European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMA/220670/2010

CHMP ASSESSMENT REPORT

FOR

Ribavirin BioPartners

International Nonproprietary Name:

Ribavirin

Procedure No. EMEA/H/C/001184

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

Page

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant BioPartners GmbH submitted on 08 May 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ribavirin BioPartners, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: Rebetol 200mg Hard Capsules
- Marketing authorisation holder: Schering Plough Limited
- Date of authorisation: 7 May 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/99/107/001-003, EU/1/99/107/005

■ *Medicinal product authorised in the Community/Member State where the application is made or European reference medicinal product:*

- Product name, strength, pharmaceutical form: Rebetol 200mg Hard Capsules
- Marketing authorisation holder: Schering Plough Europe
- Date of authorisation: 7 May 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/99/107/001-003, EU/1/99/107/005

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Rebetol® 200 mg hard capsules
- Marketing authorisation holder: Schering Plough Europe
- Date of authorisation: 7 May 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/99/107/001-003, EU/1/99/107/005
- Bioavailability study number(s): 2008-003852-30

The Rapporteur appointed by the CHMP was Dr Ian Hudson

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 08 May 2009.
- The procedure started on 27 May 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2009. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur declared that he had completed his assessment report in less than 80 days.
- During the meeting on 21 – 24 September 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 September 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 November 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 December 2009.
- During the meeting on 18 – 21 January 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ribavirin BioPartners on 20 January 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 January 2010.
- • The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 06 April 2010.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Ribavirin BioPartners. 200 mg film-coated tablets is a medicinal product containing ribavirin as an active substance. The application for 200 mg tablets was submitted under the Article 10(1) of Directive 2001/83/EC i.e. generic application referring to a reference medicinal product.

Ribavirin is a purine nucleoside analogue that is active against a number of DNA and RNA viruses. There are numbers of proposed mechanisms of action for ribavirin. These include indirect effects such as inhibition of inosine monophosphate and immunomodulatory effects and direct effects such as polymerase inhibition and interference with viral RNA capping. Ribavirin has demonstrated antiviral activity *in vitro* against respiratory syncytial virus and *in vivo* in infected cotton rats when administered intraperitoneally or by aerosol.

Pharmacokinetic properties as well as clinical efficacy and safety are documented for the reference medicinal product Rebetol. Two single dose bioequivalence studies with Ribavirin BioPartners and with the reference product Rebetol were submitted to support the application.

The indication proposed for Ribavirin BioPartners is the same as authorised for the reference medicinal product Rebetol. Rebetol is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa-2b (adults) or interferon alfa-2b (adults and children of 3-years of age or older). There is no safety or efficacy information on the use of Rebetol with other forms of interferon (i.e., not alfa-2b), or on the use of Rebetol with peginterferon alfa-2b in children or adolescents.

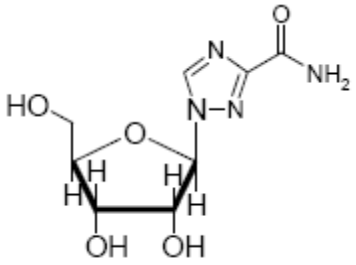
2.2 Quality aspects

Introduction

Ribavirin BioPartners is presented as film-coated tablets containing ribavirin as active substance. Only one strength of 200mg has been developed. Other ingredients are defined in the SPC, section 6.1.: microcrystalline cellulose, povidone, crospovidone, anhydrous colloidal silica, magnesium stearate, hypromellose titanium dioxide, polyethylene glycol.

The film-coated tablets are packed in PVC/PVDC/Alu blister strips. The blisters are packed in cardboard carton.

Active Substance
The chemical name of ribavirin is 1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide corresponding to the chemical formula C8H12N4O5 and molecular mass 244.21 g/mol.



It appears as a colorless powder that is freely soluble in water, slightly soluble in alcohol and very slightly soluble in dichloromethane.
Ribavirin has four asymmetric centers giving 16 potential isomers; the active substance used is enantiomerically pure.
The substance shows polymorphism, one polymorphic form is consistently formed during the active substance production and used in the manufacture of the finished product.

The compound is well known and a monograph is published in the Ph.Eur.

A valid certificate of suitability to the Ribavirin Ph. Eur. Monograph has been submitted as part of this application. The information provided regarding the manufacturing process, the specifications and stability of the active substance was assessed and approved by the European Directorate for the Quality of Medicines (EDQM). Satisfactory quality of the active substance is ensured through the CEP.
Stability results support the proposed retest period of 5 years when the active substance is stored in the proposed container closure system.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to formulate an immediate release solid dosage form containing 200mg of ribavirin per film-coated tablet and being bioequivalent to the reference product, Rebetol.

All excipients used in Ribavirin BioPartners are commonly used in pharmaceutical oral dosage form.
For the tablet core, microcrystalline cellulose is used as a filler, crospovidone as a disintegrant, povidone as a binder, anhydrous colloidal silica as a flow promoter and magnesium stearate is utilised as a lubricant. The film-coat is composed of hypromellose as a film-forming agent, polyethylene glycol as a plasticizer and titanium dioxide as a colorant.
All excipients comply with PhEur monographs. No materials of human or animal origin are used in the synthesis of the drug substance or in the manufacture of the drug product.
No formal compatibility studies between the excipients and the API are provided. However, the stability data generated is considered as a satisfactory indication of the compatibility of the formulation.

The qualitative composition of Ribavirin BioPartners film-coated tablets is different from the reference product. Dissolution studies and comparative dissolution profiles with the reference medicinal product have been provided and the dissolution characteristics are considered comparable.

The finished product will be packaged in PVC/PVDC/Aluminium blister strips which comply with the PhEur monographs and the EU food stuffs regulations.

- Manufacture of the Product

The manufacturing process is a standard wet granulation method followed by coating. The different steps are: granulation, wet sieving, drying, dry sieving, final blending, compression and the coating process. Adequate In-Process controls have been set up and a detailed description along with the process flow scheme has been provided.

There are two possible manufacturers for the finished product: both have the same responsibilities and follow the same manufacturing process. For one manufacturing site, the process validation was performed on batches with different batch sizes including one production scale batch. For the other site, a validation protocol has been provided and the validation study results will be submitted prior to the commercialisation of the product. The validation results presented show that the film-coated tablets can be manufactured reproducibly according to the agreed finished product specification which is suitable for control of this oral preparation.

- Product Specification

The finished product release and shelf-life specifications include tests for description, uniformity of dosage units (Ph. Eur.), loss on drying, hardness (Ph. Eur.), disintegration (Ph.Eur.), dissolution (Ph. Eur.), identification (HPLC, UV), assay (HPLC), purity (HPLC) and microbial limit test (Ph.Eur.).
The analytical methods have been adequately described and validated where appropriate. The same methods are used at both sites. The HPLC method for assay has been validated for specificity, linearity, accuracy, precision and robustness.

The comparative impurities profile was performed between Ribavirin BioPartners film-coated tablets and the reference medicinal product. Impurity profile was found to be satisfactory.

Batch analysis data was provided on one production scale batch and two validation scale batches for the first site and on one validation scale batch for the second site. The data shows compliance with the proposed specification limits for both sites.

- Stability of the Product

Batches manufactured for validation purposes have been placed on stability in the container closure system proposed for use in the commercial product. Stability studies were carried out under ICH conditions: 25°C±2°C/ 60 % ±5 %RH (long term) and 40°C ± 2°C / 75 % ± 5 % RH (accelerated).

The two pilot scale batches and the production scale batch have been exposed to long term storage conditions for 60 months. At accelerated conditions six months data are available for all batches.
Observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve them as Follow-up Measures after the opinion, within an agreed time-frame.

2.3 Non-Clinical aspects

The applicant provided an acceptable summary of the pharmacology, pharmacokinetics and toxicology of ribavirin based on published literature as well as reference books and information from databases. No further non-clinical studies are required and the applicant has justified why no such data were provided.

The impurity profiles of both drug substance and medicinal product are compliant with the Ph. Eur. Monograph and ICH guidance and are acceptable. The SPC is in line with that of the authorised reference product.

The lack of a formal environmental risk assessment was justified by the assumption that the introduction of the generic product would lead to interchange with the prescription of other ribavirin products marketed in Europe, which is unlikely to result in any significant increase in the combined sales volumes for all ribavirin containing products. Therefore the exposure of the environment to

ribavirin is unlikely to increase from use of the generic product. This justification was considered acceptable.

2.4 Clinical Aspects

Introduction

This application concerns a generic medicinal product that contains a single strength of 200 mg ribavirin in a film-coated tablet. The proposed SPC of the generic product is in line with the one for the reference product. To support the marketing authorisation application the applicant had conducted two single dose bioequivalence studies with parallel design, one under fasting the other under fed conditions. These studies were pivotal for the assessment.

Scientific advice was sought for the development programme. For the clinical assessment the Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of particular relevance.

GCP

All studies were complying with GCP, as claimed by the applicant. The applicant has provided a statement to the effect that clinical trial BP-IFN-RIB-001 was partly conducted outside the community and was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies in healthy volunteers.

Study BP-RIB-001

Table 1 Summary of study BP-RIB-001

Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Determine bioequivalence between a new (generic) drug product and a marketed reference product under fasting conditions	Open-label, randomised, two period crossover study	3 tablets or 3 capsules; 600 mg QD; Oral route	39 (36 completed)	Healthy Male Subjects	Single dose

Pharmacokinetics

- Methods

STUDY DESIGN

Study BP-RIB-001 was an open label, randomised, two-period, single dose crossover bioequivalence study conducted in healthy, adult subjects under fasting conditions.

The subjects were hospitalised before each administration, at least 10 hours prior to dosing. They remained in the clinical unit under permanent medical and nursing supervision for 12 hours after each administration. The subjects left the unit at + 12 h once their venous catheters had been removed and returned the following days for the blood sampling. Subjects were randomly assigned to one of two dosing sequences.

The subjects were fasted at least for 10 h before the study medication administration and for + 4 h p.a., except for water that could be taken *ad libitum* from + 2 h p.a. They were given a breakfast at + 4 h p.a., around 12 p.m. The lunch was due to be served at + 7 h p.a. and the afternoon snack at + 10 h p.a. The meals and the caloric intake were similar in both periods. Any additional food or drink intake was prohibited, with the exception of water that could be freely taken from 2 hours after study medication administration.

The volunteers came in from 3.00 p.m. on the day before administration (day -1), staying in the hospital until 8.00 p.m. of the second day (+ 12 h p.a.). Upon arrival, a basal blood sampling was made to conduct the complete analysis of haematology, clinical chemistry, and toxicology. A urine sample was also taken. In addition, a physical examination was made and blood pressure, cardiac rate, respiratory rate, temperature and body weight were determined.

Blood sampling for determination of ribavirin levels was done under basal conditions (prior to administration of study medication) and at following times over 96 h p.a : 0.5, 1, 1.15, 1.30, 1,45, 2, 2.30, 3, 4, 6, 9, 12, 24, 48, 72 and 96 h p.a.

The washout period between the two treatments was at least 21 days.

The clinical part of the study, the bioanalytical analyses as well as the statistical analyses were performed by contract research organisations.

The study protocol and consent form were reviewed and approved (with revisions) by an ethics review board.

TEST AND REFERENCE PRODUCTS

Test and reference products

Test Product (A):	Ribavirin 200 mg tablets
Manufactured by:	BioPartners GmbH
Batch No.:	E059S004
Expiry date:	May 2002
Reference Product (B):	Rebetol 200 mg capsules
Manufactured by:	Schering-Plough Ltd
Batch No.:	00P216
Expiry date:	May 2002

POPULATION(S) STUDIED

36 healthy male volunteers were enrolled in the study. One subject dropped out before period 1 and was replaced. Two subjects dropped out after period 1 and were also replaced. 36 subjects completed both study periods and were included in the statistical analysis. The participants had to be non-smokers or smokers of less than 10 cigarettes per day, aged between 18 and 50 years, and had to have a body mass index (BMI) within 19-27 kg/m^2. The mean demographic data for all enrolled subjects are presented in Table 2. The mean age of subjects was 25.67 years, with the range of 19 to 37 years. Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study.

Inclusion and exclusion criteria were acceptable for the product and for this type of study. The volunteers had committed themselves not to take any food or beverages during the trial that could interfere with the study outcome. This specifically applied to alcoholic drinks as well as to cola, caffeine or other xanthine-containing drinks. They had also committed themselves to abstain from strong physical exercise and strenuous sports activities for the entire study period, starting two days prior to the first hospitalization and finishing after the end of study. It was not allowed to drive vehicles during the active periods.

36 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Table 2 Summary of mean demographic data for enrolled subjects (N = 39)

	Age (years)	Height (cm)	Weight (kg)
Min	19	1.88	57.00
Max	37	1.59	86.50
Mean	25.67	1.7486	71.6389
SD	4.60	5.924E-03	8.1061

ANALYTICAL METHODS

The analysis was performed using a LC/MS/MS method.

The analytical method was considered adequately validated.

PHARMACOKINETIC VARIABLES

Pharmacokinetic parameters for ribavirin plasma concentration were calculated. The following pharmacokinetic parameters for ribavirin concentrations were calculated: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, extrapolated area (%), terminal elimination rate constant λ_z, and half-life of drug elimination during the terminal phase ($t_{1/2}$).

The main pharmacokinetic variables studied were $AUC_{0-ct,}$ $AUC_{0-\infty}$, C_{max} and t_{max} of ribavirin.

The parameters were derived individually for each subject from the ribavirin concentration in plasma. A non compartmental method was used for the pharmacokinetic analysis. The arithmetic means, medians, minimum, and maximum values, geometric mean = exp (mean[ln data]), standard deviations, and coefficients of variations for all parameters were calculated.

STATISTICAL METHODS

The comparison of the pharmacokinetics of the two formulations was achieved using a bioequivalence test.

The statistical analysis was based on the 90% confidence intervals for the mean ratio test/reference of the following parameters: $AUC_{0-ct,}$ $AUC_{0-\infty}$, C_{max}. This analysis was done with log-transformed data.

This method is equivalent to the double t-test procedure with a statistical signification of a 5% assuming a H_0 of no equivalence. The confidence intervals calculation was based in the residual error of the ANOVA.

The ANOVA included all the variation sources (sequence, period and treatment) that could affect the response. t_{max} comparison was done using a non-parametric statistical method. The 90% confidence interval of the ratio test/reference was calculated by means of the Hauschke method, which is insensitive to putative period effects.

According to the current European Guidelines of bioequivalence, the theoretical ranges of acceptability can be considered as well established for AUC within 0.80 to 1.25. However, for some parameters, as for C_{max}, wider ranges than the standard 0.80- to 1.25 can be justified prospectively. In this study, according to the usual pattern of administration, as well the wide therapeutic range, it was considered as reasonable to pre-establish the acceptability ranges as follows:

- Ln AUC: 20% [80% - 125%]
- Ln C_{max}: 30% [70% - 143%]
- t_{max}: 30% [70% - 130%]

In any case the significance level considered was ≤ 5% (probability of α error of 0.05)

- Results

36 out of 39 subjects completed the study and were included in the pharmacokinetic and statistical analysis. Three subjects were excluded during the conduct of the trial due to the following reasons:

- One subject dropped-out before the first treatment period due to hypertension and was replaced;
- One subject dropped-out after the first treatment period due to tonsils hypertrophy and was replaced;
- One subject dropped-out after the first treatment period due to thrombocytopenia and was replaced.

Subjects who replaced the drop-outs kept the random sequence of their precedents.

Protocol deviations that occurred during the conduct of this study were judged by the investigators not to have any significant impact on the accuracy of the study results.

The pharmacokinetic parameters obtained in the 36 subjects who were included in the analysis are presented in Table 3. The results of the statistical analysis for log-transformed data are displayed in Table 4.

Table 3 Pharmacokinetic parameters of study BP-RIB-001 (non-transformed values)

	Test			Reference		
	N	Mean*	SD**	N	Mean*	SD**
AUC_{0-t} [ng×h/ml]	36	9814.32	4681.60	36	9253.15	4018.42
$AUC_{0-\infty}$ [ng×h/ml]	36	12231.19	8290.19	36	11248.65	6362.29
C_{max} [ng/ml]	36	801.69	316.31	36	816.900	371.40
t_{max} [h]	36	median 1.25 min-max 0.5-4.0	---	36	median 1.25 min-max 0.5-4.0	---
$t_{1/2}$ [h]	36	median 33.4 min-max 6.0-131.7	---	36	median 38.8 min-max 9.3-170.0	---

$AUC_{0-\infty}$ Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} Area under the plasma concentration-time curve from time zero to t hours
C_{max} Maximum plasma concentration
t_{max} Time for maximum concentration
* Arithmetic mean
** Standard deviation

Table 4 Statistical analysis of study BP-RIB-001 (log transformed data)

Parameter	Ratio of geometric means	90% CI*	
		Lower	Upper
AUC_{0-t} ng×h/ml)	1.04	0.93	1.16
$AUC_{0-\infty}$ ng×h/ml)	1.06	0.92	1.22
C_{max} (g/ml)	1.01	0.92	1.11
t_{max} [h]	1.08	0.92	1.17

* 90% confidence intervals based on log transformed values.

The 90% confidence intervals for the ratio of geometric means of AUC_{0-t}, AUC_{0-inf}, C_{max} and t_{max} (log-transformed data) were within the limits of 80% to 125%.

For 23 cases (12 test and 11 reference curves; 32%), AUC extrapolated was higher than the normally accepted 20% of total AUC. Therefore, $AUC_{0-\infty}$ cannot be considered as a reliable parameter for the main analysis. However, most pharmacokinetic curves (55/72, 76.4%; 23 cases for the test and 22 for the reference formulation) showed below limit of quantification values at the final point of measurement (96 h) indicating that both the AUC_{0-t} and $AUC_{0-\infty}$ are equivalent for most of the subjects. Thus, based on these results and according to the protocol, AUC_{0-t} was taken instead of the $AUC_{0-\infty}$ as the main parameter.

Bioequivalence criteria of the two products under fasting conditions were within the standard bioequivalence criteria 0.8-1.25. The 600mg dose (3x200mg tablet) was selected for the bioequivalence study on the grounds that the 600mg represents the dose used in clinical practice. Ribavirin has a linear pharmacokinetics and is highly soluble; hence the 600mg dose is acceptable.

The washout period between the two study periods was 21 days, none of the pre-dose samples contained detectable levels of ribavirin. The length of washout period was long enough for the analytical method used (50 µg/ml). 12 subjects and 11 subjects, after the administration of test and reference product respectively, had the area extrapolated >20% of the AUC total. Ribavirin is highly soluble and is absorbed quickly with t_{max} around 1 to 2 h. Ribavirin accumulates in red blood cells (60:1 compared with plasma), and extremely long elimination is attributable to the redistribution from the cellular compartment. On these grounds it can be concluded that the blood collections time (96 h) was sufficient to entirely cover the absorption phase.

Safety data

54 adverse events were recorded mild to moderate in nature, headache was the most commonly reported adverse event. Overall, the medication was well tolerated and no clinically significant adverse events were detected.

Study BP-RIB-004

Table 5 Summary of study BP-RIB-004

Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Determine bioequivalence between a new (generic) drug product and a marketed reference product under fed conditions	Open-label, randomised, two period crossover study	3 tablets or 3 capsules; 600 mg QD; Oral route	59 (48 completed)	Healthy Male Subjects	Single dose

Pharmacokinetics

- Methods

STUDY DESIGN

Study BP-RIB-004 was an open label, randomised, two-period, single dose crossover bioequivalence study conducted in healthy, adult subjects under fed conditions.

The subjects were hospitalised on the evening before each administration. They remained in the clinical unit under permanent medical and nursing supervision for 24 hours after each administration. The subjects left the centre after withdrawal of the 24 h blood sample. All following activities were performed on an ambulatory basis. Subjects were randomly assigned to one of two dosing sequences.

In the morning of Day 1 of each study period, after a 10-hour overnight fast, subjects received a standardised high-calorie high-fat breakfast. Subjects completed the meal within 25 minutes. Investigational product was administered with a total of 200 ml of non-carbonated mineral water 30 minutes after the start of the meal. Within 2 hours after drug administration, only the water supplied with the drug was permitted. Approximately four (4) hours after drug administration, a lunch was served.

Blood sampling for determination of ribavirin levels was done at the following times over 96 h p.a : 0 (prior to administration), 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 9, 12, 24, 48, 72 and 96 h p.a.

The washout period between the two treatments was 21 days.

The clinical part of the study, the bioanalytical analyses as well as the statistical analyses were performed by contract research organisations.

The study protocol and consent form were reviewed and approved (with revisions) by an ethics review board.

TEST AND REFERENCE PRODUCTS

Test and reference products

Test Product (A):	Ribavirin 200 mg tablets
Manufactured by:	BioPartners GmbH
Batch No.:	8H7720
Expiry date:	July 2013
Reference Product (B):	Rebetol 200 mg capsules
Manufactured by:	Schering-Plough Ltd
Batch No.:	7RCJA11A01
Expiry date:	February 2009

POPULATION(S) STUDIED

For this study 59 subjects were screened and 48 subjects were randomised all of whom completed both study periods. All 48 subjects were included in the pharmacokinetic and safety analysis.

The participants had to be healthy male Caucasians, non-smokers or smokers of maximally 10 cigarettes per day, aged between 18 and 50 years, weighing at least 50 kg, and had to have a body mass index (BMI) within 19-27 kg/m^2. The mean demographic data for all enrolled subjects are presented in Table 6. The mean age of subjects was 40.1 years, with the range of 19 to 50 years. Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study.

During confinement, only those beverages which did not contain any alcohol, xanthine or caffeine were consumed. Subjects were advised to avoid heavy physical exertion during the time of confinement and until collection of the last blood sample in each period. Subjects were not allowed to be supine for two hours after drug administration.

It was not permitted to use any drugs for fourteen (14) days or 10 half-lives prior to the planned first drug administration. No prescription or non-prescription drugs were permitted while the subjects participated in the study, except when necessary to treat an adverse event. Before using any concomitant medication, the investigator or his representative was to be consulted.

48 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Table 6 Summary of mean demographic data for enrolled subjects (N = 48)

	Age (years)	Height (cm)	Weight (kg)
Min	19	163	58.2
Max	50	194	98.5
Mean	40.1	178.1	76.48
SD	8.2	7.2	9.2

ANALYTICAL METHODS

The analysis was performed by an LC/MS/MS system.

Within-study accuracy and precision was within the acceptance range

The analytical method was considered adequately validated.

PHARMACOKINETIC VARIABLES AND STATISTICAL METHODS

Pharmacokinetic parameters C_{max}, AUC0-t, $AUC_{0-\infty}$, T_{max}, $T_{1/2}$ were determined. PK parameters for each individual were tabulated and graphically presented. Non-compartmental analysis and the linear trapezoidal method were used to calculate AUC_{0-t}. Standard pharmacokinetic approach was used to calculate the elimination rate constant, $T_{1/2}$ and $AUC_{0-\infty}$.

Statistical analyses were performed for ribavirin plasma concentration data. Analyses of variance (ANOVA) were performed on the log-transformed pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The ANOVA model contained fixed effects for sequence, period, and treatment and a random effect for subject within sequence. Each ANOVA included a calculation of least-squares means, the difference between formulation means, and the standard error associated with this difference.

Ratios of least-squares means and 90% confidence intervals for the difference between formulation least-squares means were calculated for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} using ln-transformed data

- Results

48 out of 48 subjects completed the study and were included in the pharmacokinetic and statistical analysis. Protocol deviations that occurred during the conduct of this study were judged by the investigators not to have any significant impact on the accuracy of the study results.

The pharmacokinetic parameters obtained in the 48 subjects who were included in the analysis are presented in Table 7.

Table 7 Pharmacokinetic parameters of study BP-RIB-0041 (non-transformed values)

	Test			Reference		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
AUC_{0-t} [ng×h/ml]	48	15804	22%	48	18734	18%
$AUC_{0-\infty}$ [ng×h/ml]	19	18092	25%	19	21240	16%
C_{max} [ng/ml]	48	1078	29%	48	1141	28%
t_{max} [h]	48	2.0	1.0 – 4.00*	48	3.0	1.50 – 4.00*
$t_{1/2}$ [h]	44	46.2	19%	45	42.5	14%

* = median (range) reported rather than geometric mean (geometric CV%).

At 96 hours after post-dose, all study subjects had detectable ribavirin concentrations.

Table 8 Statistical analysis of study BP-RIB-004

Parameter	**Geometric (LS) Mean**		**Ratio of geometric means (%)**	**90% CI***	
	Test	**Reference**		**Lower**	**Upper**
AUC_{0-tz}	15804	18734	84	81	88
$AUC_{0-\infty}$	20775	22440	93	78	110
C_{max}	1078	1141	95	91	99

The C_{max} and the AUC_{0-t} meet the standard criteria for bioequivalence.

The sampling time in this study was sufficiently long (96 h, all subjects had measurable concentrations at 96 h) and therefore, it was concluded that the AUC_t covered adequately the absorption phase and AUC_t equals $AUC_{0\text{-}96h}$. According to the CHMP guideline on the investigation of bioavailability & bioequivalence, for drugs with a long half-life, a bioequivalence can be estimated using truncated AUC, as long as the total blood collection period is justified and if the absorption process is complete. It is well known that ribavirin has a very large volume of distribution and accumulates significantly in red blood cells (60:1 compared with plasma). Due to re-distribution from the cellular compartment, ribavirin has a long elimination half-life (80 h). Hence, $AUC_{0\text{-}t}$ is an appropriate parameter to conclude bioequivalence.

Safety data

27 adverse events were recorded mild to moderate in nature, headache was the most commonly reported adverse event. Two subjects experienced adverse events after both treatments. Most adverse events (18) were evaluated as drug-related. After the most frequent adverse event (headache), further adverse events were general disorders, gastrointestinal disorders, respiratory disorders, eye disorders and injury.

Most adverse events were mild in intensity. Two severe adverse events (headache and vomiting) occurred during treatment. No serious adverse events occurred in the study.

- Conclusions

Based on the presented bioequivalence studies Ribavirin BioPartners is considered bioequivalent with Rebetol.

Pharmacodynamics

No new pharmacodynamic data have been provided by the applicant. These data are not required for this particular application.

Additional data

The applicant also provided results of two further BE studies with the US reference product. In addition, one multicentre, placebo-controlled, parallel group efficacy and safety study in patients with chronic hepatitis C of genotype 2 and/or 3 was also conducted with the test product.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

The application for a generic medicinal product is based on a reference product for which no safety concern requiring specific risk minimisation activities has been identified. Therefore, a risk management plan was not considered necessary for this generic medicinal product. However, in case additional risk minimisation measures should be identified for the reference product, the applicant will have to provide an EU RMP.

- **User consultation**

The results of a user consultation of the Package leaflet have been provided and the qualitative and qualitative evaluation was considered acceptable.

Discussion on Clinical aspects

Two bioequivalence studies were conducted to support this generic application. One single-dose two-period crossover study under fasting and one under fed condition with the test and the EU reference product were submitted. The bioequivalence study under fed conditions is considered as pivotal for this application since, according to the SmPC of the reference product Rebetol, ribavirin should be administered with food.

In the fed study, a carryover from period 1 to period 2 occurred with a washout period of 21 days between the study periods. It is well known that ribavirin has a very large volume of distribution and accumulates significantly in the red blood cells (60:1 compared with plasma). Due to re-distribution from the cellular compartment, ribavirin has a long elimination half-life (80 h). This explains the significant carryover observed in period 2.

The Applicant submitted pre-dose concentrations and percentages for C_{max} in period 2 for all subjects by treatment. All subjects, except one, had ribavirin plasma concentrations in period 2 below 5% of

C_{max}. Statistical analysis was conducted for C_{max} and AUC_t using data for all subjects with pre-dose concentrations below 5% of Cmax. Bioequivalence was demonstrated. Hence, the extent of carryover observed in period 2 was within the acceptable range.

The sampling time in this study was sufficiently long (96 h, all subjects had measurable concentrations at 96 h) and therefore, it was concluded that the AUC_t adequately covered the absorption phase and that AUC_t equals $AUC_{0\text{-}96h}$. According to the CHMP guideline on the investigation of bioavailability & bioequivalence, for drugs with a long half-life, a bioequivalence can be estimated using truncated AUC, as long as the total blood collection period is justified and if the absorption process is complete. It is well known that ribavirin has a very large volume of distribution and accumulates significantly in red blood cells (60:1 compared with plasma). Due to re-distribution from the cellular compartment, ribavirin has a long elimination half-life (80 h). Hence, $AUC_{0\text{-}t}$ is an appropriate parameter to conclude bioequivalence.

Bioequivalence was demonstrated after a single dose administration. The pharmacokinetics of ribavirin is linear after single dose administration. Ribavirin accumulates with a ratio of 6:1 after multiple versus single dose administration due to very slow elimination. No saturation in elimination mechanisms or absorption has been described, indicating that the kinetics is time- and dose-independent. Hence, the single dose design is acceptable.

The bioequivalence conclusion was based on the C_{max} and $AUC_{0\text{-}96}$, which is appropriate. The test product in the bioequivalence study is identical to the product for which the marketing authorisation is applied for. The size of the biobatch was adequate.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality data. From a nonclinical perspective the applicant provided an adequate summary of the current scientific knowledge related to ribavirin, compared the impurity profiles of the test and reference products, and adequately justified the absence of an environmental risk assessment. Therefore no further non-clinical data are warranted.

With regard to the clinical data, an appropriate summary of the pharmacokinetics, pharmacodynamics, efficacy and safety of ribavirin for treatment of chronic hepatitis C was provided. Basis of this application were two single dose bioequivalence studies between the test product (200 mg strength) and the reference product, one in fasting, the other in fed conditions, the latter being considered pivotal. The overall design of these studies as well as the bioanalytical methods are considered adequate. The statistical analysis of the pharmacokinetic data from these studies showed that the target parameters $AUC_{0\text{-}96\ h}$ and C_{max} were within the acceptance limits of 0.8-1.25. Therefore, bioequivalence has been shown.

Overall, a benefit/risk ratio comparable to the reference product can therefore be concluded.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus decision that the benefit/risk ratio of Ribavirin BioPartners in the treatment of chronic hepatitis C as part of a combination regimen with peginterferon alfa-2b (adults) or interferon alfa-2b (adults, children over the age of 3 and adolescents) was favourable and therefore recommended granting of the marketing authorisation.