CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125083Orig1s000

CHEMISTRY REVIEW(S)

Chemistry, Manufacturing, and Controls (CMC) Review

Type of Review: Inter-Office Consult

1. BLA#: 125083/0 (PEGASYS® COPEGUS® [redacted] (b) (4) Pack)
2. REVIEW #: 1
3. REVIEW DATE: 3/19/2004
4. REVIEWER: Rao Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (pages 246-250)	8/4/2003

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

8. DRUG PRODUCT NAME/CODE/TYPE:

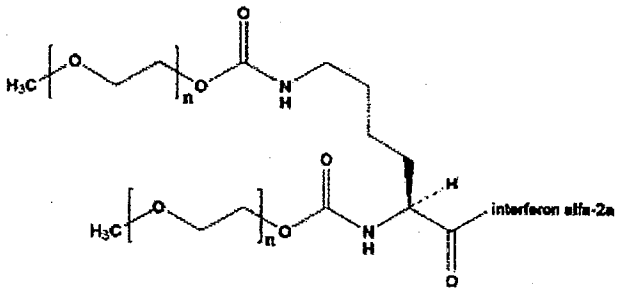
a) Proprietary Name: PEGASYS® COPEGUS® [redacted] (b) (4) Pack
b) Non-Proprietary Name (USAN): peginterferon alfa-2a (for Pegasys) and ribavirin (for Copegus)
c) Code Name/#: Ro 25-8310 (for Pegasys) and Ro 20-9963 (for Copegus)

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL CATEGORY: Antiviral
11. DOSAGE FORM: Prefilled Syringes (Pegasys) and Tablets (Copegus)
12. STRENGTH/POTENCY: 180 µg/0.5 mL (Pegasys) and 200 mg/tablet (Copegus)
13. ROUTE OF ADMINISTRATION: Subcutaneous (Pegasys) and Oral (Copegus)
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC
15. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Pegasys:

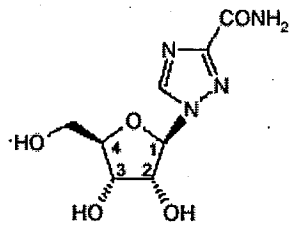
Chemical Name	Mono(N^2,N^6-dicarboxy-L-lysyl)interferon alfa-2a, diesters with polyethylene glycol monomethyl ether. The molecular mass of the pegylated part may be indicated in the name by adding a number, for example: peginterferon alfa-2a (40KD).
CAS Numbers	*CAS-198153-51-4.*

(b) (4)



Copegus:

Chemical Name: 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide
CAS Reg. No.: 36791-04-05
Molecular Formula: $C_{18}H_{12}N_4O_5$
Molecular Weight: 244.2
Structural Formula:



16. RELATED/SUPPORTING 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
STN	103964/5011	Pegasys Prefilled Syringes
NDA	21-511	Copegus (ribavirin) Tablets, 200 mg,

		for combination therapy
IND	58,827	Ribavirin Tablets for combination therapy
BB-IND	7823	Peginterferon alfa-2a and ribavirin tablets

17. NOTES/COMMENTS:

Hoffmann-La Roche Inc. submitted this BLA #125083/0 for seeking approval of PEGASYS® COPEGUS® (b) (4) Pack configuration. Each package will contain a carton with 4 Pegasys prefilled syringes (180 µg/0.5 mL), the corresponding package insert, a bottle of Copegus (200 mg) Tablets (112 or 140 or 168 tablets/bottle), the corresponding package insert, a combination Medication Guide that includes information on the combined use of Pegasys and Copegus for patients, as well as 4 safety guard needles, and 4 alcohol swabs. The applicant initially submitted this BLA to CBER on 8/4/03 which was later transferred to ODE VI (CDER) due to inter-center transfer of some BLAs. Both the Pegasys (peginterferon alfa-2a) prefilled syringes and Copegus (ribavirin) Tablets were approved as a combination therapy for the treatment of patients with chronic Hepatitis C infection under the STN# 125061/5011 and NDA# 21-511, respectively, but those approvals were only granted for the marketing of individual packages of Pegasys and Copegus.

Per the request of Ms. Karen Winestock (PM, ODE IV), in this review only the CMC information that was submitted in the BLA# 125083/0, pp 246-250, for Copegus Tablets is covered. The applicant proposed 112, 140, and 168 count Copegus Tablet bottles. Of which, 168 and 112 tablet counts and their corresponding containers/closures were previously approved (NDA# 21-511). For the 140 count bottles, the applicant stated that they are bracketed by 112 and 168 count bottles because the container/closure proposed is same as the one used for 168 count bottle, i.e., 150-cc white HDPE bottle and (b) (4) 2-piece child-resistant closure which is acceptable. Since the 140 count Copegus tablet bottle is not yet approved for marketing, the applicant should be advised to provide the CMC information (including proposed stability protocol) for this package in an information amendment to the NDA# 21-511 followed by an update in the next annual report. See Review Notes for more information.

18. CONCLUSIONS/RECOMMENDATIONS: The CMC information that was provided in the pages 246-250 of the BLA# 125083/0 is acceptable, however, the applicant should be advised to provide this information in an information amendment to the NDA# 21-511 followed by an update in the next annual report.

Rao Kambhampati

Rao V. Kambhampati Date: 3/19/04
Senior Regulatory Review Scientist (Chemist)
HFD-530, CDER

Stephen Miller

Stephen P. Miller Date: 3/23/04
Chemistry Team Leader
HFD-530, CDER

cc: Karen Winestock, CSO, HFM-585, ODE VI
Tanima Sinha, PM, HFD-530, ODE IV

19. REVIEW NOTES:

DRUG SUBSTANCE:

The chemistry, manufacturing, and controls information for the drug substance, ribavirin, remains unchanged from the information currently approved in NDA 21-511 for Copegus (ribavirin) Tablets, (submitted May 31, 2002, and approved December, 2002). This information was submitted in the original NDA, Section 4.S, Drug Substance, and amended in the November 27, 2002 response to FDA questions of November 5, 2002. The approved NDA also cross references type II DMF# (b) (4) for the synthesis of ribavirin at (b) (4)

Comments: Acceptable.

DRUG PRODUCT:

The chemistry, manufacturing, and controls information for the drug product, Copegus (ribavirin) Tablets 200 mg remains unchanged from the information currently approved in NDA 21-511, except for an additional package of Copegus Tablets containing 140 tablets in the same bottle and closure currently used for Copegus Tablets 168's. Information for the drug product was submitted in the original NDA, Section 4.P Drug Product, the amendment of November 27, 2002 (response to FDA questions), and approved (b) (4) (b) (4)

Comments: There was no change in the manufacturing of bulk tablets.

Container-Closure System:

The applicant referred to approved NDA 21-511, Section P.9.2 for a detailed description of the currently approved container/closure systems for Copegus (ribavirin) 200 mg tablets, including names of component suppliers. The approved package sizes are presented in Table 1 below. This BLA seeks approval of one additional packaging configuration (140 tablets) in a 150 cc white HDPE bottle, which is the same container-closure system used for the 168 tablet count. This tablet count is bracketed by the currently approved 112 and 168 count package sizes. Currently, bottles of 168 tablets are the only package size that is commercially available. This BLA proposes that bottles containing three different counts of Copegus tablets will be packaged with Pegasys 180 µg/0.5 mL Pre-Filled Syringes in a patient convenience pack in the following counts and container/closure systems:

. 112 tablets in a 90 cc HDPE bottle
. 140 tablets in a 150 cc bottle
. 168 tablets in a 150 cc bottle

Bottles containing 168 tablets of Copegus will continue to be sold separately, in addition to being part of the Pegasys Copegus (b) (4) Pack.

Table 1 Approved Packaging Configurations (NDA 21-511, Section P.9.2)

Copegus® Packaging Configurations	Bottle Size and Type (Square Bottles)	Closure Size and Type ((b) (4) induction seal)
(b) (4)		
Bottle of 112 tablets	90cc white HDPE bottle	(b) (4) 2-piece child-resistant closure
Bottle of 168 tablets	150cc white HDPE bottle	(b) (4) 2-piece child-resistant closure
(b) (4)		

Comments: Acceptable. However, the CMC information for 140 tablet count Copegus bottles should also be provided in an information amendment to the NDA# 21-511 followed by an update in the next annual report.

Stability:

1) Storage Conditions: Because bottles of Copegus Tablets are sold separately but were intended to also be packaged with Pegasys, and pegasys must be stored under refrigeration, we received approval for both storage conditions for Copegus Tablets in NDA 21-511 (see NDA 21- 511, section P.10.4). The approved storage conditions for Copegus (ribavirin) Tablets 200 mg are: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] or under refrigeration at 2° to 8°C (36° to 46°F).

Comments: It is acceptable to include both the room temperature and refrigerated conditions in the storage statement.

2) Stability Data and Expiration Date: Copegus (ribavirin) Tablets 200 mg are very stable physically and chemically at the two approved storage conditions (5°C and 25°C/60% RH) when stored in opaque high density polyethylene (HDPE) bottles with screw caps, which are the market package. Twenty-four months of real-time stability data for three primary stability batches were submitted in the September 4, 2002 amendment to NDA 21-511. Up to 36 months of supportive data obtained under accelerated (40°C/25% RH, 40°C/75% RH 50°C, and light chamber) and long-term conditions were included in the original NDA 21-511 (Sections P.10.1 to P.10.4) to support the currently-approved expiration date of 36 months.

Comments: The previously submitted stability data to the NDA# 21-511 support the 36 month expiration dating period for all the proposed Copegus tablet bottles.

3) Stability Commitment: The currently approved stability commitment provides for the inclusion of the first three marketed batches of each packaging configuration initially, and at least one batch of each packaging size of Copegus Tablets for each year thereafter. The storage conditions are specified as 25°C/60% RH. Revised labeling included in this BLA includes both storage conditions. Therefore, a revised stability commitment for Copegus Tablets is included in this BLA. The revised labels and stability commitment will also be submitted to NDA 21-511. The revised stability commitment for Copegus Tablets is provided below.

a. Placement:

i) New Product Program:
A minimum of three lots of each drug product (a given strength of a given dosage form) including each significantly different packaging configuration (container/closure system), i.e. bottles, blisters, and each container size, i.e. 100's, 500's are placed in the program. Thereafter, a minimum of one lot per year is placed in the program. Lots are selected such that each significantly different packaging configuration (container/closure system) including each container size is placed in the program annually. The first three marketed lots of COPEGUS (ribavirin) Tablets will be placed in the program. Included will be the first three marketed lots of each packaging configuration.

ii) Revised Product Program (Processing or Container/Closure Changes):
A minimum of three lots of each revised drug product are placed in the program if the revision is considered to have a significant impact on the stability of the product. At least one lot of each significantly different packaging configuration (container/closure system) is included. If the revision is not considered to have a significant impact on the stability of the product, then one lot in any packaging configuration is placed in the program. Special consideration is not given to minor changes known not to affect the stability of the drug product although a lot reflecting such a change may be placed in the program under the Established Product protocol.

iii) Established Product Program:
For each drug product, at least one lot is randomly selected annually, it production warrants, and placed in the program. Lots are selected such that each significantly different packaging configuration (container/closure system) and each container size is placed in the program annually. The random selection of a lot is not necessary if lot (s) of the drug product have been placed in the New Product or Revised Product Program, providing the revision is representative of the currently marketed product.

b. Sampling: Within each lot, samples of marketed packaging configurations are withdrawn from the completed packaged lot and represent a random sample of the lot.

c. Storage: Stability samples of COPEGUS (ribavirin) Tablets will be stored at 25°C/60% RH. Stability samples of those packaging configurations that may be stored under refrigerated conditions will also be stored at 5°C.

d. Testing Schedule: Upon completion of packaging, the COPEGUS (ribavirin) Tablet batches will be scheduled for testing according to the following schedule:

Shelf-Life (Months)	Testing Schedule (Months)
36	0, 3, 6, 9, 12, 18, 24, 36

*If the stability of the product warrants and if an extension of the expiration date is desired, the 48 month test interval is added to the schedule.
For established products, the 3, 6, 9, and 18 month test intervals may be omitted.
The tests to be performed are those tests listed in the stability specifications for the drug product.

Comments: The proposed revised stability protocol is acceptable. However, as indicated in the BLA, this information was not submitted in an amendment to the NDA# 21-511, therefore, the applicant should be advised to provide this information in an information amendment to the NDA# 21-511 followed by an update in the next annual report.

Memorandum

Date: December 10, 2003

To: BLA File, STN 125083/0, Peginterferon alfa-2a co-packaged with Ribavirin, Hoffmann-La Roche Inc., (License # 0136)
Kassa Ayalew, M.D., Committee Chair, OND/ODEVI/DTBIMP, HFM-582

From: Chiang Syin, Ph.D., CDER/OC/DMPQ/TFRB, HFD-328

Subject: Complete Review Memo – Treatment of adults with chronic hepatitis C who have compensated liver disease and who have not been previously treated with interferon alfa

Through: Cynthia Whitmarsh, Acting Chief, CDER/OC/DMPQ/TFRB

Recommendation Approval

Information Reviewed I only reviewed the following information:

- 125083/0 Summary and CMC sections
- 125083/0.1 Updated facility information
- 125083/0.4 Additional establishment information describing the packaging operations

Review Summary Hoffmann La-Roche, Inc. (HLR) submitted a biologics license application on August 4, 2003, for the combination packaging of PEGASYS (peginterferon alfa-2a, BLA 103964) and COPEGUS (Ribavirin, NDA 21-511) therapy for the treatment of chromic hepatitis C. Currently the Pegasys supplement (103964/5011) for the addition of prefilled syringes (PFS) dosage form is under review. The Agency has previously approved on December 3, 2002, under the STN 103964/5000 to allow PEGASYS alone or in combination with COPEGUS, for the same indication. The information submitted in this BLA supports the combination packaging of Pegasys and Copegus in a Convenience Pack. HLR did not propose to change the container-closure system of either licensed product. The primary and secondary packaging for PEGASYS PFS remains unchanged; for Copegus, the primary packaging also remains the same. Both packaged products will be placed into a new carton (tertiary packaging for Pegasys PFS, secondary packaging for Copegus tablets) at HLR Nutley, NJ facility, resulting in only labeling changes for these combination packages.

The PEGASYS® COPEGUS® Convenience Pack provides a one-month supply of

Pegasys and Copegus. Each package contains a carton with 4 PEGASYS 180 mcg pre-filled syringes, a bottle of Copegus tablets, and package inserts/medication guide, as well as 4 needles and 4 alcohol swabs. The Convenience Packs are customized based on the requirement of different total daily ribavirin dose (1200, 1000, or 800 mcg of Copegus). HLR referred to the CMC information in the BLA 103964/0 and NDA 21-511. HLR indicated that all approved CMC information is unchanged. Therefore, I did not review the information in the original BLA 103964.

For this BLA, HLR provided the following CMC information:

- Pegasys Copegus [redacted] (b) (4) Pack
  - Establishment information
  - Packaging description
  - Copegus
  - Container-Closure System (140 tablet count)
  - Updated stability commitment for NDA 21-511 to include both approved storage conditions (5°C ad 25°C/60% RH)

Both the PEGASYS® and COPEGUS® products are packaged separately as per the approved applications and stored as labeled products until a Packaging Order is issued for the [redacted] (b) (4) Pack. Pegasys is stored at 2 to 8°C and Copegus is stored at room temperature (15 to 30°C) or 2 to 8°C as approved. Only the Pegasys prefilled syringes are used for the [redacted] (b) (4) Packs are manually packaged into final carton. I have not reviewed the stability commitment to the Copegus NDA since it is product reviewer's responsibility.

After considering the facts that all CMC information remains unchanged from the original applications (PEGASYS BLA and COPEGUS NDA), and the prefilled syringe supplement is expected to be approved soon with all objectionable observations resolved from the pre-approval inspection (verified by Carol Rehkopf, the DMPQ reviewer, who performed the inspection at HLR's Basel and Kaiseraugst sites in May 2003), I conclude a pre-license inspection for the manufacturing facilities would not be necessary.

This BLA is really involving a co-packaging step for the final configuration of the Convenience Packs. I consider this BLA is acceptable for approval.

Review Follow-up

- Pre-licensing inspection waiver memo.
- Memo for categorical exclusion under 21 CFR 25.31 (b).

cc: Karen Winestock, Regulatory Project Manager, HFM-585