CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

REVIEWER	: Prabhu Rajagopalan, Ph. D.
NDA	: 20903
TYPE	: 1P
DRUGS (ROUTE OF ADMINISTRATION)	: Interferon α-2b (subcutaneous) and ribavirin (oral)
APPLICANT	: Schering Corporation.
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BACKGROUND

Ribavirin (1-β-D-Ribofuranosyl-1-H-1,2,4-triazole-3-carboxamide) is a nucleoside analog. This purine analog, first synthesized in the early 1970s, has been shown to possess *in vitro* antiviral activity against some DNA and RNA viruses. The antiviral activity of ribavirin against hepatitis C virus has not been demonstrated so far.

Schering Corporation, the Applicant of the NDA under review, has evaluated the efficacy of combination treatment of ribavirin and interferon α-2b (INTRON® A) in the treatment of chronic hepatitis C infection. A formal dose ranging study has not been completed by the Applicant. For Phase 3 clinical trials, the licensed dose of interferon for chronic hepatitis C was chosen and the ribavirin dose was based on previous clinical experience. Two pivotal clinical trials (C95-144 [US centers] and I95-145 [international centers]) have been completed by the Applicant in relapsed chronic hepatitis C patients previously treated with interferon. Two other pivotal clinical trials (C95-132 [US centers] and I95-143 [international centers]) in interferon naïve chronic hepatitis C patients are in progress. The efficacy data for this NDA come from the first two studies and safety data have been derived from all four studies.

SYNOPSIS

The important features in the pharmacokinetics and disposition of interferon and ribavirin are presented in this synopsis. A detailed review begins on page 6.

INTERFERON α-2b

The pharmacokinetics of interferon were studied after single and multiple dose subcutaneous administration in patients with compensated chronic hepatitis C. These patients received 3 million IU of interferon three times a week with or without ribavirin. After 4 weeks of multiple dosing with ribavirin, the mean (SD) interferon C_{max} and $AUC_{0-\infty}$ values were 22.8 (6.6) IU/mL and 357 (107) IU.h/mL, respectively. Following multiple dose administration, an approximately 1.5 to 2 fold increase was seen in interferon C_{max} and $AUC_{0-\infty}$ values when compared to administration of a single dose. The mean half-life values ranged from 5 to 7 hours. Significant pharmacokinetic interaction was not seen upon concomitant administration of interferon and ribavirin.

RIBAVIRIN

GENERAL COMMENT

Ribavirin partitions into red blood cells. In general, blood samples collected for determination of ribavirin concentrations in pharmacokinetic studies were placed on wet ice and centrifuged (at 4 °C) within 30 minutes of sample collection. By doing so, the Applicant might have minimized, but did not completely stop, the *ex vivo* partitioning of ribavirin into red blood cells. Therefore, it is likely that plasma ribavirin concentrations were underestimated in pharmacokinetic assessments.

ABSORPTION

Following oral administration, ribavirin was absorbed with an average t_{max} value of 1.5 hours. In general, the pharmacokinetics of ribavirin were variable. In 12 patients receiving ribavirin 600 mg b.i.d. with interferon, mean ribavirin C_{max} and AUC_{12} values were 3480 ng/mL and 30300 ng.h/mL, respectively after 4 weeks of treatment. In these subjects, C_{max} values ranged and AUC_{12} values ranged Based on AUC_{12} values, the mean accumulation index of ribavirin was 5.75 . In 27 patients receiving ribavirin 1000 mg/day (600 mg in the morning and 400 mg in the evening) with interferon, mean (range) ribavirin C_{max} and AUC_{12} values were 3230 ng/mL and 27800 ng.h/mL, respectively after 4 weeks of treatment.

The presence of food in the gastrointestinal tract appears to increase the bioavailability of ribavirin. Mean ribavirin C_{max} and AUC_{0-t} increased by approximately 70% (for AUC_{0-t} 90% CI : [147 - 198]) in the presence of food. Efficacy studies were conducted without instructions regarding drug administration relative to food consumption. This is the reason for not providing a recommendation in the label regarding the time of drug administration with respect to food consumption.

The Applicant conducted a study to assess the effect of antacid (Mylanta®) administration on the pharmacokinetics of ribavirin. While the mean C_{max} value was unchanged, the mean ribavirin AUC_{0-t} value was lower by 14% (90% CI : [1 - 25]) upon concomitant administration of ribavirin and antacid. This is not considered to be clinically important.

DOSE PROPORTIONALITY

The Applicant assessed the dose proportionality in the pharmacokinetic parameters of ribavirin after single dose administration of 400, 800 and 1200 mg of ribavirin. An equal number of male and female subjects participated in this study. Based on mean data from both males and females, the increases in AUC were dose proportional, however, C_{max} increased in a less than dose proportional manner. The percent of drug eliminated unchanged in the urine decreased as the dose increased. These observations, in the opinion of the Reviewer, may indicate saturable absorption of ribavirin in the gastrointestinal tract.

ABSOLUTE BIOAVAILABILITY

The absolute bioavailability of ribavirin was estimated by the stable isotope technique. Subjects received 150 mg of $^{13}C_3$-ribavirin intravenously and 400 mg of ribavirin orally. The absolute bioavailability of ribavirin was estimated to be ~ 60%.

BIOEQUIVALENCY

The capsule formulation manufactured by was used in some Phase 3 clinical trials. The Applicant conducted bioequivalence studies to compare the capsule formulation to the proposed market formulation (SP). The differences between these two formulations are

A *single dose (200 mg)*, parallel study design was employed in the bioequivalence study. The point estimates for SP formulation C_{max} and AUC were respectively with respect to formulation. In the bioequivalence study, A *single dose (600 mg)* of ribavirin was administered in this study. capsule was the reference product and capsule was the test product. The point estimates for C_{max} and AUC were

The results of this study indicates that the two formulations are bioequivalent. The point estimates for C_{max} and AUC_{0-12} were respectively.

DISTRIBUTION

The Applicant has characterized the pharmacokinetics of ribavirin after intravenous administration (as part of the absolute bioavailability study) and has conducted a mass balance study with ^{14}C–ribavirin.

The mean steady state volume of distribution after intravenous administration of 150 mg of ribavirin was 241 L and the mean residence time was 7.8 hours. The systemic clearance averaged 40.5 L/h (0.5 L/h/kg) after the intravenous dose of 150 mg. *In vitro* protein binding studies indicate that ribavirin does not bind to plasma proteins in the concentration range 0.2 to 20 µg/mL. The results from a ^{14}C-ribavirin study in six subjects indicate that the average apparent volume of distribution of ribavirin upon oral administration is large (2825 ± 255 L). This large volume of distribution may be due to extensive tissue uptake of ribavirin. Sequestration of ribavirin (presumably in the form of 5'-phosphates) within red blood cells has been reported by the Applicant and by other researchers. In a previously published report, the ratio of ribavirin concentrations in red blood cells to plasma, at steady-state, was calculated to be greater than 60.

METABOLISM AND ELIMINATION

In vitro studies indicate that the metabolism of ribavirin is not mediated by cytochrome P450 enzymes. It has been proposed that ribavirin undergoes deribosylation followed by amide hydrolysis to form 1,2,4,-triazole-3-carboxylic acid. Indeed, analysis of pooled urine samples obtained from a ^{14}C-ribavirin study conducted by the Applicant indicate the presence of 1,2,4-triazole-3-carboxamide and 1,2,4-triazole-3-carboxylic acid.

Following oral administration of 600 mg of ^{14}C-ribavirin, 61% and 12% of the orally administered radioactivity was recovered in urine and feces, respectively within 336 hours of dosing. Unchanged ribavirin in urine accounted for 17% of the administered dose. The mean terminal phase plasma half-life of ribavirin (when administered with interferon) after multiple dose administration was 274 hours.

DRUG INTERACTIONS

A significant pharmacokinetic interaction was not observed upon concomitant administration of ribavirin and interferon.

SPECIAL POPULATION

The Applicant conducted a single dose pharmacokinetic study in patients with hepatic dysfunction. Mean ribavirin C_{max} increased gradually as a result of increasing degree of hepatic dysfunction. However, significant differences were not seen in AUC_{0-t} values, in part, due to large variability in data. The effect of hepatic dysfunction on the multiple dose pharmacokinetics of ribavirin is not known.

Renal dysfunction resulted in significant changes in the single dose (400 mg) pharmacokinetics of ribavirin. Mean ribavirin C_{max} increased by approximately 2- fold, from 630 ng/mL in healthy subjects to 1161 ng/mL in subjects with impaired renal function (creatinine clearance between 10 to 30 mL/min). In these subjects, average AUC_{0-t} increased by three fold, from 9646 ng.h/mL to 31687 ng.h/mL. Since the impact of renal dysfunction on the multiple dose pharmacokinetics of ribavirin cannot be predicted, the Applicant will place the following statement in the WARNINGS section of the label "Combination INTRON A / REBETOL therapy should be used with caution in patients with creatinine clearance < 50 mL/min". This cutoff value was chosen from Phase III efficacy trials, in which subjects with serum creatinine value as high as 1.4 mg/dL (corresponding to an estimated creatinine clearance value of ~50 mL/min) participated.

The pharmacokinetics of ribavirin have not been assessed in the pediatric or geriatric patient population.

PK-PD CORRELATION

No studies have been performed. The Applicant is conducting a dose ranging study. Interim analysis results are presented in this review.

PK-DEMOGRAPHIC VARIABLE CORRELATION

The results of the population pharmacokinetic analysis are not clinically relevant due to the low statistical significance (r^2 = 0.29) of the model developed by the Applicant. A consultation was obtained from Dr. He Sun.

DISSOLUTION METHOD

The Applicant has proposed the following dissolution method:

This dissolution method and the dissolution specification, proposed by the Applicant are acceptable.

RECOMMENDATION

The human pharmacokinetic studies submitted under NDA 20903 provides an understanding of the pharmacokinetics of ribavirin when administered with interferon α-2b and fulfills the requirements of Section 320 of the Code of Federal Regulations (21 CFR). Adequate pharmacokinetic information have been provided to support approval of Intron® A / REBETOL® combination.

LABEL

The proposed label is attached to this review.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS BRIEFING

The briefing was held on April 16, 1998 and was attended by Drs. Malinowski, Reynolds, Ajayi, Pelsor, Lazor, Nguyen, Mahayini, Lesko, Chen, Bashaw, Jenkins and Rajagopalan.

PHASE IV COMMITMENTS

In a meeting on May 5, 1998, the Applicant agreed to assess the feasibility of potential clinical trial designs that might produce relevant data to address the question of whether dosing REBETOL with or without food in the clinical setting markedly changes the safety or efficacy profile.

5/13/98

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