CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-511

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-511	Submission Date(s): June 3, 2002 ADD OTHER DATES
Brand Name	Copegus
Generic Name	Ribavirin
Reviewer	Kellie Schoolar Reynolds, Pharm.D. and Jooran Kim, Pharm.D.
Secondary Reviewer	Arzu Selen, Ph.D.
Pharmacometrics Reviewer	Jenny J. Zheng, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation III
ORM division	Division of Antiviral Drug Products
Applicant	Hoffman La Roche
Relevant IND(s)	IND 58,827
Formulation; Strength(s)	200 mg tablets
Indication	Chronic hepatitis C virus (in combination with peginterferon alpha 2a)

1 Executive Summary

The applicant submitted NDA 21-511 to seek approval of Copegus™ (ribavirin) for use in combination with Pegasys® (peginterferon alpha-2a) for the treatment of chronic hepatitis C virus. CBER is reviewing BLA 125061-0 for peginterferon alpha-2a combination use with ribavirin. Peginterferon alpha-2a is approved as monotherapy for the treatment of hepatitis C.

The applicant submitted this application under 505 (b)(1), although some of the information is based on literature and gives the appearance of a 505 (b)(2) application. The NDA includes three bioavailability and bioequivalence studies, a single dose food effect study (proposed commercial tablet), a multiple dose food effect study (Schering Rebetol capsules), and multiple dose pharmacokinetic data from a subset of patients in the pivotal clinical trials. For most clinical pharmacology information, the applicant references literature articles. However, the applicant does not provide the raw data for review. Most of the clinical pharmacology information provided in references is the same information reviewed under NDA 20-903 (Rebetol, ribavirin from Schering Corporation). The raw data and full study reports were provided with NDA 20-903. NDA 21-511 is a 505 (b)(1) application, and the applicant does not have the right of reference to the raw data supporting the referenced clinical pharmacology studies. Although the clinical pharmacology information is of limited value in the current application, a summary is included as an appendix to this review (page 20). The applicant conducted studies deemed essential to drug approval during the review cycle. Other important clinical pharmacology studies will be Phase 4 commitments.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the information submitted to the Human Pharmacokinetics and Biopharmaceutics Section of NDA 21-511. In general, the information presented is acceptable and supports approval of the proposed ribavirin 200 mg tablet formulation. There were some problems noted in the biopharmaceutics studies, including inadequate washout period and predose ribavirin concentrations prior to period 1. However, these problems do not alter the overall conclusions of the studies.

Based on review of the clinical pharmacology and biopharmaceutics information, there are several recommendations-

- The applicant should provide information, including data, about the metabolic route and enzymes involved in the metabolism of ribavirin.

- The applicant should determine appropriate dosing recommendations for patients with renal impairment. Until the dosing recommendations are established, the label will indicate that patients with CrCl< 50 mL/min should not receive ribavirin. The safety data from the pivotal clinical trials evaluating the combination of peginterferon alpha-2a plus ribavirin support this cutoff value.

- The applicant should determine the effect of hepatic impairment on ribavirin pharmacokinetics.

- The applicant should further evaluate the relationship between body weight and ribavirin exposure. The evaluations should include an assessment of the impact on safety and efficacy.

- The applicant should determine whether race affects ribavirin pharmacokinetics.

- The applicant should determine whether ribavirin induces CYP enzymes.

- The applicant should determine the extent to which ribavirin is bound to plasma proteins.

1.2 Phase IV Commitments

The following Phase IV commitments are related to clinical pharmacology:

- Determine the metabolic route and enzymes involved in the metabolism of ribavirin.

- Determine appropriate dosing recommendations for patients with renal impairment.

- Determine the effect of hepatic impairment on ribavirin pharmacokinetics.

- [redacted]

- Determine whether race affects ribavirin pharmacokinetics.

- Determine whether ribavirin induces CYP enzymes.

- Determine the extent to which ribavirin is bound to plasma proteins.

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The proposed indication for COPEGUS™ (ribavirin) tablets, in combination with PEGASYS® (Peginterferon alpha-2a), is the treatment of chronic hepatitis C in patients with compensated liver disease. Current approved therapies for chronic hepatitis C are:

PEGASYS (Peginterferon alpha-2a) monotherapy; Roche
PEGINTRON (peginterferon alpha-2b) monotherapy; Schering
INTRON A (Interferon alpha-2b) monotherapy; Schering
PEGINTRON (peginterferon alpha-2b) plus REBETOL (ribavirin); Schering
INTRON A (Interferon alpha-2b) plus REBETOL (ribavirin); Schering

Ribavirin monotherapy is not effective for treatment of chronic hepatitis C. The mechanism by which ribavirin plus interferon alpha exerts its effects against HCV is not known.

The applicant submitted six studies in support of ribavirin tablet approval. In addition to the biopharmaceutics studies, they submitted a small phase 2 study that evaluated the safety and efficacy of peginterferon alpha-2a (PEG-IFN alpha-2a) plus ribavirin (capsules); the study included a food effect assessment. The application includes two phase 3 clinical trials evaluating the safety and efficacy of PEG-IFN alpha-2a plus ribavirin in the treatment of chronic hepatitis C. For a majority of the clinical pharmacology information, the applicant relied on literature information. Most of the clinical pharmacology information provided in references is the same information reviewed under NDA 20-903 (Rebetol, ribavirin from Schering Corporation). The raw data and full study reports were provided with NDA 20-903. NDA 21-511 is a 505 (b)(1) application, and the applicant does not have the right of reference to the raw data supporting the referenced clinical pharmacology studies. Although the clinical pharmacology information is of limited value in the current application, a summary is included as an appendix to this review (page 20). The applicant conducted studies deemed essential to drug approval during the review cycle. Other important clinical pharmacology studies will be Phase 4 commitments.

The following dosing recommendations will appear in the COPEGUS label:

Genotype	PEGASYS Dose (injection)	COPEGUS Dose (oral)- divided twice daily, administer with food.	Duration
Genotype 1 or 4	180 µg once per week	<75 kg = 1000 mg per day ≥75 kg = 1200 mg per day	48 weeks 48 weeks
Genotype 2 or 3	180 µg once per week	800 mg per day	24 weeks

The dosing recommendations are based on the results of the phase 3 clinical trials. The applicant selected ribavirin doses for evaluation based on the approved doses of REBETOL. The applicant did not conduct any ribavirin dose ranging studies.

The current application supports the following conclusions.

Clinical Pharmacology

- Sequestration of ribavirin (presumably in the form of 5'-phosphates) within red blood cells has been reported. The ratio of ribavirin concentrations in red blood cells to plasma, at steady-state, was greater than 60.

- Ribavirin PK parameters do not change over time with chronic dosing.

- In study NV15801 (pivotal clinical trial), full concentration vs time profiles were collected from a subset of patients. For subjects receiving PEG-IFN alpha 2a once weekly and 1000 mg ribavirin per day (patients <75 kg; n=12), the mean ± SD week-12 AUC_{0-12h} and Cmax were 29.6 ± 8.2 μg*hr/mL and 3139 ± 850 ng/mL, respectively. For subjects receiving PEG-IFN alpha 2a once weekly and 1200 mg ribavirin per day (patients ≥75 kg; n=39), the mean ± SD week-12 AUC_{0-12h} and Cmax were 25.4 ± 7.1 μg*hr/mL and 2748 ± 818 ng/mL, respectively.

- The applicant did not evaluate the effect of renal impairment on ribavirin pharmacokinetics. The safety data from the pivotal clinical trials support administration of ribavirin to patients with CrCl ≥ 50 mL/min.

- The applicant did not evaluate the effect of hepatic impairment on ribavirin pharmacokinetics. The safety data from the pivotal clinical trials support administration of ribavirin to patients with mild hepatic impairment (Child-Pugh Class A).

- The phase 3 data indicate that efficacy was lower in heavy patients compared to light patients. The applicant evaluated the relationship between weight and ribavirin concentration in both pivotal clinical trials. A pharmacometrics consult indicates ribavirin exposure is associated with body weight. Heavy patients tend to have lower exposure. However, body weight explains only a small portion (~15%) of the variability in ribavirin exposure.

- Dose adjustments are not needed due to sex or age (elderly). The current application does not address pediatric patients. The data submitted by the applicant do not allow an assessment of the effect of race on ribavirin pharmacokinetics.

- Ribavirin is not a substrate for CYP enzymes and does not inhibit CYP enzymes. Adequate data are not available to determine whether ribavirin induces CYP enzymes. The application does not provide any information regarding P-glycoprotein (PGP) interactions.

- The label specifies coadministration of ribavirin with PEG-IFN alpha-2a. Data indicate a PK interaction between the two products is not likely. The pivotal clinical trials were conducted with the combination of PEG-IFN alpha-2a and ribavirin. Thus, even if there is a pharmacokinetic interaction, the safety and efficacy of the combination is known.

Biopharmaceutics

- The applicant used formulations F3 and F6 in pivotal clinical trials, but will market formulation F12. The 3 formulations are almost identical. The applicant conducted a randomized crossover study (NR16231) to evaluate the bioequivalence of ribavirin tablets intended for commercial use to ribavirin tablets used in clinical trials. There were quantifiable Period 1 predose concentrations, which make the integrity of the study questionable. The Division of Scientific Investigations (DSI) inspected the analytical and clinical sites for the study. The reports indicate that the eleven subjects with

quantifiable Period 1 predose concentrations should be excluded from bioequivalence calculations. Deleting the subjects with quantifiable Period 1 predose concentrations does not alter the conclusion of bioequivalence. Thus, the formulations are bioequivalent.

- The proposed commercial Roche ribavirin tablet is bioequivalent to the currently marketed Schering ribavirin capsule.

- The two tablet formulations used in pivotal clinical trials (F3 and F6) provide similar ribavirin exposure (AUC) to each other, although the dissolution rate is slower for the F6 formulation. Cmax may be slightly lower for the F6 formulation, compared to the F3 formulation.

- In a parallel study, mean AUC and Cmax are 5 to 20% lower for the clinical trial Roche ribavirin formulations (F3 and F6) compared to the currently marketed Schering ribavirin capsule formulation.

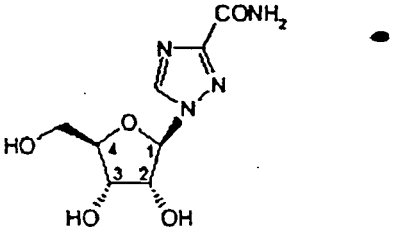
- There is a significant effect of food on ribavirin exposure. Following a high fat meal, ribavirin AUC increased by approximately 42% and Cmax increased by approximately 66%. The label includes information about the effect of food. The label recommends that patients take ribavirin with food, as done in clinical trials.

4 Review

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Summary of the physical-chemical properties of ribavirin

Property	Description
Chemical name	1-β-D-Ribofuranosyl1-1H-1,2,4-triazole-3-carboxamide
Structural formula	
Molecular formula	$C_8H_{12}N_4O_5$
Molecular weight	244.2
Appearance	White to off-white powder; may contain lumps
Crystal form	Crystalline
Melting point	[redacted]
Partition coefficient Log P (1-octanol/water)	[redacted]
Dissociation constant (pKa)	[redacted]

Quantitative Formulation

Ingredients	Weight per tablet	Function
Ribavirin	200 mg	Active ingredient
Pregelatinized starch Sodium starch glycolate Microcrystalline cellulose Corn starch Magnesium stearate	[redacted]	[redacted]
Film Coat- Chromatone-P [redacted] or Opadry Pink [redacted] Ethylcellulose [redacted] Triacetin	[redacted]	[redacted]

4.1.2 What is the proposed mechanism of drug action and therapeutic indications?

Proposed indication

Ribavirin in combination with peginterferon alpha-2a is indicated in patients who have not been previously treated with interferon alpha and are at least 18 years of age for the treatment of chronic hepatitis C. The indication is limited to patients [redacted] with compensated liver disease.

Proposed mechanism of action
Ribavirin is a synthetic nucleoside that has shown in vitro activity against some RNA and DNA viruses. It also has immunomodulatory activity. The mechanism by which ribavirin plus interferon alpha exerts it effects against HCV is not known.

4.1.3 What is the proposed dosage and route of administration?

The proposed daily dose of ribavirin is 800 mg to 1200 mg administered orally in two divided doses. The dose is individualized to the patient depending on baseline disease characteristics (genotype), response to therapy, and tolerability of the regimen. Patients should take ribavirin with food.

Dosing recommendations

Genotype	PEGASYS Dose (injection)	COPEGUS Dose (oral)	Duration
Genotype 1 or 4	180 µg once per week	<75 kg = 1000 mg per day ≥75 kg = 1200 mg per day	48 weeks 48 weeks
Genotype 2 or 3	180 µg once per week	800 mg per day	24 weeks

The label also recommends dose modifications, based on adverse events
If severe adverse reactions or laboratory abnormalities develop during combination COPEGUS/PEGASYS therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, COPEGUS/PEGASYS therapy should be discontinued.

COPEGUS should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped.

The dose of COPEGUS should be reduced to 600 mg per day (200 mg in the morning and 400 mg in the evening) if either of the following is confirmed:

- A patient without significant cardiovascular disease experiences a fall in hemoglobin to <10 g/dL and ≥8.5 g/dL or
- A patient with stable cardiovascular disease experiences a fall in hemoglobin by ≥2 g/dL during any 4 weeks of treatment.

COPEGUS should be discontinued under the following circumstances:

- If a patient without significant cardiovascular disease experiences a confirmed decrease in hemoglobin to < 8.5 g/dL.
- If a patient with stable cardiovascular disease maintains a hemoglobin value <12 g/dL despite 4 weeks on a reduced dose.

Once the patient's COPEGUS dose has been withheld due to either a laboratory abnormality or clinical manifestations, an attempt may be made to restart COPEGUS at 600 mg daily and further increase the dose to 800 mg daily depending upon the physician's judgment. However, it is not recommended that COPEGUS be increased to its original assigned dose (1000 mg to 1200 mg).

Renal Impairment
COPEGUS should not be used in patients with creatinine clearance <50 mL/min.

4.1.4 What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study?

There are two pivotal phase 3 clinical trials in this application.

Study NV15801 was designed to demonstrate superiority of PEG-IFN alpha-2a and ribavirin combination therapy over IFN alpha-2b and ribavirin combination therapy. Patients received one of the following treatments in this randomized, multicenter, partially blinded, active-controlled and placebo-controlled study.

- PEG-IFN alpha-2a (180 µg) once weekly (N = 227)
- PEG-IFN alpha-2a (180 µg) once weekly plus ribavirin (1000 or 1200 mg) daily (N = 465)
- 3 MIU of IFN alpha-2b three times weekly plus ribavirin (1000 or 1200 mg) daily (N = 457)

All treatments were for 48 weeks, with a 24-week treatment-free follow-up.

Study NV 15942 was designed to evaluate treatment duration for PEG-IFN alpha 2a and ribavirin combination therapy and ribavirin dose. Patients received one of the following four treatments in this randomized, multicenter, partially blinded study.

- PEG-IFN alpha-2a 180 µg and 800 mg of ribavirin for 24 weeks (N = 207)
- PEG-IFN alpha-2a 180 µg and 1000 or 1200 mg of ribavirin for 24 weeks (N = 280)
- PEG-IFN alpha-2a 180 µg and 800 mg of ribavirin for 48 weeks (N = 361)
- PEG-IFN alpha-2a 180 µg and 1000 or 1200 mg of ribavirin for 48 weeks (N = 436)

All treatment groups had a 24-week treatment-free follow-up.

The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Anemia (hemoglobin <10 g/dL) was observed in approximately 13% of patients who received PEG-IFN alpha-2a plus ribavirin in the pivotal clinical trials.

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy parameter in the clinical trials was a combined sustained virological and biochemical response at week 72 (24 weeks following completion of treatment). A patient was considered a sustained responder with a normal serum ALT concentration and an undetectable HCV RNA titer at the end of the follow-up period. At the time clinical trials were designed, the combined virological and biochemical response was standard. However, the current standard endpoint is sustained suppression of HCV RNA 24 weeks following cessation of therapy.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The concentration of ribavirin in human plasma was determined by a validated [redacted] method using [redacted] The assay is acceptable. See section 4.6 for further details.

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

4.2.3.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The current application does not include additional adequate information to assess dose proportionality. The applicant evaluated the safety and efficacy of ribavirin at all of the proposed doses (800 mg per day, 1000 mg per day in pts <75 kg, 1200 mg per day in pts ≥75kg). Full pharmacokinetic profiles or trough concentration data are available for each of those doses. The applicant did not provide pharmacokinetic data from patients who received 600 mg ribavirin per day. Patients who experience ribavirin associated adverse events may have their ribavirin dose reduced to 600 mg per day.

4.2.3.2 Do PK parameters change with time following chronic dosing?

Pharmacokinetic data collected in the two pivotal clinical trials indicate that ribavirin PK parameters do not change with time following chronic dosing.

In study NV15492, trough samples were collected from a subset of patients at weeks 4, 8, 12, 24, and 48. The data for the 4 groups are summarized in the table below. It is likely that some subjects did not reach steady-state by the week four assessment. Trough concentrations do not change between weeks 8 and 48.

Summary of Ribavirin Trough Concentrations at 24 and 48 Weeks of Combination Treatment
Arithmetic mean ± SD (N)

Ribavirin Dose and Duration	Week 4	Week 8	Week 12	Week 24	Week 48
800 mg/d, 24 wks	1427 ± 566 N = 21	1667 ± 492 N = 22	1705 ± 339 N = 21	1761 ± 512 N=19	not applicable
1000 or 1200 mg/d, 24 wks	2038 ± 727 N = 32	2144 ± 606 N = 34	2363 ± 940 N = 33	2096 ± 906 N = 31	not applicable
800 mg/d, 48 wks	1514 ± 516 N = 35	1774 ± 690 N = 37	1719 ± 550 N = 38	1823 ± 507 N = 34	1640 ± 587 N = 29
1000 or 1200 mg/d, 48 wks	1825 ± 560 N = 31	2133 ± 669 N = 31	2167 ± 610 N = 32	2272 ± 761 N = 31	1997 ± 629 N = 22

In study NV15801, full concentration vs time profiles were collected from a subset of patients at weeks 12 and 48. For subjects receiving PEG-IFN alpha 2a once weekly and 1000 or 1200 mg ribavirin per day, the mean ± SD week-12 AUC_{0-12h} and Cmax were 26.3 ± 7.5 μg*hr/mL and 2840 ± 834 ng/mL, respectively (N = 51). The week-48 AUC_{0-12h} and Cmax were 24.5 ± 9.4 μg*hr/mL and 2852 ± 1266 ng/mL, respectively (N = 36).

It is difficult to compare single dose PK to multiple dose PK, because most single dose studies were conducted under fasting conditions and subjects received a 600 mg dose. In the multiple-dose studies discussed above, subjects took ribavirin with food (not standardized meals) and received 1000 mg per day (400 mg in am; 600 mg in pm) or 1200 mg per day (600 mg bid). However, in single-dose studies in healthy volunteers, $AUC_{0-\infty}$ following administration of 600 mg ribavirin ranged from approximately 22 to 28 μg*hr/mL. Thus, apparent clearance is similar following single and multiple doses of ribavirin. Terminal half-life was 177 ± 116 hours at week 48 in study NV15801, which is similar to the mean elimination half-life estimated following single doses (130 to 160 hours).

4.2.3.3 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?
There is no formal relationship established between ribavirin concentrations and efficacy or safety. The applicant selected the ribavirin doses for evaluation (800 mg per day or 1000 or 1200 mg/day)

based on previous large clinical trials. The previous investigators did not evaluate ribavirin dose or concentration-response relationships.

The issue of weight-based dosing of ribavirin is not resolved. This issue was first raised in BLA supplement 103949/99-1488 from Schering (pegylated interferon A + ribavirin). The applicant (Schering) conducted analyses indicating that efficacy was lower in heavy patients, compared to light patients. In addition, toxicity was greater in the lighter patients compared to heavier patients. Based on their analyses, Schering proposed daily doses of 800 to 1400 mg, based on weight category. The weight based regimen was not approved, because Schering did not provide adequate PK, safety, and efficacy data to indicate that the weight-based regimen is safe and effective. Schering is conducting a large Phase 4 study to evaluate the weight-based regimen.

The Roche ribavirin application does not include a proposal for a weight based dosing regimen. The phase 3 data do indicate that efficacy was lower in heavy patients compared to light patients. The applicant evaluated the relationship between weight and ribavirin concentration in both pivotal clinical trials. This topic is discussed further in section 4.3.2.7 of this review.

4.2.4 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

HCV patients participated in all ribavirin PK studies submitted in this application, there were no healthy volunteers.

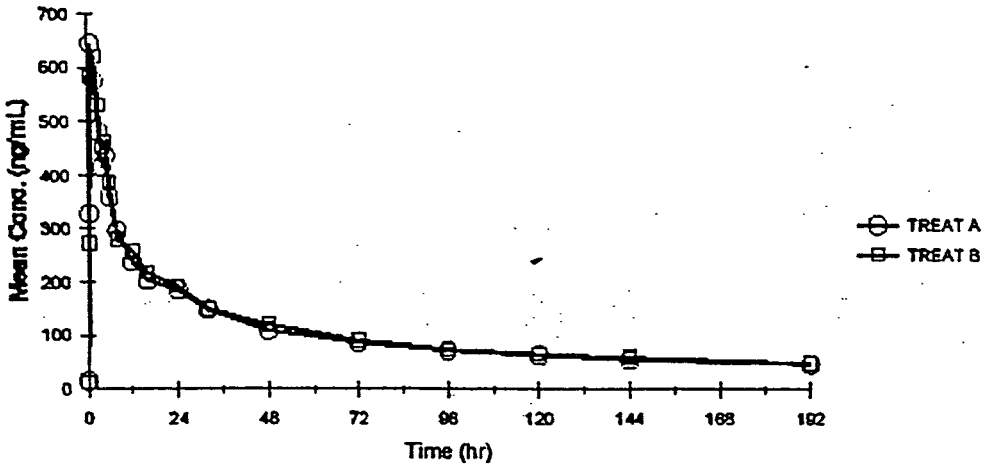
4.2.4.1 What are the basic PK parameters for ribavirin?

Results from study BP16320 summarize ribavirin pharmacokinetics following administration of a single 600 mg dose to fasted subjects.

Ribavirin Pharmacokinetic Parameters Following 600 mg Single Dose

Parameter (Units)	Geometric mean (%CV) N = 40	
AUC (0-192h) (µg*h/mL)	19.8 (31.2)	
Cmax (ng/mL)	695 (32.9)	
Tmax (h) (Median and range)	2.0 (0.5 – 6.0)	
AUC∞ (µg*h/mL)	28.2 (32.4)	N=34
T½ (h) (Harmonic mean)	127 (31.5)	N=34

The following figure illustrates the concentrations vs. time profile following administration of a single 600 mg dose of ribavirin (Study BP16320). Note: treatment A is Schering ribavirin and treatment B is Roche ribavirin.

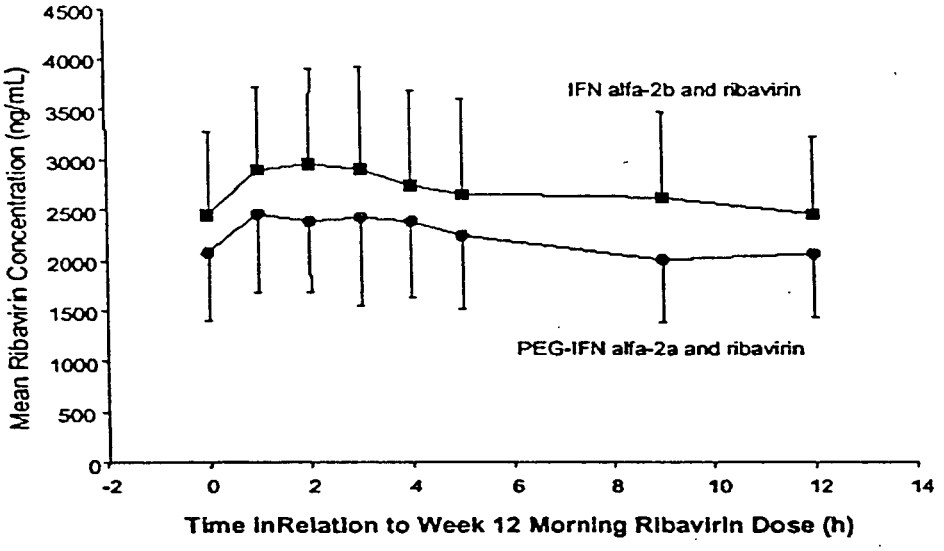


Results from study NV15801 summarize ribavirin pharmacokinetics following administration of 1000 or 1200 mg daily (based on weight; divided bid). Subjects took ribavirin with food.

Mean ± SD Ribavirin Pharmacokinetic Parameters Following 1000 mg or 1200 mg daily for 12 weeks (Roche ribavirin)

Parameter	1000 mg (n=12)	1200 mg (n=39)
Tmax (hr)	1.8 ± 1.2	2.7 ± 2.4
Cmax (ng/mL)	3139 ± 850	2748 ± 818
$AUC_{0\text{-}12hr}$ (µg*hr/mL)	29.6 ± 8.2	25.4 ± 7.1

The following figure illustrates the concentrations vs. time profile following administration of 1000 or 1200 mg daily (based on weight; divided bid). Subjects took ribavirin with food. Subjects did not receive any specific instructions regarding the content (calories, fat) of meals. (Study NV15801). The figure includes data for subjects receiving each treatment. The PEG-IFN alpha-2a and ribavirin treatment includes the Roche ribavirin tablets. Subjects in both groups received the same ribavirin dose (1000 or 1200 mg per day).



4.2.4.2 Do mass balance data suggest renal or hepatic routes of elimination?

The applicant did not provide human mass balance data.

4.2.4.3 What are the routes of metabolism for ribavirin?

The applicant did not provide information about the routes of metabolism for ribavirin.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, sex, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

There is some evidence that ribavirin exposure is higher in patients with lower body weight.

The applicant did not evaluate the effect of renal impairment, hepatic impairment, or race on ribavirin pharmacokinetics.

4.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied; what dosage regimen adjustments, if any, are recommended for each of these subgroups?

4.3.2.1 elderly patients

No dose adjustment is suggested for elderly patients, based on the pivotal clinical trials. The applicant did not evaluate the effect of age on ribavirin pharmacokinetics.

4.3.2.2 pediatric patients

Roche did not submit data from pediatric patients. The label will not include pharmacokinetic, efficacy, safety, or dosing information for pediatric patients.

4.3.2.3 sex

No dose adjustment is needed. When corrected for body weight, ribavirin pharmacokinetics are similar in men and women

4.3.2.4 race

The data submitted by the applicant do not allow an assessment of the effect of race on ribavirin pharmacokinetics.

The following observations are from the two pivotal clinical trials of PEG-IFN alpha-2a and ribavirin combination therapy (Dr. William Tauber's comments in the Advisory Committee Background Package):

NV15801: Response rates were lower in Black and Hispanic patients compared with the response rate in Caucasians. African Americans made up the vast majority of Black patients enrolled (48/53). The response rate in Asian patients on the other hand was higher than Caucasians. The validity of these observations is somewhat questionable due to the very low numbers of minority patients that were enrolled in this study.

NV15942: About 90% of the participants in this study were Caucasian. Minority participants were few in number and were not equally distributed across geographic regions making observations regarding their efficacy and regional differences very problematic.

4.3.2.5 renal impairment

The applicant did not evaluate the effect of renal impairment on ribavirin pharmacokinetics.

The label will reflect the population evaluated in clinical efficacy and safety studies (CrCl >50 mL/min).

4.3.2.6 hepatic impairment

The applicant did not evaluate the effect of hepatic impairment on ribavirin pharmacokinetics.

The label will reflect the population evaluated in clinical efficacy and safety studies (Child-Pugh Class A).

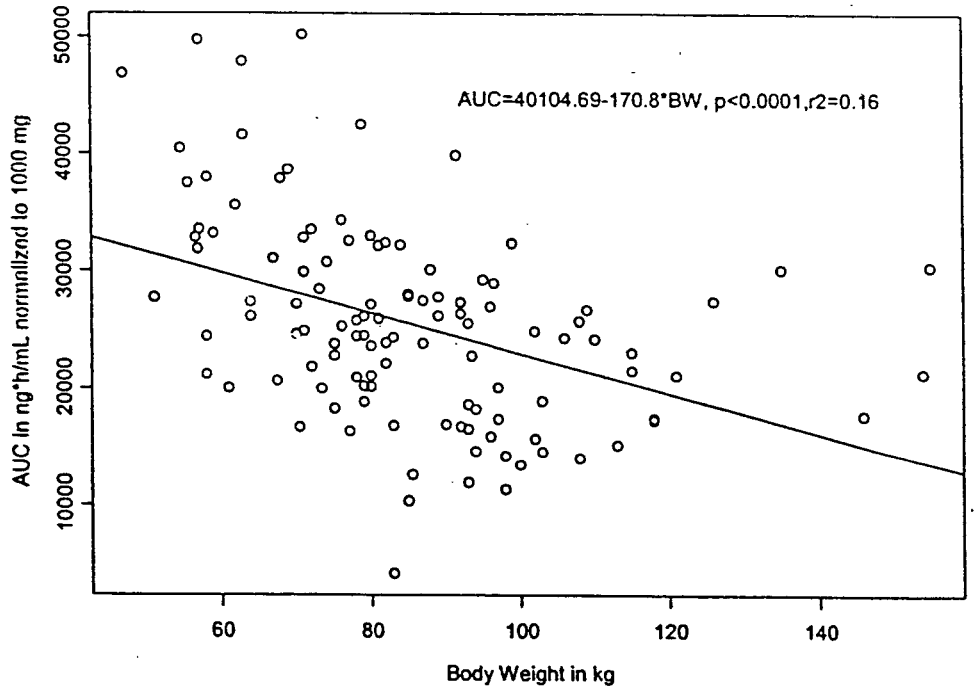
4.3.2.7 body weight

As indicated in section 4.2.3.3 of this review, there is evidence that body weight affects ribavirin exposure. Of interest is the effect of body weight on ribavirin exposure following multiple doses of ribavirin. Jenny J. Zheng, Ph.D, completed a pharmacometrics (PM) review.

Study NV15801

Week 12 full concentration vs time profiles are available for 51 patients who received the Roche combination treatment of PEG-IFN alpha-2a plus 1000 or 1200 mg ribavirin daily (divided bid). Data are available for 11 patients who received 1000 mg ribavirin (weight range 47 to 79 kg) and for 40 patients who received 1200 mg ribavirin (weight range 73 to 154 kg). Although the weight cutoff for the 1000 mg vs 1200 mg dose was 75 kg, a patient weighing 79 kg received 1000 mg and a patient weighing 73 kg received 1200 mg. The discrepancies may be due to weight changes during the study.

The following figure (from Jenny J. Zheng, PhD's review) shows the relationship between body weight and ribavirin AUC, normalized to a 1000 mg dose of ribavirin.

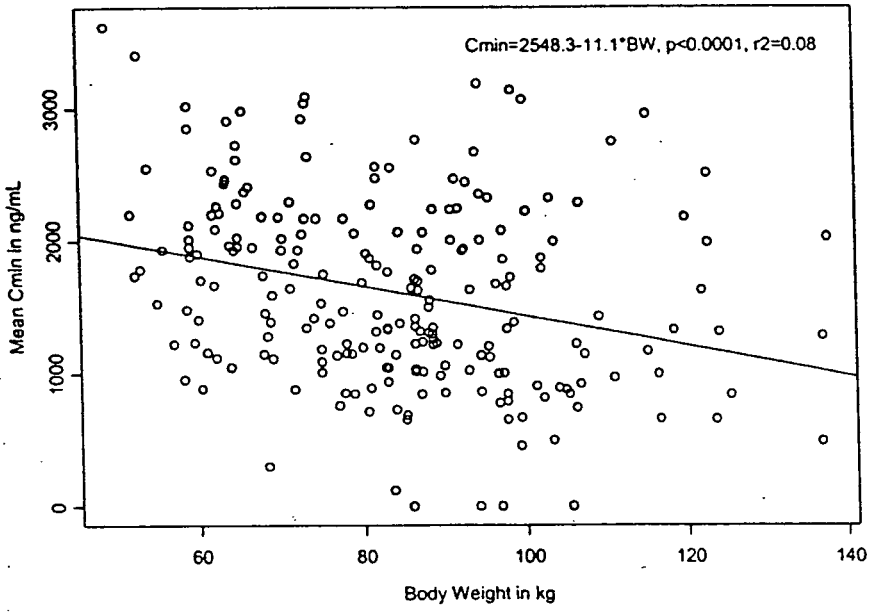


The above figure indicates there is a relationship between body weight and ribavirin exposure. A linear regression analysis between AUC or Cmax and body weight was conducted. The analysis showed that exposure of ribavirin was statistically significantly correlated with the body weight. However, the correlation explained only 15% and 16% variability in AUC and Cmax, respectively.

Study NV15942

Ribavirin trough concentration are available from patients who received 800 mg ribavirin per day for 24 or 48 weeks (Groups A and C) or 1000 or 1200 mg per day (based on body weight) for 24 or 48 weeks (Groups B and D).

The following figure (from Jenny J. Zheng, PhD's review) shows the relationship between body weight and ribavirin Cmin, normalized to a 1000 mg dose of ribavirin.



The above figure indicates there is a relationship between body weight and ribavirin exposure. A linear regression analysis between trough concentration and body weight was conducted. The analysis showed that exposure of ribavirin was statistically significantly correlated with the body weight. However, the correlation explained only 8% of variability in trough concentration.

The overall conclusion of the PM consult is that exposure of ribavirin is associated with body weight. Heavy patients tend to have lower exposure. However, the body weight explained only a small portion (8 to 16%) of the variability. The assessment of impact of body weight on efficacy and safety should rely on the understanding of the exposure vs efficacy and safety relationship.

4.3.2.8 pregnancy and lactation

Ribavirin is contraindicated in pregnant women. Ribavirin may cause birth defects and/or death of the exposed fetus. It is not known whether ribavirin is excreted in breast milk.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

As discussed in section 4.5.4, food increases the bioavailability of ribavirin.

There are no known dose adjustments due to drug-drug interactions. However, as indicated in section 4.4.2, the applicant did not provide information about some possible mechanisms of drug-drug interactions.

The applicant did not evaluate the effect of any other extrinsic factors on ribavirin exposure.

4.4.2 Drug-drug interactions

4.4.2.1 is the drug a substrate of CYP enzymes?

Ribavirin is not a substrate of CYP enzymes.

An in vitro stability study of ribavirin in human liver microsomes and cDNA expressed enzymes (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4) was performed to determine if CYP enzymes are involved in the metabolism of ribavirin. Ribavirin was incubated with human liver microsomes and cDNA expressed enzymes in the presence and absence of NADPH. The peak area ratios of ribavirin over ^{13}C labeled ribavirin (internal standard) in the incubations were determined at 0 and 30 minutes following incubations at 37°C. The differences between these determinations were used as an indicator of the extent of metabolism. Each incubation was performed in triplicate and each sample was analyzed twice. The % ribavirin remaining after 30 minutes ranged from 96 ± 3% to 115 ± 16% for all enzymes evaluated.

4.4.2.2 is the drug an inhibitor and/or an inducer of CYP enzymes?

Ribavirin does not inhibit CYP enzymes. The applicant did not provide information indicating whether ribavirin induces CYP enzymes.

An in vitro study was conducted that assessed the CYP enzyme inhibition potential of ribavirin using pooled human liver microsomes and specific probe substrates for CYP1A2, 2A6, 2C9, 2C19, 2E1, 2D6, and 3A4. The in vitro incubation was on a 96 well plate in a 37°C water bath. The reaction was started by addition of NADPH. The incubation time was 10 minutes. Known specific inhibitors for each enzyme were included as positive controls.

Probe substrates and their final concentrations in the assay are as follows-

Enzyme	Probe substrate	Concentration
1A2	ethoxyresorufin	[redacted]
2A6	coumarin	[redacted]
2C9	tolbutamide	[redacted]
2C19	S-mephenytcin	[redacted]
2D6	(+)-bufurolol	[redacted]
2E1	chlorzoxazone	[redacted]
3A4	midazolam	[redacted]

The following table summarizes the results.

Ribavirin conc.	Enzyme activity (% of control) Average and %CV						
	1A2	2A6	2C9	2C19	2D6	2E1	3A4
2 µM	86.9 (8.5)	96.3 (6.9)	92.5 (19.1)	96.6 (8.1)	95.1 (4.6)	100.5 (3.9)	89.7 (18.0)
10 µM	90.9 (21.2)	99.2 (8.2)	95.6 (14.9)	90.4 (4.3)	96.6 (3.1)	93.0 (14.2)	98.4 (16.1)
25 µM	115.4 (29.3)	102.3 (13.6)	93.9 (18.2)	93.2 (2.4)	98.4 (10.9)	134.7 (7.6)	97.5 (14.1)
50 µM	133.0 (13.2)	108.8 (4.5)	98.0 (11.5)	90.4 (5.5)	111.4 (2.8)	102.2 (22.9)	114.7 (13.9)

4.4.2.3 is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No data are available that address this topic.

4.4.2.4 does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The label specifies coadministration of ribavirin with PEG-IFN alpha-2a. PK data from Study NV15801 indicate ribavirin does not alter PEG-IFN alpha-2a pharmacokinetics.

The pivotal clinical trials were conducted with the combination of PEG-IFN alpha-2a and ribavirin. Thus, even if there is a pharmacokinetic interaction, the safety and efficacy of the combination is known.

4.4.2.5 is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

The efficacy of ribavirin plus interferons is probably due to a pharmacodynamic interaction, but the interaction is not well-understood.

4.4.2.7 are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

As indicated in section 4.4.2.2, adequate data are not available to determine whether ribavirin induces CYP enzymes.

Also, there is in vitro evidence that ribavirin inhibits phosphorylation of zidovudine and stavudine. The clinical significance of these findings is not known. However, the efficacy of these nucleoside reverse transcriptase inhibitors may be decreased in patients taking ribavirin. (Reference: B. Mansori, et. al., Antimicrobial Agents and Chemotherapy, 1987, vol 31, p 1613-1617)

The applicant did not provide information about the metabolic route of ribavirin. The applicant did not provide information about the protein binding of ribavirin.

4.5 General Biopharmaceutics

4.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Permeability data are not available, so the BCS class cannot be determined. Ribavirin is highly soluble; it is freely soluble (>140 mg/mL) in aqueous media across the pH range of 1 to 6.8.

4.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The applicant used formulation F3 and F6 in pivotal clinical trials, but will market formulation F12. The 3 formulations are almost identical (See individual study review for NR16231).

The applicant conducted a randomized crossover study (NR16231) to evaluate the bioequivalence of ribavirin tablets intended for commercial use to ribavirin tablets used in clinical trials. As discussed in the review of this study, there were quantifiable pre-dose concentrations in Period 1 and Period 2. The quantifiable pre-dose concentrations in Period 2 are likely due to an inadequate wash-out period. The quantifiable Period 1 pre-dose concentrations make the integrity of the study questionable. The Division of Scientific Investigations inspected the analytical and clinical sites for the study. The reports indicate that the eleven subjects with quantifiable Period 1 predose concentrations should be excluded from bioequivalence calculations. Deleting the subjects with quantifiable Period 1 predose concentrations does not alter the conclusion of bioequivalence. When the subjects are deleted the 90% CIs for AUC and Cmax are (91 to 108) and (86 to 106), respectively. Thus, the formulations are bioequivalent.

4.5.3 In addition to the pivotal bioequivalence study, what relevant formulation comparisons are made in relative bioavailability or bioequivalence studies?

Study BP16320 evaluated the bioequivalence between the proposed commercial tablet formulation and the currently marketed capsule formulation (Rebetol, Schering). The study indicates the proposed commercial Roche ribavirin 200-mg tablet is bioequivalent to the currently marketed Schering ribavirin 200-mg capsule, when given as 3 x 200 mg tablets or capsules.

Study NP15904 was a parallel study that evaluated the bioequivalence of two clinical trial ribavirin tablet formulations (F3 and F6) that had different dissolution profiles. The two tablet formulations used in pivotal clinical trials provide similar ribavirin exposure (AUC), although the dissolution rate is slower for the F6 formulation. Cmax may be slightly lower for the F6 formulation, compared to the F3 formulation.

Study NP15904 also compared the two clinical trial ribavirin tablet formulations to the commercially available ribavirin capsule (Rebetol®, Schering). In this parallel study, mean AUC and Cmax are 5 to 20% lower for the clinical Roche ribavirin formulations compared to the currently marketed Schering ribavirin capsule formulation.

4.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Based on Study NR16230 results, the ribavirin tablet intended for commercial use has a significant food effect with oral administration. Following a high fat meal, ribavirin AUC_{0-192h} increased by approximately 42% and Cmax increased by approximately 66%. The label includes information about the effect of food. The label recommends that patients take ribavirin with food, as done in clinical trials.

The applicant also evaluated the effect of food on multiple dose pharmacokinetics of ribavirin in a parallel design Phase 2 study (NV15800). This study used the marketed ribavirin capsule (Rebetol, Schering). A previous single dose study submitted with NDA 20903 indicated a high fat meal administered with the ribavirin capsule increases ribavirin bioavailability by 70%. In Study 15800, there were a number of factors that made it difficult to determine the true food effect. However the results suggest that effect of patients' typical meals on the multiple dose pharmacokinetics of ribavirin is more modest than the effect observed in the single dose, high-fat food effect studies.

4.5.5 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The applicant proposes the following dissolution method and specification.

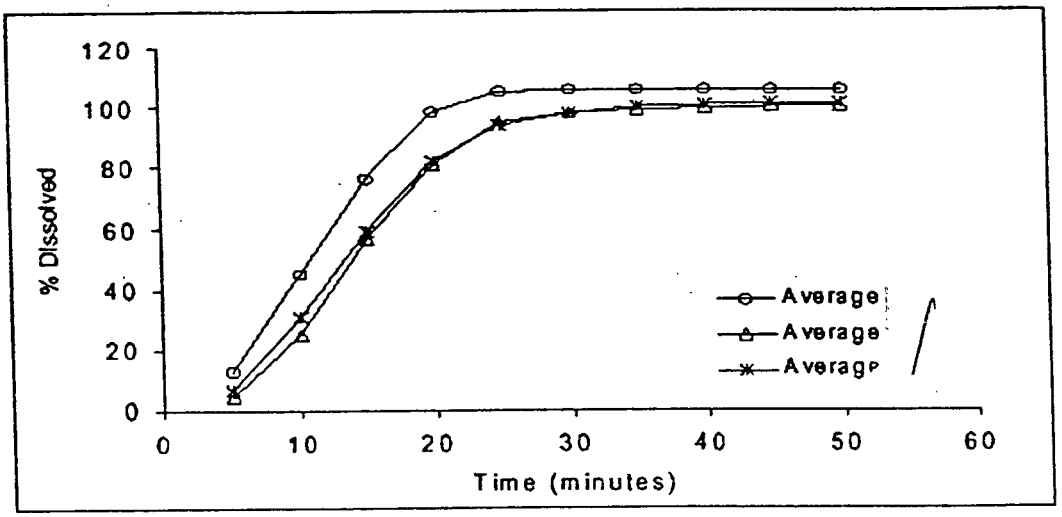
Apparatus- Paddles (USP apparatus 2)
Medium- Deionized water, 900 mL
Temperature- 37 ± 0.5°C
Rotation speed- 50 rpm
Specification- Q = ___ in 30 minutes

The method and specification are acceptable.

Dissolution medium selection

A study was conducted to compare the dissolution characteristics of three clinical batches of ribavirin film-coated 200 mg tablets in ___. The three batches represent formulations used in different stages of drug development. The results for Batch C199970 (proposed market formulation) are summarized in the following figure and table.

Batch C199970 after storage of 3 months at ambient conditions- % dissolved



Batch C199970 after storage of 3 months at ambient conditions
% Dissolved ± SD

Time (minutes)	% Dissolved (± SD)		
5	13 (± 3.0)	4 (± 2.3)	7 (± 2.5)
10	45 (± 9.3)	25 (± 8.8)	30 (± 8.5)
15	76 (± 12.2)	56 (± 15.9)	59 (± 12.8)
20	99 (± 4.8)	81 (± 13.6)	83 (± 11.9)
25	105 (± 1.7)	95 (± 9.6)	94 (± 7.8)
30	106 (± 2.1)	98 (± 7.2)	98 (± 3.3)
35	106 (± 2.2)	99 (± 5.7)	100 (± 1.7)
40	106 (± 2.2)	99 (± 4.5)	101 (± 2.2)
45	106 (± 2.2)	100 (± 3.8)	101 (± 2.4)
50	106 (±2.2)	100 (± 3.3)	101 (± 2.4)

Results indicate that all three media yielded qualitatively similar dissolution profiles for each batch of tablets. Due to the similarity of the three media, and [redacted] was selected as the dissolution medium for the ribavirin 200 mg tablets.

Apparatus and rotation speed selection

USP apparatus 2 (paddles) is commonly used for tablets, so no other apparatus was evaluated. Because dissolution typically becomes less discriminating when the apparatus is used at a higher speed, speeds higher than 50 rpm were not evaluated.

Dissolution specification

The following table shows the individual tablet dissolution results for 12 tablets from batch C199970. This batch of the to-be-marketed formulation was used in the pivotal bioequivalence study.

Individual Tablet Dissolution Data for Batch C199970

Time (min)	% Dissolved 1	2	3	4	5	6	7	8	9	10	11	12	Average %	SD	Range, % Min	Max
0													0	0		
5													11	1.6		
10													41	4.4		
15													71	9.3		
20													93	5.3		
25													101	1.2		
30													102	1.7		

Based on these data, the applicants proposed specification of Q = — in 30 minutes is acceptable.

4.6 Analytical

4.6.1 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

The selected assay measures total ribavirin in plasma. Measuring total ribavirin concentrations appears to be acceptable.

4.6.2 What bioanalytical methods are used to assess concentrations?

The concentrations of ribavirin in human plasma were determined using a validated — — method with —.

4.6.2.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The method was validated over a concentration range of ! — The range is acceptable for the biopharmaceutics studies. Concentrations in the pivotal clinical trials were : — , so samples were diluted. The applicant provided adequate validation and quality control data for diluted samples.

4.6.2.3 What are the accuracy, precision and selectivity at these limits?

Precision ranged from 91 to 98% and accuracy ranged from 94 to 102%. Chromatograms indicate the assay is specific for ribavirin.

4.6.2.4 What is the sample stability under the conditions used in the study?

Sample stability is acceptable under the conditions used in the studies. Ribavirin is stable for at least — at 22°C in human plasma, for at least — at 4°C and for at least — freeze-thaw cycles. Ribavirin is stable in heparinized human plasma for at least — at -20°C and in EDTA human plasma for at least — at -20°C.

5 Labeling

Will include final PK labeling in DFS version of label.

6 Appendix

1 Page(s) Withheld

NDA 21-511
Reviewer: Kellie Schoolar Reynolds, Pharm.D.

6.2 Appendix- Individual study reviews

PIVOTAL BIOEQUIVALENCE STUDY OF ROCHE RIBAVIRIN TABLETS INTENDED FOR COMMERCIAL USE AND ROCHE RIBAVIRIN TABLETS USED IN CLINICAL STUDIES IN INDIVIDUALS WITH CURRENT OR PREVIOUS CHRONIC HEPATITIS C (CHC) INFECTION
(PROTOCOL NR16231)

OBJECTIVES: The study objective was to determine the bioequivalence of Roche ribavirin tablets intended for commercial use and Roche ribavirin tablets used in clinical studies.

SUBJECTS: A total of 33 male and 13 female subjects with current or previous CHC were evaluable for PK analysis. The age range was 18-65 years and weight range was 54-107 kg.

DESIGN: This was an open-label, single-dose, randomized, crossover, bioequivalence study. Subjects were randomized to receive the following treatments:

Treatment A (ref): 600 mg (200 mg x 3) ribavirin clinical trial formulation
Treatment B (test): 600 mg (200 mg x 3) ribavirin intended for commercial use

Both treatments were administered under fasted conditions. There was a 7-10 day washout between Periods 1 and 2. The washout began after the 192-hour blood sample was collected in Period 1.

FORMULATIONS: Ribavirin tablets intended for commercial use: light pink film-coated tablets containing 200 mg ribavirin (Lot No.: C199970). Ribavirin tablets used in clinical studies: tablets containing 200 mg ribavirin (Lot No. C195039).

Quantitative Formulation of Clinical Trial and Proposed Market Formulation

Ingredients	Weight per tablet		Function
	Clinical trial formulations (F3/F6)	Proposed commercial formulation (F12)	
Ribavirin	200 mg	200 mg	Active ingredient
Pregelatinized starch			
Sodium starch glycolate			
Microcrystalline cellulose			
Corn starch			
Magnesium stearate			
Film Coat-			
Opadry Peach**			
Chromatone-P			
Triacetin			

** Opadry Peach and Chromatone-P are identical

ANALYTICAL METHODS: The plasma concentrations of ribavirin were determined by at the The detection limit was set to The performance of the assay is summarized in the table below.

Table 1. Assay performance for the determination of ribavirin in human plasma

	Ribavirin
Calibration curve range	
Limit of quantitation	
QC concentrations, ng/mL	
QC precision (%CV)	2-8.5%
QC bias (% nominal)	94.1-98%

SAMPLE COLLECTION: Blood samples were collected for quantitative determination of ribavirin plasma concentrations at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, 144 and 192 hours after administration.

PHARMACOKINETIC ANALYSIS: AUC_{0-192h}, C_{max}, t_{max}, and t1/2 were determined using noncompartmental methods. Equivalence was concluded if the 90%-confidence interval for the ratio of the mean values for the Roche intended commercial product (Treatment B) and the Roche clinical trial material (Treatment A) for AUC_{0-192h} and C_{max} was within the interval 0.8-1.25. The AUC_{0-192h} and C_{max} were logarithmically transformed before statistical analysis. The analysis of data and hypothesis testing were performed using an ANOVA-model with the factors 'sequence,' 'subject within sequence,' 'period' and 'treatment.'

PHARMACOKINETIC RESULTS: Table 2 summarizes the bioequivalence test results.

Table 2: Mean pharmacokinetic parameters (CV%), 90%CI values and geometric mean ratios for ribavirin in Treatment B (proposed commercial) vs. A (clinical trial material)

Parameter	Treatment	Geometric mean (%CV)	Test/Reference Comparison	
			B/A ratio (%)	90% CI
AUC_{0-192h} (µg*h/mL)	A	15.1 (31.2)	101	94, 109
	B	15.2 (36.7)		
C_{max} (ng/mL)	A	664 (42.2)	98	90, 106
	B	649 (42.6)		

Carry-over effects

The secondary analysis demonstrated a significant period effect for AUC0-inf (p-value = 0.0016). This result is attributed to the presence of residual ribavirin in the plasma of subjects after the washout between period 1 and period 2.

Predose ribavirin concentrations in period 1

Eleven subjects had predose ribavirin concentrations in period 1. The majority of ribavirin predose concentrations above the detection limit were <10% of Cmax. Three of these subjects had ribavirin predose concentrations that corresponded to approximately 20% of their Cmax values. One subject had a predose concentration of [redacted], which was also Cmax. For this subject, ribavirin concentrations declined for the entire sampling period after the predose sample. The subjects included in this study had hepatitis C infection; however, individuals receiving ribavirin in the previous 6 months were to be excluded. It is possible that some individuals may not have had an adequately long washout of ribavirin after multiple dosing before entering the study.

Due to the observation discussed above, we sent the following requests to the sponsor. Our request is in bold font, followed by the applicant's response (paraphrased).

Please repeat the statistical analysis for this study (point estimates and 90% confidence intervals for AUC and C_{max} ratios) excluding these eleven subjects.

As requested, the statistical analysis was repeated excluding these 11 subjects, and the results are provided in the table below. Bioequivalence was also demonstrated when the 11 subjects with predose ribavirin concentrations in period 1 were excluded from the statistical analysis.

Estimates of Bioequivalence of Roche Ribavirin Following 600 mg of Intended Commercial Tablets (Trt B) Relative to Clinical Trial Tablets (Trt A) – Excluding 11 Subjects with Period 1 Predose Concentrations

Parameter	Treatment	Geometric mean	Test/Reference Comparison	
			B/A ratio (%)	90% CI
AUC_{0-192h} (µg*h/mL)	A	15.50	99	91, 108
	B	15.4		
C_{max} (ng/mL)	A	671	95	86, 106
	B	640		

Please provide a full description of your investigation into the explanation for the detectable predose concentrations in Period 1.

An investigation into the possible reasons for the detectable predose concentrations of ribavirin in period 1 was conducted, and no explanation was found. The factors investigated included the following:

The clinical site was queried about the 11 subjects with quantifiable predose ribavirin concentrations in period 1. In this study, as in other clinical pharmacology studies conducted by Roche, any deviations from the protocol and information about hemolysed samples are collected in the relevant "Sample Remarks" section of the case report form for each sample.

The clinical site and monitor were asked to review case report forms and source documents to determine if dosing or sample collection had been done incorrectly in these patients. There was no documented evidence that the clinical conduct of the study contributed to the predose ribavirin concentrations in period 1 in the 11 subjects.

The bioanalytical lab was questioned about possible errors in assay conduct resulting in contaminated samples or incorrect results ([redacted] a carryover effect across samples); however, there was no documented evidence of errors. The bioanalytical lab reassayed the 11 quantifiable Period 1 predose samples in duplicate and reported confirmatory results (reassay of quantifiable predose samples when results are expected to be below the limit of quantitation is a standard procedure).

DISCUSSION/CONCLUSIONS

The quantifiable Period 1 predose concentrations make the integrity of the study questionable. The Division of Scientific Investigations inspected the analytical and clinical sites for the study. The reports indicate that the eleven subjects with quantifiable Period 1 predose concentrations should be excluded from bioequivalence calculations. Deleting the subjects with quantifiable Period 1 predose concentrations does not alter the conclusion of bioequivalence. When the subjects are deleted the 90% CIs for AUC and Cmax are (91 to 108) and (86 to 106), respectively. Thus, the formulations are bioequivalent.

FOOD EFFECT BIOAVAILABILITY STUDY OF ROCHE RIBAVIRIN TABLETS INTENDED FOR COMMERCIAL USE IN INDIVIDUALS WITH CURRENT OR PREVIOUS CHRONIC HEPATITIS C (CHC) INFECTION (PROTOCOL NR16230)

OBJECTIVES: The study objective was to determine the effect of food on the pharmacokinetics of ribavirin after oral administration of Roche ribavirin tablets intended for commercial use.

SUBJECTS: A total of 31 male and 15 female subjects with current or previous CHC were evaluable for PK analysis. The age range was 31 to 61 years and the weight range was 51 to 118 kg.

DESIGN: This was an open-label, single-dose, single-center, crossover, food effect study. Subjects received the following two single-dose treatments in a randomized crossover fashion:

Treatment A: 600 mg ribavirin (200 mg x 3) under fasting conditions
Treatment B: 600 mg ribavirin (200 mg x 3) following a high fat meal

There was a 7-10 day washout between Periods 1 and 2. The washout began after the 192 hour blood sample was collected in Period 1.

For the fasted treatment, subjects fasted beginning midnight the day before dosing. The study drug was administered between 7:00 and 9:00 in the morning. For the fed treatment, subjects consumed a standard high fat (50% of total caloric content of the meal), high caloric (approximately 1000 calories) breakfast. Subjects took the study drug within 10 minutes after completing the meal. For both treatments, subjects received a light lunch approximately 4 hours after drug administration and dinner approximately 10 hours post-dose.

FORMULATIONS: Light pink film-coated tablets containing 200 mg (Lot No.: C199970) were supplied by Roche.

ANALYTICAL METHODS: The plasma concentrations of ribavirin were determined by [redacted] at the [redacted] The detection limit was set to [redacted] .. The performance of the assay is summarized in the table below.

Table 1. Assay performance for the determination of ribavirin in human plasma

	Ribavirin
Calibration curve range	[redacted]
Limit of quantitation	[redacted]
QC concentrations, ng/mL	[redacted]
QC precision (%CV)	2.6-8.3
QC bias (% nominal)	95-98.1

SAMPLE COLLECTION: Blood samples were collected at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, 144 and 192 hours after ribavirin administration.

PHARMACOKINETIC ANALYSIS: Pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-192h} and $t_{1/2}$) were determined using non-compartmental analysis. The magnitude of the food effect was determined using the mean ratio of the exposure measures in the fed vs. fasted state. 90% confidence intervals for the ratio were determined. The AUC_{0-192h} and C_{max} values were logarithmically transformed before statistical analysis. The analysis of data and hypothesis testing were performed using an analysis of variance-model with the factors 'sequence,' 'subject within sequence,' 'period' and 'treatment.'

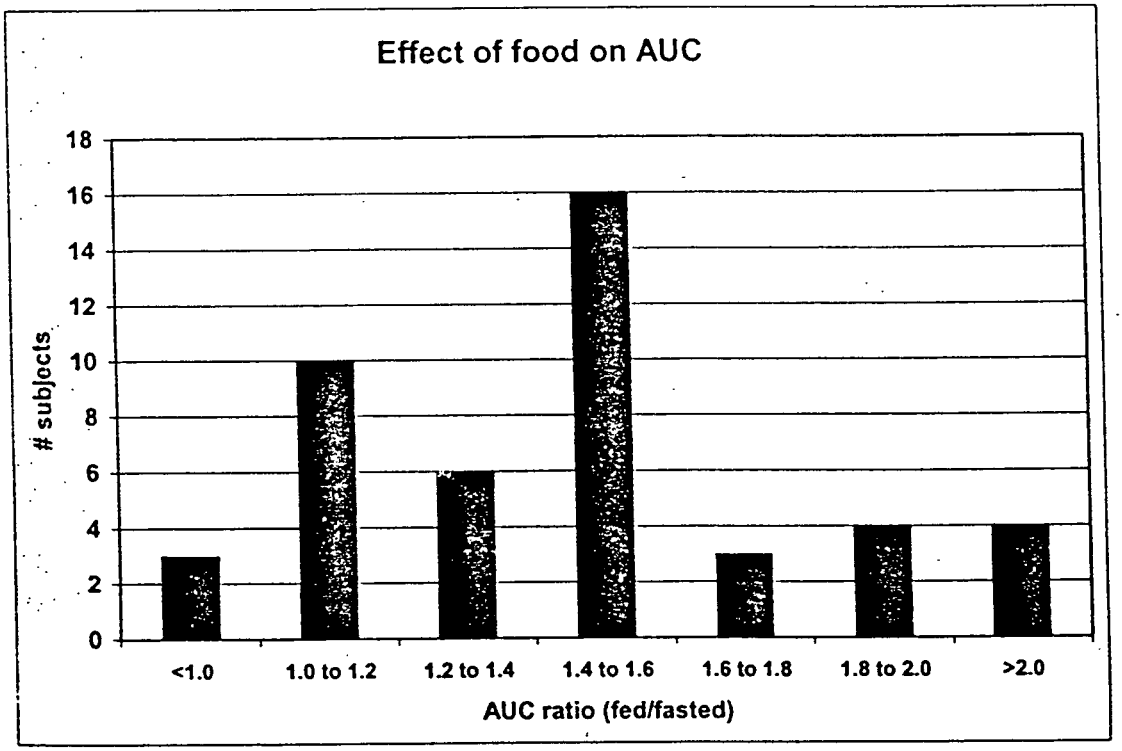
PHARMACOKINETIC RESULTS: Pharmacokinetic parameters are summarized in the table below.

Table 2. Ribavirin Pharmacokinetic Parameters Following 600 mg Single Dose
Geometric Mean (%CV)

Parameter (Units)	Fasted (N=46)		Fed (N=46)	
AUC (0-192h) (μg*h/mL)	17.87 (32.3)		25.41 (30.5)	
Cmax (ng/mL)	662.0 (43.7)		1097.8 (34.9)	
Tmax (h) (Median and range)	2.0		4.0	
AUC∞ (μg*h/mL)	29.10 (37.9)	N=41	38.76 (31.9)	N=39
T½ (h)	151 (29.9)	N=37	160 (34.5)	N=39
Cl/F (L/h)	20.62 (40.9)	N=41	15.48 (33.3)	N=39

The geometric mean ratios (90 % CI) for $AUC_{0\text{-}192h}$ and C_{max} were 1.42 (1.34, 1.51) and 1.66 (1.52, 1.81), respectively, indicating a significant effect of food on ribavirin exposure. T_{max} values were also increased with food (4 hr vs. 2 hr).

The figure below illustrates the distribution of AUC ratios in individual subjects.



Carry-over effects: There was a significant period effect for $AUC_{0\text{-}192}$ (p-value = 0.0026). This result is attributed to the presence of residual ribavirin in the plasma of subjects after the 7 to 10 day washout between periods, starting after the period-1 192 hour blood sample (total washout of 15 to 18 days between doses). There was residual ribavirin in the period 2 pre-dose plasma sample for 45 subjects. Because food increases the bioavailability of ribavirin, there was greater carry-over from treatment B (fed) to treatment A (fasted) than from treatment A to treatment B. All evaluable period 2 predose samples contained residual drug from period 1. For subjects that received the fed treatment in period 1, on average, the period 2 predose concentration was 4.4% of the individual subject's Cmax (range 0.4% to 13.7%; one >8%). For subjects that received the fasted treatment in period 1, on average, the period 2 predose concentration was 1.7% of the individual subject's Cmax (range 0.7% to 4.4%).

DISCUSSION: As indicated above, there was residual ribavirin in the period 2 predose plasma sample for 45 subjects. The crossover design of the study decreases the impact of the carry-over. However, because there was greater carry-over from treatment B to treatment A than from treatment A to treatment B, the carry-over leads to an underestimate of the food-effect. Due to the magnitude of the carry-over, the impact on the study results is small. It acceptable to state that administration of ribavirin with a high-fat meal increases AUC and Cmax by approximately 42% and 66%, respectively. These results are consistent with the food effect observed with the current marketed Schering ribavirin product (Rebetol®); administration with a high fat meals increases AUC and Cmax by approximately 70%.

It should also be noted that there were four plasma sampling discrepancies that took place throughout the study (example- 2 sample label were switched). The applicant resolved the discrepancies in an acceptable manner. In addition, the four samples do not have a significant impact on the study results.

CONCLUSIONS: Following a high fat meal, ribavirin $AUC_{0\text{-}192h}$ increased by approximately 42% and Cmax increased by approximately 66%. The label includes information about the effect of food. The label recommends that patients take ribavirin with food, as done in clinical trials.

BIOEQUIVALENCE STUDY OF RIBAVIRIN FORMULATIONS REBETOL® AND RO 20-9963 IN INDIVIDUALS WITH CURRENT OR PREVIOUS CHRONIC HEPATITIS C (CHC) INFECTION (PROTOCOL BP16320)

OBJECTIVES: The study objective was to determine the bioequivalence of Roche ribavirin tablets intended for commercial use with Schering ribavirin capsules (Rebetol •) that are commercially available.

SUBJECTS: A total of 18 male and 22 female subjects with current or previous CHC were evaluable for PK analysis. The age range was 24 to 65 years and the weight range was 44 to 103 kg.

DESIGN: This was a Phase I, open-label, single-dose, single-center, crossover, bioequivalence study. Subjects were randomized to receive the following treatments:

Treatment A (ref): 600 mg (200 mg x 3) Schering ribavirin capsules
Treatment B (test): 600 mg (200 mg x 3) Roche ribavirin tablets (proposed commercial)

Both treatments were administered under fasted conditions. There was a 7-10 day washout between Periods 1 and 2. The washout began after the 192-hour blood sample was collected in Period 1.

FORMULATIONS: Ro 20-996: light pink film-coated tablets containing 200 mg ribavirin Ro 20-9963/J10-00 (Lot No.: C199970) supplied by Roche. Rebetol: currently marketed oral formulation of ribavirin (200 mg capsule) was used.

ANALYTICAL METHODS: The plasma concentrations of ribavirin were determined by ——— at the ——— The detection limit was set to ———
The performance of the assay is summarized in Table 1:

Table 1. Assay performance for the determination of ribavirin in human plasma

	Ribavirin
Calibration curve range	———
Limit of quantitation	———
QC concentrations, ng/mL	———
QC precision (%CV)	2.2-9.1%
QC bias (% nominal)	95.5-100%

SAMPLE COLLECTION: Blood samples were obtained at predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, 144, and 192 hours post dosing of ribavirin during each treatment period.

PHARMACOKINETIC ANALYSIS: $AUC_{0\text{-}192h}$, C_{max}, t_{max}, and t1/2 were determined using noncompartmental methods. Equivalence was concluded if the 90%-confidence interval for the ratio of the mean values for the Roche intended commercial product (Treatment B) and the approved Schering capsule formulation (Treatment A) for $AUC_{0\text{-}192h}$ and C_{max} was within the interval 0.8-1.25. The $AUC_{0\text{-}192h}$ and C_{max} were logarithmically transformed before statistical analysis. The analysis of data and hypothesis testing were performed using an ANOVA-model with the factors 'subject', 'period', and 'treatment.'

PHARMACOKINETIC RESULTS: Mean pharmacokinetic parameters are summarized in Table 2.

Table 2. Ribavirin Pharmacokinetic Parameters Following 600 mg Single Dose
Treatment A (Schering) and Treatment B (Roche)
Geometric mean (%CV)

Parameter (Units)	Treatment A (Schering)		Treatment B (Roche)	
AUC (0-192h) (µg*h/mL)	19.0 (29.6)		19.8 (31.2)	
Cmax (ng/mL)	672 (32.6)		695 (32.9)	
Tmax (h) (Median and range)	1.0 ———		2.0 ———	
AUC∞ (µg*h/mL)	26.8 (24.8)	N=34	28.2 (32.4)	N=34
T½ (h) (Harmonic mean)	133 (27.2)	N=34	127 (31.5)	N=34

Table 3 summarizes the bioequivalence test results.

Table 3: Mean pharmacokinetic parameters (CV%), 90%CI values and geometric mean ratios for ribavirin in Treatment B (Roche proposed commercial formulation) vs. A (Schering marketed formulation)

Parameter	Treatment	Geometric mean (%CV)	Test / Reference Comparison	
			Ratio (%)	90% CI
$AUC_{0\text{-}192h}$ (µg*h/mL)	A B	19.0 (29.6) 19.8 (31.2)	104	99, 110
C_{max} (ng/mL)	A B	672 (32.6) 695 (32.9)	103	95, 112

Carry-over effects: There was a significant period effect for $AUC_{0\text{-}192h}$ (p=0.0001). This result is attributed to the presence of residual ribavirin in the plasma of subjects after the 7 to 10 day washout starting after the 192 hour blood sample (total washout of 15 to 18 days between doses) between period 1 and period 2. There was residual ribavirin in the period 2 predose plasma sample for 39 of the 40 subjects. For 32 of the subjects, the predose concentration was <5% of Cmax. For the remaining seven subjects, the predose concentration was 5-10% of Cmax. The carry-over was similar for both sequences- the mean predose/Cmax percentage was 3-4% for both sequences. The carry-over does not alter the conclusions of the study.

CONCLUSIONS

The proposed commercial Roche ribavirin tablet is bioequivalent to the currently marketed Schering ribavirin capsule.

RELATIVE BIOAVAILABILITY STUDY OF RIVAVIRIN ADMINISTERED ORALLY AS TABLET VERSUS CAPSULE FORMS TO PATIENTS WITH CHRONIC HEPATITIS C (CHC) INFECTION (PROTOCOL NP15904)

BACKGROUND:
At the time this study was designed, manufacturing changes to the ribavirin tablet had been made, and tablets from the modified manufacturing process were supplied to ongoing clinical studies. There were no formulation (excipient) modifications, but aspects of the manufacturing process were revised. Dissolution profiles of the tablets manufactured before versus after the manufacturing modifications were dissimilar. Prior to the manufacturing changes, the tablet (designated as formulation F3) showed very rapid dissolution- virtually complete dissolution within 10 minutes. After the manufacturing changes, the tablet (designated as formulation F6) showed slower dissolution- approximately 30% dissolved in 10 minutes and complete dissolution by 30 minutes.

Because of the changes made during drug development and the differing dissolution profiles of the two tablet formulations, this study was designed to evaluate the relative performance of the two ribavirin tablet dosage forms (F3 versus F6) developed by Roche to the commercially available ribavirin capsule (Schering's Rebetol®)

OBJECTIVES: The primary objective of the study was to evaluate the relative bioavailability of ribavirin when administered orally as a tablet (2 Roche formulations) versus capsule (Roche) formulation.

The secondary objective was to determine bioequivalence of two ribavirin tablet formulations, F3 versus F6, representative of drug products used in pivotal clinical studies NV15801 and NV15942.

SUBJECTS: A total of 119 male and female subjects with current or previous CHC were evaluable for pharmacokinetic analysis. The demographic characteristics are for each treatment group are:

Treatment	Sex	Weight range (kg)	Age range (years)
A	7F/32M	50 to 114	34 to 65
B	19F/21M	57 to 104	32 to 63
C	16F/24M	54 to 97	28 to 52

DESIGN: This was an open-label, single-dose, randomized, parallel study. Subjects were randomized to one of three treatment groups and received a single 600 mg dose of ribavirin as follows:

Group A: Roche ribavirin tablet lot C193518 (formulation F3)
Group B: Roche ribavirin tablet lot C194999 (formulation F6)
Group C: Schering's commercially available ribavirin capsule (Rebetol), assigned lot C198149

Ribavirin was administered under fasted conditions in all groups.

FORMULATIONS: Roche ribavirin clinical formulations: tablets containing 200 mg ribavirin (Lot Nos.: C193518, C194999) supplied by Roche. REBETOL: currently marketed oral formulation (200 mg capsule).

ANALYTICAL METHODS: The plasma concentrations of ribavirin were determined by [redacted] at the [redacted] The detection limit was set to [redacted]
The performance of the assay is summarized in Table 1.

Table 1. Assay performance for the determination of ribavirin in human plasma

	Ribavirin
Calibration curve range	[redacted]
Limit of quantitation	[redacted]
QC concentrations, ng/mL	[redacted]
QC precision (%CV)	2.7-7.3%
QC bias (% nominal)	99.5-102%

SAMPLE COLLECTION: Blood samples were collected for quantitative determination of ribavirin plasma concentrations at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, 144, 192 hours after dosing.

PHARMACOKINETIC ANALYSIS: Pharmacokinetic parameters (AUC_{0-192h}, Cmax, Tmax, $AUC\infty$, Cl/F, $t_{1/2}$) were determined using non-compartmental analysis. An ANOVA model with main effects of treatment, center, and body weight was applied to logarithmically transformed values of AUC_{0-192} and Cmax. Least squares means differences between pairs of treatments and corresponding 90% confidence limits, and the intersubject variance were calculated.

PHARMACOKINETIC RESULTS: Pharmacokinetic parameters are summarized in Table 2.

Table 2: Summary of ribavirin pharmacokinetics following ribavirin 600 mg as two Roche tablets (Treatments A and B) and Schering capsule (Treatment C)- Geometric mean (%CV)

Parameter	Treatment A (N=39) Roche- F3		Treatment B (N=40) Roche- F6		Treatment C (N=40) Schering	
AUC_{0-192} (µg*hr/mL)	14.9 (24.7)		14.7 (32.3)		17.6 (21.7)	
Cmax (ng/mL)	753 (26.7)		661 (39.4)		820 (40.1)	
Tmax (h) Median (range)	1.0		1.5		2.0	
$AUC\infty$ (µg*hr/mL)	22.3 (30.6)	N=33	22.6 (35.2)	N=31	24.9 (29.5)	N=32
T1/2 (h)	157 (43.0)	N=33	150 (41.7)	N=31	144 (35.9)	N=32
Cl/F (L/h)	26.87 (32.8)	N=33	26.51 (52.6)	N=31	24.14 (26.2)	N=32

Administration of a single, oral 600 mg dose of ribavirin as a capsule resulted in higher systemic exposure to ribavirin than after either of the ribavirin tablet formulations.

Relative bioavailability assessment

Table 3. Relative bioavailability assessment of Roche ribavirin tablets (Treatments A and B) vs. Schering ribavirin capsules (Treatment C)

Comparison	Parameter	Ratio	90% Confidence Interval
Treatment A vs C	AUC_{0-192h}	0.88	0.78 to 0.99
	Cmax	0.95	0.82 to 1.10
Treatment B vs C	AUC_{0-192h}	0.83	0.74 to 0.93
	Cmax	0.80	0.69 to 0.92
Treatment B vs C *(deleting 2 outliers)	AUC_{0-192h}	0.89	0.81 to 0.98
	Cmax	0.86	0.76 to 0.98

*See outlier discussion, following Table 4

Bioequivalence assessment

Table 4. Bioequivalence assessment of Two Roche Ribavirin Formulations

Comparison	Parameter	Ratio	90% Confidence Interval
Treatment B vs A	AUC_{0-192h}	0.95	0.84 to 1.06
	Cmax	0.84	0.73 to 0.97
Treatment B vs A *(deleting 2 outliers)	AUC_{0-192h}	1.01	0.92 to 1.11
	Cmax	0.90	0.80 to 1.03

*See outlier discussion, below

Outlier discussion

The applicant determined that two subjects in treatment group B were statistical outliers. The applicant used residual plots for the outlier assessment. One subject had AUC_{192h} and Cmax values of 5.8 µg*hr/mL and — /mL, the other had AUC_{192h} and Cmax values of 3.2 µg*hr/mL and —

A PHASE II, OPEN-LABEL, SAFETY STUDY EVALUATING COMBINATION THERAPY WITH PEGINTERFERON ALFA-2A AND RIBAVIRIN IN THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C (PROTOCOL NV15800)

OBJECTIVES:
1. To obtain initial safety and tolerability information for the combination of PEG-IFN alpha-2a and ribavirin in patients with CHC.
2. To determine whether there is a major effect of food on the safety and tolerability of this regimen.

SUBJECTS: A total of 20 adult subjects with chronic HCV participated in the study. Nine subjects took ribavirin with food, and 11 subjects took ribavirin without food. Evaluable pharmacokinetic data are available for five subjects who took ribavirin with food and 10 subjects who took ribavirin without food. The following demographic characteristics apply to the 15 subject with evaluable PK data: there were 5 females and 10 males, the age range was 30 to 52 years and the weight range was 57 to 100 kg.

DESIGN: This was a randomized, open-label, parallel-group study at 2 centers. All subjects received PEG-IFN alpha-2a injection 180 µg once weekly. Subjects received ribavirin in two divided doses per day (400 mg in the morning and 600 mg in the evening for patients of body weight <75 kg; 600 mg in the morning and 600 mg in the evening for those of body weight ≥ 75 kg). Nine subjects took ribavirin with food, and 11 subjects took ribavirin without food. Both drugs were administered for 24 weeks in patients infected with HCV genotype non-1 and for 48 weeks in patients infected with HCV genotype 1.

FORMULATIONS:
Ribavirin was supplied as 200 mg Rebetol® capsules from Schering.
PEG-IFN alpha-2a was supplied in 2-mL vials; each vial contained 1 mL of 180 µg/mL solution.

ANALYTICAL METHODS: The plasma concentrations of ribavirin were determined by [redacted] at the [redacted] The detection limit was set to [redacted] The performance of the assay is summarized in Table 1:

Table 1. Assay performance for the determination of ribavirin in human plasma

	Ribavirin
Calibration curve range	[redacted]
Limit of quantitation	[redacted]
QC concentrations, ng/mL	[redacted]
QC precision (%CV)	6.2-7.5%
QC bias (% nominal)	94.0-101.7%

SAMPLE COLLECTION: On day 1 of week 12 or later, blood samples were obtained immediately before the morning dose and 1, 2, 3, 4, 5 hours and between 7 and 9 hours after the dose.

PHARMACOKINETIC ANALYSIS: AUC_{0-12h}, C_{max}, t_{max}, and CL/F were determined using noncompartmental methods. The ribavirin concentration at 12 hours was the average of ribavirin concentrations determined immediately before three morning doses.

PHARMACOKINETIC RESULTS:
The applicant summarizes the pharmacokinetic results as follows.

Table 2. Ribavirin Pharmacokinetic Parameters Following At Least 12 Weeks of Treatment
Arithmetic mean ± SD (range)

Parameter (Units)	Fed (n=5)	Fasted (n=10)
Average daily dose (mg)	1000 ± 245 (600 to 1200)	1040 ± 246 (600 to 1200)
AUC (0-12h) (µg*h/mL)	34.6 ± 7.7	30.7 ± 7.2
Cmax (ng/mL)	3938 ± 1052	3461 ± 1071
Tmax (h)	2 ± 1 (1 to 4)	2 ± 1 (1 to 4)

It is difficult to determine the effect of food, for several reasons:
1. Parallel design of study
2. Small sample size, with evaluable PK data from only 5 subjects in the fed treatment
3. The applicant dose-adjusted the PK data for subjects who received 600 mg per day. The dose of 600 mg was administered to subjects who met dose reduction criteria (reduction in hemoglobin level). To dose adjust the PK data, the applicant multiplied the plasma concentration data by a factor of 1.25. It is not clear why a factor of 1.25 was selected. The dose adjustment was performed for one subject in the fed group and two in the fasted group. At the time PK samples were collected, the three subjects had been taking the 600 mg dose for at least three weeks.

Using the values in the above table, AUC_{0-12} and Cmax were 12% and 14% higher, respectively, for the fed group compared to the fasted group. The food effect from the current study is more modest than the food effect observed in the single-dose crossover study (NR16230), where AUC and Cmax increased by 42% and 66%, respectively. A previous single-dose study with the Rebetol formulation used in this study resulted in a 70% increase in bioavailability with a high fat meal. The difference may be due to meal content (high fat, high calorie vs more modest content), multiple-dose design, or parallel design. It is not surprising that a multiple-dose study with a more modest meal content shows a lower effect of food. However, the current study does not allow an accurate quantification of food effect.

CONCLUSIONS

In this multiple-dose study, AUC_{0-12} and Cmax were 12% and 14% higher, respectively, for the fed group compared to the fasted group. However, due to study design and study conduct issues outlined above, the current study does not allow an accurate quantification of food effect.

6.3 Pharmacometrics Consult

CLINICAL PHAMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA number:	21-511
Submission date:	May 31, 2002
Product:	combination use of PEGASYS® (peginterferon alfa-2a) and Copegus™ (ribavirin)
Sponsor:	Hoffmann-La Roche, Inc.
Type of submission:	Original NDA
Primary Reviewer:	Kellie Reynolds, Pharm.D.
PM reviewer:	Jenny J Zheng, Ph.D.

The sponsor submitted an original Biologics License Application (BLA) and original New Drug Application (NDA 021-511) for Pegasys (peginterferon alfa-2a) and Copegus™ (ribavirin) combination therapy for the treatment of chronic hepatitis C.

Evidence was found in clinical studies that response rate was lower in heavy patients. The issue of relationship between exposure and body weight was discussed in section 4.2.3.3 and 4.3.2.7 of Dr. Reynolds review. PM consult was requested to explore if the exposure of ribavirin is related to the body weight.

Pharmacokinetic data were collected in two phase 3 studies, NV15801 and NV15492. Please refer to section 4.1.4 for the study design of these two studies.
In study NV15492, patients received one of the following four treatments in this randomized, multicenter, partially blinded study.

- PEG-IFN alpha-2a 180 µg and 800 mg of ribavirin for 24 weeks
- PEG-IFN alpha-2a 180 µg and 1000 or 1200 mg of ribavirin for 24 weeks
- PEG-IFN alpha-2a 180 µg and 800 mg of ribavirin for 48 weeks
- PEG-IFN alpha-2a 180 µg and 1000 or 1200 mg of ribavirin for 48 weeks

Trough samples were collected in total of 218 patients at weeks 4, 8, 12, 24, and 48. Among the 218 patients, 78 subjects received PEG-IFN alpha-2a and ribavirin 1000/1200 mg for 24 weeks, 36 subjects received PEG-IFN alpha-2a and ribavirin 800 mg for 24 Weeks, 42 patients received PEG-IFN alpha-2a and ribavirin 1000/1200 mg for 48 Weeks, and 62 subjects received PEG-IFN alpha-2a and ribavirin 800 mg for 48 Weeks. In order to compare trough concentrations between doses, observed trough concentrations were normalized to the dose of 1000 mg. The box plots of normalized trough concentrations at week 4, 8, 12, 24, and 48 weeks are shown in Figure 1. As shown in the Figure 1, the steady state might have been reached at week 4. Therefore, a mean trough concentration was calculated using the concentrations at weeks 4, 8, 12, 24 and 48 (only for the subjects in 48 weeks treatment group) for each subject. The mean trough concentrations from both 24 and 48 weeks were pooled for exploring the association between trough concentration and body weight. A linear regression analysis between the trough concentration and body weight was conducted. The results, as shown in Figure 2, indicated that the exposure was decreased when bodyweight increased. The correlation between trough concentration and body weight was statistically significant. However, the correlation explained only 8% of variability.

In Study NV 15801, patients received one of the following treatments in this randomized, multicenter, partially blinded, active-controlled and placebo-controlled study.

- PEG-IFN alpha-2a (180 µg) once weekly (N = 227)
- PEG-IFN alpha-2a (180 µg) once weekly plus ribavirin (1000 or 1200 mg) daily (N = 465)
- 3 MIU of IFN alpha-2b three times weekly plus ribavirin (1000 or 1200 mg) daily (N = 457)

All treatments were for 48 weeks, with a 24-week treatment-free follow-up. Full concentration vs time profiles were collected from 116 patients at weeks 12 and 48. AUC and Cmax from these subjects were normalized to 1000 mg dose. Since it is believed that the steady state would be achieved at week 12, a mean normalized AUC or Cmax of weeks 12 and 48 was calculated for each subject. A linear regression analysis between AUC or Cmax and body weight was conducted and the results are shown in Figure 3

and 4. The analysis showed that exposure of ribavirin was statistically significantly correlated with the body weight. However, the correlation explained only 15% and 16% variability in AUC and Cmax, respectively.

CONCLUSION:
The exposure of ribavirin is associated with body weight. Heavy patients tend to have lower exposure. However, the body weight explained only small portion (about 15%) of the variability.

RECOMMENDATION:
It is recommended that the sponsor conduct PK/PD analysis to further explore exposure vs efficacy/safety relationship. Pharmacokinetic data showed that exposure was decreased in heavy subjects. However, assessment of impact of body weight on efficacy/safety would rely on the understanding the exposure vs efficacy/safety relationship.

/S/

Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

Figure 1. Box plot of the trough concentrations

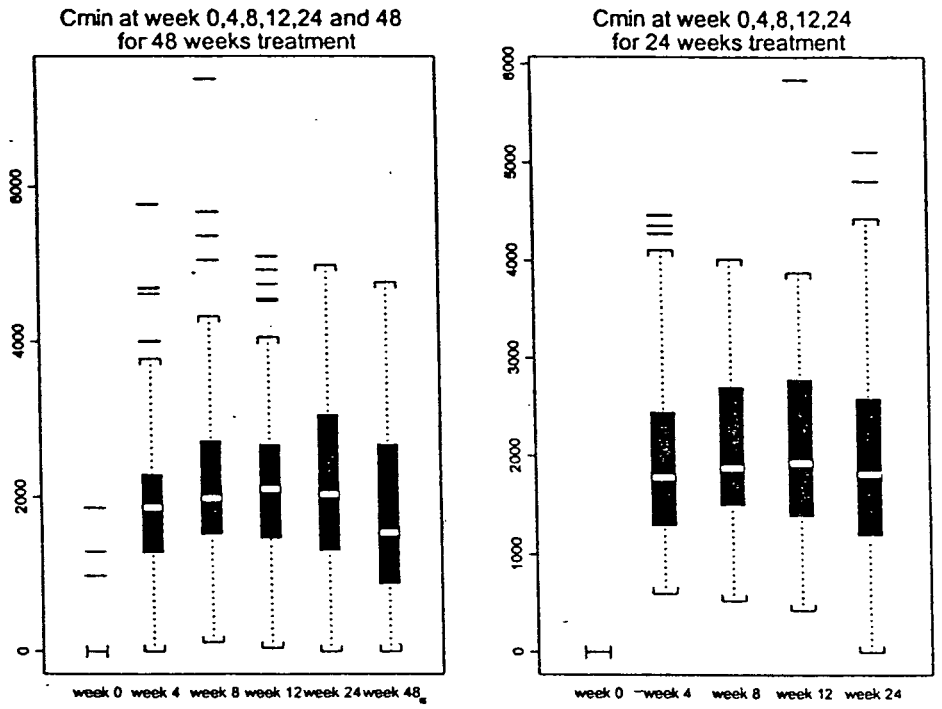


Figure 2. The correlation of trough concentration with body weight

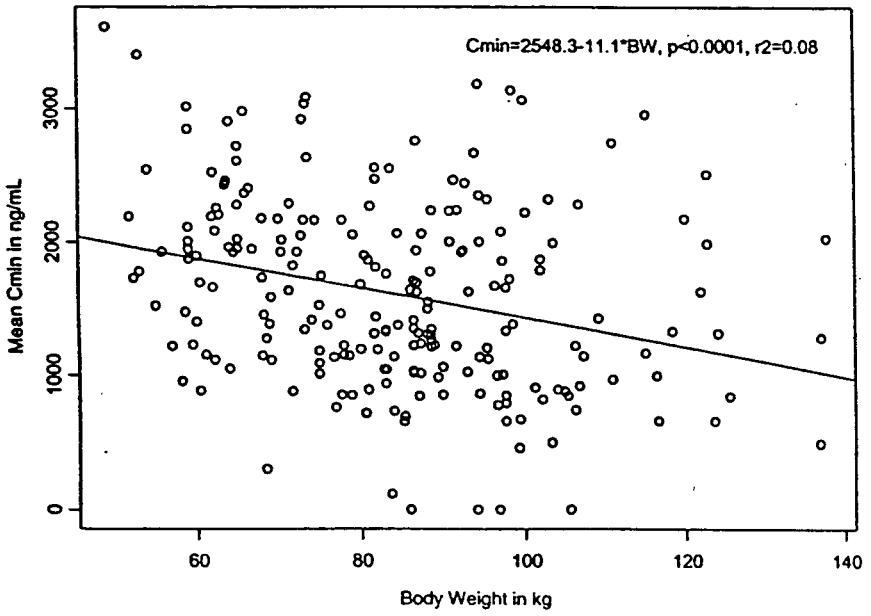


Figure 3. The correlation of AUC at steady state with the body weight

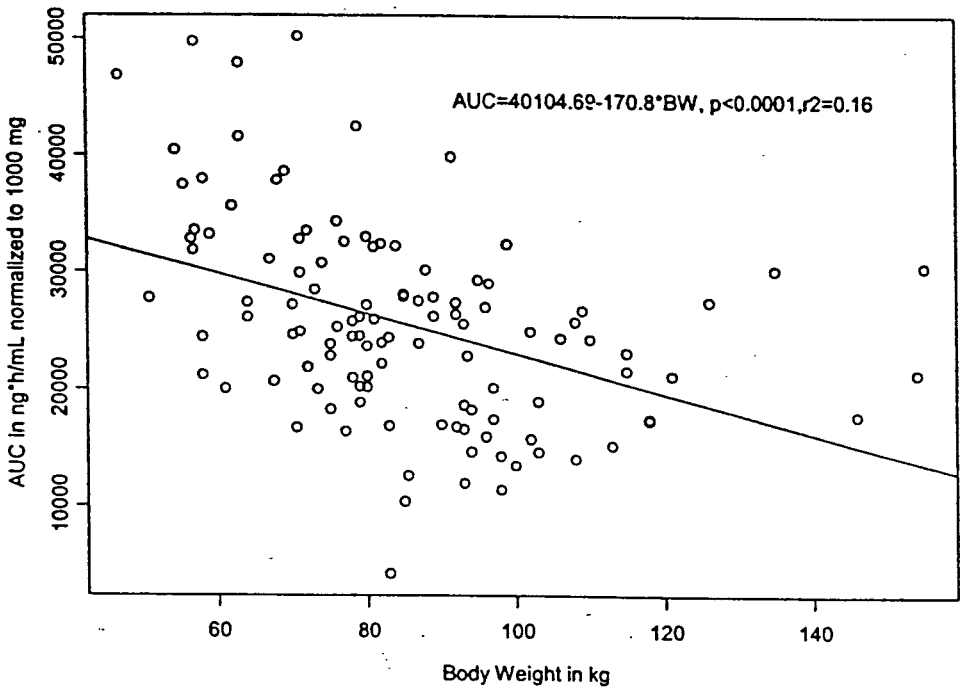


Figure 4. The correlation of Cmax with body weight