

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-546

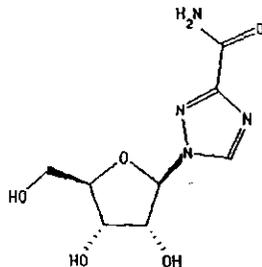
PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-546
Sequence number/date/type of submission: 29 January 2003
Information to sponsor: Yes (X)
Sponsor and/or agent: Schering Corporation, 2000 Galloping Hill Road,
Kenilworth, New Jersey 07033
Manufacturer for drug substance: Schering Corporation
Reviewer name: Hao Zhang, M.D
Division name: Division of Antiviral Drug Products
HFD #: HFD-530
Review completion date: 13 July 2003

Drug:

Trade name: Rebetol
Generic name (list alphabetically): Ribavirin
Chemical name: 1-(beta)-D-ribofuranosyl-1 H -1,2,4-triazole-3-carboxamide
Synonyms: ICN-1229, RTCA, Varazid, Viramid, and Virazole
CAS registry number: 36791-04-5
Molecular formula/molecular weight: C₈H₁₂N₄O₅; 244.21
Structure:



Relevant INDs/NDAs/DMFs: IND 49,923 (Schering Corp)
NDA 20,903 (Schering Corp)
Drug class: Antiviral Nucleoside
Indication: Indication: Treatment of HCV
Clinical formulation: Rebetol is a clear, colorless to light yellow bubble gum-flavored . . . Each milliliter contains 40 mg of ribavirin and the inactive ingredients sodium citrate, citric acid, sodium benzoate, glycerin, sucrose, sorbitol, propylene glycol, and water
Route of administration: Oral
Proposed use: Rebetol (ribavirin,) in combination with Intron A® for the treatment of chronic hepatitis C among previously untreated pediatric patients ≥ 3 years old

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor is requesting a priority review for the NDA 21-546 since there are currently no other approved treatments in pediatric patients ≥ 3 years of age. The Pharmacology and Toxicology reviewer agrees to assign this NDA for Priority Review based on that there is no effective treatment options approved for pediatric chronic hepatitis C.

The sponsor is requesting approval to market Rebetol® (15 mg/kg/day) — to be used as part of combination therapy with Intron A® (3MIU/m² TIW) for the treatment of hepatitis C among previously untreated pediatric patients ≥ 3 years of age. The drug product, Rebetol® —, is approvable in the perspective of Pharmacology and Toxicology.

B. Recommendation for Nonclinical Studies

None

C. Recommendations on Labeling

Minor label revisions are recommended in the Carcinogenesis, Mutagenesis, and Impairment of Fertility Section (See Appendix, Summary of NDA Labeling Review, Page 2).

II. Summary of Nonclinical Findings

No Pharmacology and Toxicology data were included in this NDA submission. Instead, the sponsor referred to NDA 20-903 for the non-clinical pharmacology and toxicology data of Rebetol®.

III. Administrative

A. Reviewer signature: Hao Zhang, M.D.

B. Supervisor signature: Concurrence

Non-Concurrence

C. cc: list:

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**APPEARS THIS WAY
ON ORIGINAL**

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY :

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

II. SAFETY PHARMACOLOGY:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

III. PHARMACOKINETICS/TOXICOKINETICS:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

IV. GENERAL TOXICOLOGY

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

V. GENETIC TOXICOLOGY:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

VI. CARCINOGENICITY:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998; Pharmacologist's Review of NDA _____, by the reviewer; September 2002)

As part of a Phase 4 Post-Marketing Agreement, a 6-month carcinogenicity study in p53 (+/-) C57BL/6 mice (p53 knock-out mice) with ribavirin was conducted and completed by the sponsor. This study was reviewed (Re: Pharmacologist's Review of _____). Prior to the conduct of the 6-month carcinogenicity study, the CAC-EC reviewed and approved the dose levels and protocol design for this study.

Labeling Recommendations:

Label revisions are recommended as follows:

Carcinogenesis and Mutagenesis:

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg

adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

VIII. SPECIAL TOXICOLOGY STUDIES:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998)

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Refer to NDA 20-903 (Re: Pharmacologist's Review of NDA 20-903 by Dr. David Morse; May 1998; Pharmacologist's Review of NDA ~~20-903~~ by the reviewer; September 2002)

X. APPENDIX/ATTACHMENTS:

Summary of NDA Labeling Review

The reviewer recommended the following label changes to replace the current **Carcinogenesis and Mutagenesis** section (as of July 13, 2003):

Carcinogenesis and Mutagenesis Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1 X the maximum recommended human 24-hour dose of

ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility Ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women and partners of fertile women should not receive REBETOL unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (eg, 15 half-lives of clearance for ribavirin).

REBETOL should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 - 0.8 X the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially-total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

Animal Toxicology Long-term studies in the mouse and rat (18 - 24 months; doses of 20 - 75 and 10 - 40 mg/kg/day, respectively {estimated human equivalent doses of 1.67 - 6.25 and 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin}) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

Pregnancy Category X (see CONTRAINDICATIONS)

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive REBETOL unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months posttherapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days.

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with REBETOL and for the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, physicians should report such cases by calling 1-800-727-7064.

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