin. Ribavirin has two known polymorphic forms, Form I and Form II. The Form II, the more stable form _____ is used for the production of Copegus™ (ribavirin) Tablets. The USP reference standard for ribavirin drug substance is also Form II. The specifications for drug substance included: _____

_____ Batch analysis was provided for _____ lots (_____ at _____ scale, _____ at _____ scale and _____ at _____ scale). The stability data were provided for _____ lots. The long term data included 36 months data for _____ lot, _____ data for _____ lots, and _____ data for _____ lots. Under long term storage conditions, the total impurities content was increased by a maximum of _____ in comparison to the initial time point indicating that the drug substance is very stable when stored at 25°C/60%RH. The proposed re-test period of _____ is acceptable.

The drug product, Copegus™, is an oral tablet. Each tablet contains 200 mg of ribavirin as active ingredient and is light pink to pink colored, flat, oval-shaped, film-coated, and engraved with RIB 200 on one side and ROCHE on the other side. The total weight of the tablet is _____. The components and composition of the _____ include ribavirin _____, pregelatinized starch (_____), sodium starch glycolate _____, microcrystalline cellulose (_____), corn starch (_____) and magnesium stearate (_____) and the film-coat include Chromatone-P, _____ or Opadry Pink _____, ethylcellulose (_____) and triacetin _____. Copegus tablets are produced by _____ pharmaceutical operations that include _____

_____ The in-process controls included _____

_____ The specification for tablet included _____, average weight, identity by HPLC _____ impurities (individual, unspecified, and total) by HPLC, assay of ribavirin by HPLC, _____ dissolution, _____. The batch analysis was provided for _____ batches. Of which _____ were _____ batches (_____)

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tablets) were _____ batches (_____ tablets), and _____ were _____ batches (_____ tablets). The _____ batches were made by slightly different _____ or _____ step. The stability data were provided for _____ batches (_____ data for _____ batches and _____ data for _____ batch) and _____ batches (36 months data for _____ batches and _____ data for _____ batch). The tablets were packaged in bottles of _____, and _____ tablet counts which are same as the intended commercial packages. The statistical analysis was provided for _____ batches and _____ batches. No significant decrease in ribavirin assay value and significant increase in the impurities content were observed during the long-term storage for 36 months, however, _____ was observed at some of the time points. This _____ is considered within the acceptance criterion _____, therefore, it is of no safety concern. The proposed expiration dating period of 36 months when stored at 25°C/60%RH or under refrigeration (2-8°C) is acceptable.

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

COPEGUS (ribavirin) Tablets in combination with PEGASYS (peginterferon alfa-2a) Injection is indicated for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not been previously treated with interferon alfa and for patients in whom efficacy was demonstrated including patients with compensated cirrhosis. The dosing recommendations are summarized in the following table:

Genotype	PEGASYS Dose	COPEGUS Dose	Duration
Genotype 1,4	180 µg	<75 kg = 1000 mg	48 weeks
		≥75 kg = 1200 mg	48 weeks
Genotype 2,3	180 µg	800 mg	24 weeks

The Copegus tablets (200 mg of ribavirin/tablet) are packaged in _____ bottles of _____ 168, _____ tablet counts, however, only 168 count bottles will be marketed at launch. The bottles are recommended to be stored at 25°C (77°F); excursions are permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]. On the basis of the stability data and statistical analysis of the data, the proposed expiration dating period of 36 months is acceptable.

C. Basis for Approval, Approvable, or Not-Approval Recommendation

The original NDA submission and amendments there to provided adequate information on the chemistry, manufacturing, and controls for the production of Copegus (ribavirin) Tablets, 200 mg.

The ribavirin drug substance is currently used in the following marketed products, Virazole Aerosol and Rebetol Capsules by other Applicants. This Applicant will use USP quality ribavirin in the manufacturing of Copegus tablets. The manufacturing

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and packaging processes and in-process controls used for the drug substance by the DMF Holder and for the drug product by the Applicant are acceptable. Adequate batch analysis data were provided for the drug substance and drug product. The specifications for the drug substance are slightly different from those of the USP ribavirin, for example, they contained additional tests (_____) acceptance criteria for individual and total unspecified impurities and the TLC identity test was replaced by more sensitive HPLC. Upon comment, the Applicant agreed to tighten the acceptance criterion for the _____ in the drug substance specifications from the initially proposed _____. The Applicant was informed to tighten the acceptance criterion for individual unspecified impurities from _____, which was based on the highest daily dose given to patients. The remaining initially proposed drug substance specifications and the proposed drug product specifications are acceptable. The submitted long-term stability data supports the proposed retest period of _____ for the ribavirin drug substance. The long-term stability data for primary and supportive batches of the Copegus tablet bottles and statistical analysis of the data supports the proposed expiration dating period of 36 months at 25°C/60%RH or under refrigeration. However, the Applicant was advised to monitor the first _____ lots of the drug product for _____.

The trade name, CopegusTM, was found to be acceptable by the DMETS (HFD-420) and DAVDP (HFD-530). The established name for the drug substance, ribavirin, is same as the USAN name. Some changes were recommended to the package insert and bottle labels and these changes will be incorporated by the Applicant in the final printed documents.

The _____ an alternate packager for Copegus tablets, had to be withdrawn by the Applicant due to the Warning Letter received by _____. All other facilities that are involved in the manufacturing, packaging, and testing of the drug substance and drug product were found to be acceptable by DMPQ (HFD-324). The dissolution method including the acceptance criteria is acceptable to the biopharm reviewer (HFD-530). The analytical methods validation is pending. 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

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B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. CC Block

cc:

Org. NDA 21-511
HFD-530/Division File
HFD-830/DD/CChen

HFD-530/Chem Reviewer/RKambhampati
HFD-530/Chem Team Leader/SMiller
HFD-530/PM/DSullivan

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