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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

# BLA 103949/5002

# Clinical Pharmacology and Biopharmaceutics Review

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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| **BL/BLA** | : 103949/99-1488 | **REVIEWER:** Jooran S. Kim, Pharm.D. | |
| **TYPE** | : Consult for BLA Supplement | **SUBMISSION DATE** | : 2/5/01 |
| **DRUG** | : Ribavirin (200 mg oral capsules) | **DATE RECEIVED** | : 3/5/01 |
| **SPONSOR** | : Schering Corporation | **DRAFT REVIEW** | : 8/6/01 |

### BACKGROUND

Ribavirin was approved in 1998 for the treatment of chronic hepatitis C, in combination with interferon A (INTRON A). Although in vitro data suggest that ribavirin may possess antiviral activity against some DNA and RNA viruses, the mechanism of action for antiviral activity has not yet been elucidated. The current approved dose of ribavirin (given with INTRON A) is:

| Weight (kg) | Dose of Ribavirin (divided bid) |
|---|---|
| ≤ 75 kg | 1000 mg/day |
| >75 kg | 1200 mg/day |

A pegylated formulation of interferon A (PEG-INTRON) was recently approved by CBER for the treatment of chronic hepatitis C as monotherapy. The approved dose is 1.0 μg/kg weekly. A combination supplement has been submitted to CBER to seek approval for PEG-INTRON + ribavirin as dual therapy for chronic hepatitis C. This submission is currently under review.

**Summary of Ribavirin Pharmacokinetics** (please refer to Dr. Rajagopalan's review of ribavirin completed on 5/13/98)

Generally, the pharmacokinetics of ribavirin are variable. In subjects that received ribavirin 600 mg in the morning and 400 mg in the evening for 4 weeks, $C_{max}$ and $AUC_{12}$ values were 3230 [ ] ng/mL and 27800 [ ] ng*h/mL, respectively. For those that received ribavirin 600 mg bid, $C_{max}$ was approximately 3480 [ ] ng/mL and $AUC_{12}$ was 30300 [ ] ng*h/mL. $T_{max}$ of ribavirin was around 1.5 hours. Following single doses of ribavirin (400, 800 and 1200 mg), AUC was dose proportional, whereas $C_{max}$ was less than dose proportional. The percentage of unchanged drug eliminated in the urine decreased as the dose increased. These findings suggest that there may be saturable absorption of ribavirin in the GI tract and saturable urinary elimination. The bioavailability of ribavirin increased significantly (70%) with food. In regards to ribavirin metabolism, in vitro studies indicate that ribavirin is not metabolized by cytochrome P450 enzymes. It is, however, postulated that ribavirin may undergo deribosylation followed by amide hydrolysis. The apparent terminal half-life of ribavirin is approximately 274 hours after multiple dose administration. The long half-life may be due to sequestration of ribavirin into red blood cells. To date, the highest ribavirin dose the Agency has reviewed is 1200 mg/day.

### CBER Consult

The applicant submitted a BLA supplement (BL 103949/BLA 99-1488) to CBER seeking approval of PEG-INTRON plus ribavirin for the treatment of chronic hepatitis C. The pivotal trial is C/I 98-580. CBER consulted the Antivirals pharmacokinetics review team at CDER to evaluate a weight-based dosing regimen of ribavirin (administered with PEG-INTRON) proposed by the applicant. The following treatment arms were studied in C/I 98-580:

Treatment A: PEG-Intron 1.5 μg/kg qw plus Ribavirin 800 mg/day x 48 wks

Treatment B: PEG-Intron 1.5 μg/kg qw plus Ribavirin 1000/1200 mg/day x 4 wks
**then**
PEG-Intron 0.5 μg/kg qw plus Ribavirin 1000/1200 mg/day x 44 wks
Treatment C: Intron A 3MIU tiw plus Ribavirin 1000/1200 mg/day x 48 wks

Treatment A was superior to Treatments B and C, and therefore, PEG-INTRON 1.5 ug/kg once per week is being considered for approval. Based on a logistic regression analysis (and population PK and PK/PD analyses), the applicant has proposed the following dosing regimen of ribavirin, when used in combination with PEG-INTRON 1.5 μg/kg once a week:

| Weight (kg) | Dose of Ribavirin (divided bid) |
|---|---|
| <40 to 64 | 800 mg/day |
| 65 to 85 | 1000 mg/day |
| 86 to 105 | 1200 mg/day |
| > 105 | 1400 mg/day |

The pharmacokinetics review team consulted pharmacometric (PM) specialists, Drs. Jenny Zheng and Sue-Chi Lee, for this review. The purpose of this PM consult was to determine if the applicant's analyses supported the proposed dosing regimen of ribavirin. In addition to C/I 98-580, the applicant submitted the report for Study [ ] (SCH 54031: Safety and tolerability of combined ribavirin and PEG-Interferon alfa-2b in subjects with chronic hepatitis C) to support the weight-based dosing regimen of ribavirin. Data from this study were not reviewed because subjects weighing > 105 kg were not enrolled (upper limit was 96 kg), PEG-INTRON doses were completely different to those studied in C/I 98-580, and there were a small number of patients (n=6) per dosing arm. Therefore, the PM consult focused on Study C/I 98-580.

Later in the review cycle, the CBER review team indicated they were considering a 600 mg/day ribavirin dose for patients who weigh less than 60 kg. The PK and PM consults did not evaluate the appropriateness of the 600 mg/day dose, because the submitted analyses did not address that dose in the proposal.

Dr. Lee mainly reviewed the population PK study from C/I 98-580. At this time, the PK/PD data are insufficient to support the applicant's weight-based dosing proposal. We may address this dosing proposal further once the sponsor has addressed the comments from her review. The sponsor has indicated that a study using the weight-based dosing of ribavirin is currently ongoing.

Jooran S. Kim, Pharm.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

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**BLA:** 99-1488 (STN:103949/5002) **DOCUMENT DATE:** 2/5/01
**BB IND:** [redacted] **SUBMISSION DATE:** 3/29/01
**PRODUCT:** PEG-Intron and REBETOL
(Peginterferon alfa-2b for injection and ribavirin capsules)
**SPONSOR:** Schering
2000 Galloping Hill Road, Kenilworth, NJ 07033
**TYPE OF SUBMISSION:** Supplemental application **REVIEWER:** Sue-Chih Lee, Ph.D.
Consult from CBER

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## NOTE

The supplemental application was submitted to CBER to support the use of PEG-interferon alfa-2b and ribavirin for the treatment of chronic hepatitis C. Ribavirin is approved for use with interferon alfa-2b (Intron A) for the same indication while PEG-Intron monotherapy is approved for the treatment of chronic hepatitis C in patients not previously treated with interferon alpha who have compensated liver disease. In the supplemental application, the sponsor also proposes a new weight-based dosing regimen for ribavirin. Hence, a consult was made to the Division of Antiviral Drug Products in CDER to review this proposed dosing recommendation. This review addresses only the population PK and PD analyses for ribavirin. Dr. Jooran Kim is the primary Clinical Pharmacology and Biopharmaceutics Reviewer for this submission.

## REVIEW

The proposed dosing regimen for ribavirin in the PEG-Intron and REBETOL dual therapy is listed in the table below. For easy comparison, the approved dosing regimen for ribavirin in the Intron A and REBETOL combination therapy is also included in the table.

| Product | Body Wt. (kg) | Ribavirin BID Doses (mg) |
|---|---|---|
| PEG-Intron and REBETOL (Proposed) | Proposed Weight-Based Dosing Regimen for Ribavirin | |
| | [redacted] | [redacted] |
| | 65-85 | 400/600 |
| | 86-105 | 600/600 |
| | > 105 | 600/800 |
| Intron A and REBETOL (Approved) | Approved Dosing Regimen for Ribavirin | |
| | ≤ 75 | 400/600 |
| | > 75 | 600/600 |

The PK/PD analyses for ribavirin was conducted to support the weight-based dosing regimen for ribavirin in the PEG-Intron and REBETOL dual therapy. The analysis used data from clinical study C/I98-580 which was conducted in patients with chronic hepatitis C to evaluate the safety and efficacy of two PEG-Intron/REBETOL regimens compared to standard therapy of INTRON A/REBETOL. This was a multicenter, randomized, open-labeled, active-controlled, parallel group Phase III study with a treatment period of 48 weeks and a 24-week follow-up. A total of 1580 patients were randomized and 1530 were treated. The three treatments were:

a) I/R; N=505 — INTRON A (3 MIU SC TIW)
Rebetol (≤75 kg: BID as 400 mg/600 mg;
>75 kg: BID as 600 mg/600 mg)

b) PEG 1.5/R; N=511 — PEG-Intron (1.5 μg/kg SC QW)
REBETOL (BID as 400 mg/400 mg)

c) PEG 0.5/R N=514 — PEG-Intron (1.5 μg/kg SC QW for 4 weeks
then 0.5 μg/kg SC QW for 44 weeks)
Rebetol (≤75 kg: BID as 400 mg/600 mg;
>75 kg: BID as 600 mg/600 mg)

Single serum samples for determination of ribavirin concentrations were obtained at treatment weeks 12, 24, and 48 during routine clinic visits.

## A. Population PK Analysis

A total of 2911 valid concentrations from 1367 patients comprised the data set. Covariates in the analysis included body weight, age, gender, serum creatinine, and creatinine clearance. The demographics are given in the table below:

Table A1.1 Summary of Patient Demographics

| Study | N (N F N M) | Age (yr) | Weight (kg) | Sr.Cr. (mg/dL) | CLcr(mL/hr) | Race(C/B/O)[3] | Treatment(A,B,C)[4] |
|---|---|---|---|---|---|---|---|
| ALL | 1367(468, 899) | 44 (21-68) | 82.5 (38-181) | 0.79 (0.38-1.47) | 135 (53-340) | (1227,63, 77) | (458, 448, 461) |
| C98580[1] | 910(306, 604) | 44 (22-68) | 86.4 (43-181) | 0.80 (0.40-1.40) | 141 (53-340) | ( 796,61, 53) | (303, 301, 306) |
| I98580[2] | 457(162, 295) | 42 (21-68) | 74.6 (38-131) | 0.78 (0.38-1.47) | 125 (54-269) | ( 431,2, 24) | (155, 147, 155) |

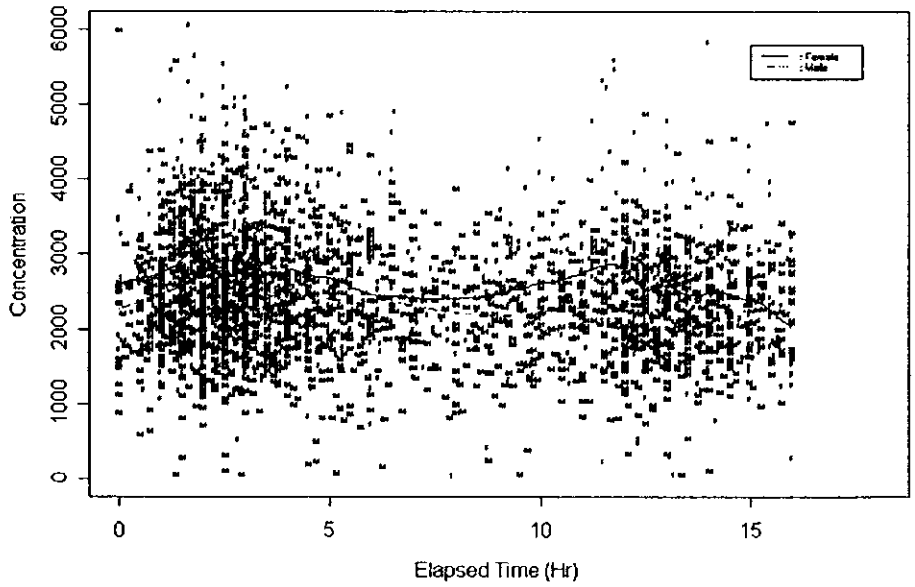
[1]US centers.
[2]Non-US centers from same protocol.
[3]Caucasian, Black and others
[4]Treatment A: Intron-A + Ribavirin; Treatment B: PEG1.5/R; Treatment C: PEG0.5/R

The concentration-elapsed time plot is shown below. The peak and trough fluctuation is not pronounced after multiple doses of ribavirin. Therefore, a steady-state infusion model was used to fit the ribavirin concentrations with ribavirin apparent clearance ($CL_{app}$) as the primary pharmacokinetic parameter, i.e.,

$$Css = Dose/24/CLapp$$

where Dose was the total daily ribavirin dose and $CL_{app}$ was the apparent clearance of ribavirin.

Figure: Ribavirin Concentrations vs. Elapsed Time between Last Dose and Blood Sampling




Note: Data points are designated by genders (M: male; F: female). Two smoothing lines are added (dash line: males; solid line: females)

Apparent clearance ($CL_{app}$) was modeled as a function of covariates, including age, body weight, gender, serum creatinine, and creatinine clearance. Apparent clearance was assumed to be log-normally distributed. The residual variability included both additive and constant CV (coefficient of variation) terms. Covariate evaluation was included in the model building process. The contribution of a covariate in a model was determined by the increase in the objective function from the model with the covariate removed (reduced model). This increase was compared to a Chi-square distribution for statistical significance ($\alpha$= 0.005). Mixed-effects modeling was employed to analyze the data. The model building and parameter estimation were carried out using NONMEM.

*Sponsor's analysis results and conclusion:*

The sponsor concluded that body weight affected the apparent clearance of ribavirin, and was the most important covariate. Other covariates in the model (Model 11) included age, gender, and serum creatinine. Incorporating different power functions for subjects younger and older than 40 years did not improve the objective function significantly. Clearance increased as a function of body weight and reduced as age or serum creatinine increased. Mean ribavirin clearance estimates were 18.3 L/hr for a typical male patient, and 13.5 L/hr for a typical female patient. The intersubject variability was 24%. The residual variability was 17% at the ribavirin concentration level of 2500 ng/mL.

## B. PD Analyses

Data:
Only patients receiving Treatment B (PEG-Intron 1.5μg/kg + ribavirin 800 mg/day) were included in the efficacy analysis since PEG-Intron dose level influenced the efficacy outcome.

Efficacy (448 patients):
Sustained virologic response was used as the efficacy measure and was defined as loss of detectable serum HCV-RNA (defined as qPCR < 100 copies/mL) at or after follow-up week 12. Logistic regression was performed and covariates examined were HCV genotype, baseline viral load (using $2x10^6$ copies/mL as the cutoff), ribavirin steady state concentration and age.

Toxicity (1341 patients):
Toxicity event was defined as having a hemoglobin level of <10.5 g/dL at treatment week 4. Again logistic regression was performed and covariates investigated were ribavirin Css and baseline hemoglobin level; body weight and age.

*Sponsor's analysis results and conclusion:*

The following results are based on the sponsor's population PK and PD analyses and simulations.

Efficacy: Higher ribavirin concentrations were associated with a higher chance of response. HCV genotype and baseline viral load had substantial impact on response, with HCV genotype one and high baseline virus count having the lowest chance of response. Age was less influential but statistically significant.

Safety: Ribavirin concentration and baseline hemoglobin level were the most important factors; patients with high ribavirin concentration and low baseline hemoglobin had the highest risk of experiencing toxicity. Body weight and age were also included in the toxicity model for their statistical significance.

Simulation results: The four ribavirin dosage regimens (in combination with PEG-Intron 1.5 mg/kg) evaluated are as follows:

- S1: 800 mg/day for every patient;
- S2: 1000/1200 mg/day based on WT ≤75/>75 kg;
- S3: 13 mg/kg/day; and
- S4: 800/1000/1200 mg/day based on WT <65/65-85/>85 kg;

The predicted sustained response rate and hematological toxicity event rate are given in the two tables below. Simulation scenarios S3 and S4 most closely resembles the proposed weight-based dosing regimen. The sponsor considers that these regimens are superior to the fixed 800 mg/day dosage in response rate and their toxicity event rates will still be lower than that for a ribavirin dose of 1000/1200 mg/day (Simulation scenario S2). (Reviewer's note: The sponsor did not indicate the weight range used in the simulation for the open-ended weight categories.)

**Table 1** Response Rates for the Four Ribavirin Dose Regimens.

| Dose Regimen | Overall | Genotype Non-1 | Genotype 1 |
|---|---|---|---|
| S1: 800 mg/day | 58.3 | 83.8 | 46.3 |
| S2: 1000/1200 mg/day | 66.8 | 88.8 | 56.3 |
| S3: 13 mg/kg/day | 65.0 | 87.6 | 54.3 |
| S4: 800/1000/1200 mg/day | 64.6 | 87.6 | 53.7 |

Note: Responses are in percent.

**Table 2** Toxicity Event Rates for the Four Ribavirin Dose Regimens: (Event: Hemoglobin at Treatment week 4 < 10.5 g/dL)

| Dose regimen | Event Rate (%) |
|---|---|
| S1: 800 mg/day | 5.6 |
| S2: 1000/1200 mg/day | 10.3 |
| S3: 13 mg/kg/day | 7.8 |
| S4: 800/1000/1200 mg/day | 8.1 |

## CONCLUSION

It is noted that the data set used in the analyses may contain errors, certain assumptions are explicitly or implicitly made in the model without adequate supporting evidence, and the final simulations do not provide an estimate of safety and efficacy for each weight range as specified in the proposed weight-based dosing recommendation. (See below for specific comments.) Therefore, the PK/PD information provided is insufficient to support the weight based dosing regimen as proposed by the sponsor.

## COMMENTS

The efficacy and safety measures used in the analyses were considered appropriate by Dr. Libero Marzella, the Medical Officer in CBER.

After a review of the PK/PD information provided regarding ribavirin, we communicated most of the following comments to the sponsor. The comments in italic are those yet to be conveyed to the sponsor.

1) Regarding the population PK (PPK) analysis:

a. The ribavirin concentration-time profile at steady state was assumed to be flat. (The scatter plot provided pooled all doses together causing a wider spread of concentrations at any given time point.) The sponsor did not discuss the error associated with this assumption. This error may be assessed through simulations using Phase I/II data.

b. It appears that total body weight was used in the calculations of creatinine clearance. The sponsor should revise the calculations by using the ideal body weight instead. Additionally, it is noted that at least 25% of the patients had serum creatinine below 0.8 mg/dL with the lowest being 0.38 mg/dL. Please explain or correct as appropriate.

c. The PPK model has an implicit assumption of dose proportionality. The sponsor should provide information that confirms dose proportionality up to the highest recommended dose (1400 mg/day) upon multiple dosing.

*d. The 1000 mg/day dose was administered as two doses (400 mg plus 600 mg). The sponsor should assess the error in parameter estimate arising from this dosing regimen.*

e. The sponsor allowed separate estimates of covariate "coefficients" for male and female subjects in the PPK analysis. This reviewer has reanalyzed the data by treating gender as one covariate and keeping coefficients for all other covariates the same for both genders. We recommend the latter method be used unless there are reasons to do otherwise.

f. Although weight appears to be a statistically significant factor for exposure (or Css), the sponsor did not provide information on how incorporating weight into the model changes the variabilities. (Based on this reviewer's analysis, the reduction in variabilities is low. Therefore, weight does not lend itself as an apparent factor for dose adjustment. Further examination on how the dose adjustment translates into better risk/benefit ratio is needed. In this regard, the sponsor did perform PD analyses for both efficacy and safety.)

2) Regarding the PD analyses:

Through simulation, the sponsor compared the safety and efficacy of the weight-based dosing regimens to those of the clinical trial dose (800 mg/day). This assessment was conducted lumping all patients together. The sponsor should conduct simulations to evaluate the impact on safety and efficacy for each weight range specified in the weight-based dosing recommendation. This simulation should take into account the PK and PD variabilities/distributions. *Since some weight categories are open-ended (e.g. >105 kg), the sponsor should indicate the actual weight ranges used in the simulation with justifications.*

## RECOMMENDATION

The PK/PD information provided is insufficient to support the weight based dosing regimen as proposed by the sponsor. The sponsor should address the above comments. Once the sponsor provides the requested information, we can re-evaluate the weight-based dosing regimen.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT initialed by Kellie Reynolds, Pharm.D. _____

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling