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APPLICATION NUMBER:

21-511

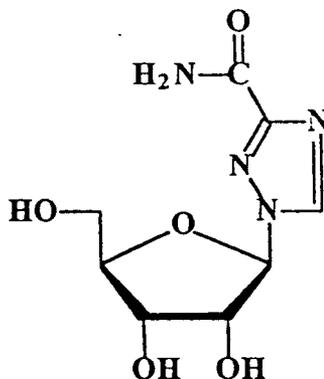
MICROBIOLOGY REVIEW(S)

Microbiology Review
Division of Antiviral Drug Products (HFD-530)

NDA: 21-511	Serial #: 000	Reviewer:	N. Battula
Date submitted:	May 31, 2002	Date received:	June 4, 2002
Date assigned:	June 6, 2002	Date reviewed:	November 20, 2002
Sponsor:	Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110		

Product name(s):
Non-proprietary: Ribavirin and pegylated Interferon alfa-2a
Proprietary: Copegus™ and Pegasys®
Chemical: 1-β-D-1*H*-ribofuranosyl-1, 2,4-triazole-3-carboxamide
Mol. Formula = C₈H₁₂N₄O₅ Mol. Weight = 244.21

Structural formula:



Dosage form: Tablets (200 mg)
Route of administration: Oral
Indication: Treatment of chronic hepatitis C
Related documents: BB-INDs — and 7,823 and IND 58,827

BACKGROUND and SUMMARY: This application submitted by Hoffmann-LaRoche Inc. is a composite submission consisting of a New Drug Application (NDA 21-511) and a Biologics License Application (BLA # 125061). The NDA 21-511 for Copegus™ (ribavirin) is being reviewed by the Division of Antiviral Drug Products, CDER and the BLA for Pegasys® (pegylated interferon alfa-2a) is being reviewed by the Division of

Clinical Trial Design and Analysis, CBER. The NDA review dealing with the microbiology portion of the submission is principally confined to the Copegus™ portion of the application. According to the applicant Copegus™ is the trade name proposed for the market formulation of ribavirin to be used together with pegylated interferon alfa-2a.

The indication sought in this application is for the use of Copegus™ (ribavirin) in combination with Pegasys® (pegylatedinterferon alfa-2a) for the treatment of patients with hepatitis C _____ with compensated liver disease who are naïve to interferon alfa and are at least 18 year of age. In support of the proposed indication Hoffmann-LaRoche Inc. conducted two similarly designed international Phase 3 clinical studies, NV15801 and NV15942. Study NV 15801 is "A Phase III, Randomized, Multicenter, Efficacy and Safety Study Comparing the Combination of Pegylated Interferon alfa-2a and Ribavirin to Rebetron in the Treatment of Patients With Chronic HCV Infection." Study NV15942 is "A Phase III, Randomized, Multicenter, Efficacy and Safety Study Examining the Effects of the Duration of Treatment and the Daily Dose of Ribavirin in Patients With Chronic Hepatitis C Virus Infection Treated With the Combination of Peginterferon alfa-2a and Ribavirin."

To evaluate the in vitro anti-HCV activity of ribavirin or other potential anti-HCV agents or their mechanism of action, presently there are no cell culture systems that can support the replication of HCV. Accordingly, the applicant has not provided data that address the in vitro anti-HCV activity of ribavirin. Previous clinical studies conducted to determine the in vivo anti-HCV activity demonstrated a lack of anti-HCV activity. In _____ the application for _____ was not approvable for lack of efficacy as evaluated by a variety of criteria including:

In 1998 the application for combination of ribavirin + interferon alfa-2b therapy (NDA 20-903) for the treatment of chronic hepatitis C was approved. The approval was based on sustained virologic response for 24 and 48 weeks was more effective with ribavirin + interferon alfa-2b than treatment with interferon alfa-2b + placebo. Additionally, combination therapy with ribavirin + interferon alfa-2b compared to interferon alfa-2b + placebo showed histological improvement in the post-treatment follow-up biopsy compared to the pre-study biopsy. Thus, in chronic HCV infection the current treatment of choice is the combination use of an interferon product and ribavirin because monotherapy with ribavirin was ineffective.

Publications in the open literature suggest that ribavirin inhibits the replication of several RNA and DNA viruses but the specific mechanism(s) of inhibition has not been established. In support of potential mechanism of inhibition of virus replication by ribavirin, several hypotheses, which are not mutually exclusive, have been proposed. The proposed potential mechanism includes both direct and indirect mechanisms ⁽¹⁾ of inhibition of viral replication by ribavirin. Direct mechanisms of ribavirin inhibition include (a) inhibition of viral RNA-dependent RNA polymerase ⁽²⁾ and (b) acting as an RNA mutagen "error catastrophe" a hypothesis ⁽³⁾ which suggests that increases in mutations in the viral genome drastically reduce the viral fitness. Indirect mechanisms of ribavirin inhibition include (a) inhibition of the host enzyme inosine monophosphate dehydrogenase ^(4,5) and (b) enhancement of host T-cell-mediated immunity against viral infection ^(6,7).

As is the case with ribavirin, for interferons also multiple and complex modes of viral inhibition, both by direct and indirect mechanisms, have been proposed. However, the specific mechanism(s) of inhibition of chronic HCV infection by interferons has not been established. Thus, the mechanism of HCV inhibition by ribavirin and interferon alfa-2a could be due to pleotropic but undefined effects. Therefore, the package insert for the use of Copegus™ in combination with Pegasys® states that the mechanism by which the combination of ribavirin and an interferon product exerts its effects against HCV RNA has not been established.

CONCLUSIONS: In controlled clinical trials, HCV infected subjects treated with Copegus™ (ribavirin) in combination with Pegasys® demonstrated antiviral activity as determined by sustained decreases in HCV RNA. However, the mechanism by which the inhibition of HCV RNA by combination therapy with Copegus™ Pegasys® has not been established.

Draft microbiology label: Mechanism of Action: Ribavirin is a synthetic nucleoside analog. The mechanism by which the combination of ribavirin and an interferon product exerts its effects against HCV RNA has not been established.

RECOMMENDATION: In HCV infected subjects the combination use of Copegus™ (ribavirin) with Pegasys® demonstrated antiviral activity and there were no microbiology related safety issues. Therefore, with respect to microbiology this application is recommended for approval.

REFERENCES:

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- of chronic HCV infection. *Hepatology* 35: 1002-1009
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 4. Streeter, DG et al., (1973) Mechanism of action of 1- β -D-1*H*-ribofuranosyl-1, 2,4-triazole-3-carboxamide (virazole), a new broad-spectrum antiviral agent. *Proc. Natl. Acad. Sci. USA*: 70: 1174-1178
 5. Muller WEG et al., (1977) Virazole (1- β -D-1*H*-ribofuranosyl-1, 2,4-triazole-3-carboxamide): a cytostatic agent. *Biochem. Pharmacol.* 26: 1071-1075
 6. Fang et al., (2000) Ribavirin enhancement of hepatitis C virus core antigen-specific type-1 T- helper cell response correlates with the increased IL-2 level. *J. Hepatol.* 33: 791-798
 7. Cramp, ME et al., (2000) Hepatitis C virus-specific T-cell reactivity during interferon and ribavirin treatment in chronic hepatitis C. *Gastroenterology.* 118: 346-355

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Concurrence:

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