European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref.: EMEA/158307/2009

ASSESSMENT REPORT
FOR

Ribavirin Teva

International Nonproprietary Name: **Ribavirin**

Procedure No. EMEA/H/C/001018

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

1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 08 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ribavirin Teva, 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).

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: **Virazole, poeder voor inhalatievloeistof**
  - Marketing authorisation holder: **ICN Pharmaceuticals Inc**
  - Date of authorisation: **01-06-1988**
  - Marketing authorisation granted by:
    - Member State (EEA): **The Netherlands**
      - National procedure
  - Marketing authorisation number: **RVG 12588**

- 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: **07-05-1999**
  - Marketing authorisation granted by:
    - Community
  - Community Marketing authorisation numbers: **EU/1/99/107/001, EU/1/99/107/002, EU/1/99/107/003 and EU/1/99/107/001-005**
  - Bioavailability study numbers: **R07-1285**

The Rapporteur appointed by the CHMP was 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.

An application was filed in Latvia and withdrawn by applicant after authorisation.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 8 May 2008
- The procedure started on 28 May 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2008.
- During the meeting on 22-25 September 2008, 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 26 September 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 October 2008.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 November 2008.
- During the CHMP meeting on 18 December 2008, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the List of Outstanding Issues on 24 December 2008.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 January 2009.
- During the meeting on 19-22 January 2008, 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 Teva on 22 January 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 January 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 31 March 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Ribavirin Teva 200 mg hard capsules is a generic medicinal product containing ribavirin as an active substance.

Ribavirin is a purine nucleoside analogue which 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 have been well demonstrated for the reference medicinal product Rebetol. A single dose bioequivalence study with the Ribavirin Teva and with the reference product Rebetol was submitted to support the application.

The indication proposed for Ribavirin Teva 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

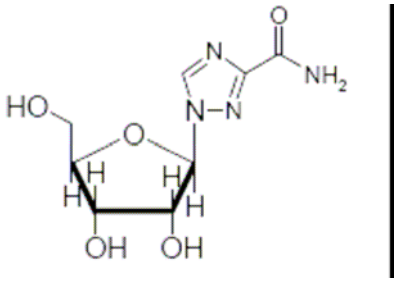
Introduction

Ribavirin Teva is presented as hard gelatin capsules containing 200 mg of ribavirin (active substance). Capsules are white, opaque and imprinted with blue ink. The excipients used in the preparation of Ribavirin Teva are well known excipients used in the capsule preparations such as calcium hydrogen phosphate, croscarmellose sodium, povidone and magnesium stearate (present in capsule content), gelatin and titanium dioxide (present in capsule shell), shellac, titanium dioxide and indigo carmine (present in printing ink).

The capsules are packed in polyvinyl chloride / polyethylene / polyvinylidene chloride blisters (PVC/PE/PVdC blisters).

Active Substance

The active substance is chemically designated as 1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide (Chemical Name) or 1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,2,4-triazole-3-carboxamide (Chemical IUPAC Name) and has the following structure:



Ribavirin is a white crystalline powder freely soluble in water, slightly soluble in ethanol (96%). It has a specific optical rotation between -33.0° and -37.0° (dried basis 10mg/ml, t=20°C), pH 4.0-6.5.

Ribavirin may exist in two polymorphic forms A and B which are distinguishable by their melting range. One form crystallised from aqueous ethanol melts at 166 ~ 168 °C (form A) while form crystallised from ethanol has a melting range of 174 ~ 176 ºC 9 form B). The commercially utilised manufacturing process is optimised to produce the desired polymorph.

- Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure. A three step synthesis involving coupling step, ammonolysis and re-crystallisation has been well described. Critical parameters and accompanying in-process controls to ensure quality of the final compound, have been defined.

Confirmation of the chemical structure of ribavirin was provided by elemental analysis (confirmation of the determined elementary composition), spectroscopic methods as IR, ^{1}H-NMR, ^{13}C-NMR, MS, X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC). X-ray diffraction studies and DSC confirm the morphology of ribavirin and confirm the proposed polymorphic form to be consistent with the compendia standard.

Potential impurities have been well discussed in relation to their origin and potential carry-over into the final drug substance.

- Specification

The active substance specification includes tests for physical appearance and solubility, identification (IR), specific rotation, loss of drying, pH, sulphated ash, heavy metals, related substances (HPLC), assay (HPLC), bulk and tapped density, particle size distribution, polymorphism (content of the form B), melting range and residual solvents (GC). The specification generally complies with the Ph Eur monograph for ribavirin with additional in-house tests for which suitable validation data are provided.

A detailed description for all analytical methods was provided. Most of the methods are Ph Eur apart from particle size, polymorph testing, melting range, related substances and residual solvents. Full method validation data was provided for the non compendial (in-house) analytical methods.

Particle size (laser diffraction) was suitably validated for repeatability, intermediate precision and robustness. Two HPLC methods were proposed for assay and related substances. One is the same as the Ph Eur and the other is an in-house method. The latter method was suitably validated with respect to system precision, linearity, range, accuracy, recovery, method precision, limit of detection and limit of quantitation. The limit test for residue of polymorph form and determination of melting point has been suitably validated with respect to specificity, precision, accuracy, detection limit and robustness.

Impurities have been evaluated and found to be acceptable from the point of view of safety.

The GC method for residual solvents has been suitably validated for reproducibility, linearity, method precision, accuracy (recovery), limit of detection and limit of quantitation. All residual solvent acceptance criteria are in line with ICH recommended limits and proposed limits for impurities comply with the Ph Eur monograph for ribavirin.

In general analytical methods proposed are suitable to control the quality of the active substance.

Data on five consecutive batches of ribavirin was provided by the ASMF Holder. In addition data on six batches of ribavirin used in the manufacture of the biobatch and other pilot batches was provided by the manufacturer of the medicinal product. All batches represented full scale production and complied with the requirements in the active substance specification.

- Stability

Stability studies were carried out according to ICH guidelines for real time (25°C/60% RH) and accelerated conditions (40°C/75% RH). Data for three validation batches are given with 60 months real time and 6 months accelerated data. In addition, further eight batches were also subjected to stability studies. Data obtained under real time and accelerated testing showed all results to comply with the proposed specification. No specific trends were evident.

Additionally, data from photostability study (UV light exposure), and from stressed degradation studies (including exposure to heat, acid and base degradation and oxidative conditions) was provided. Under stress testing both the sample batches and the reference standard degraded with the same trend and formation of similar degradation products.

The stability studies confirmed the proposed re-test period.

Medicinal Product

- Pharmaceutical development

The aim of the pharmaceutical development was to obtain an immediate release capsule, containing quantitatively and qualitatively the same drug substance as the reference medicinal product and to be bioequivalent.

Similarity to the reference medicinal product was addressed by way of composition comparisons, dissolution studies, solubility studies and comparative impurity profiles.

Compositions of Ribavirin Teva capsules and the reference medicinal product are similar. Ribavirin Teva capsules contain calcium hydrogen phosphate, croscarmellose sodium, povidone and magnesium stearate. The reference product contains microcrystalline cellulose, lactose, croscarmellose sodium and magnesium stearate. Similarity between two products was also shown with dissolution testing. Dissolution studies were carried out in line with the Ph Eur. The dissolution profiles for both products were similar.

Solubility of ribavirin was tested in buffered solution over the physiological pH range 1.0 to 7.5. It was found to be high in all cases.

An impurity comparison of Ribavirin Teva active substance and the reference product was undertaken. Results showed no degradation to occur as a result of the manufacturing process as the impurity profile for the drug substance was similar to that of the product. In addition, Teva's ribavirin capsules and the reference product showed levels of impurities to be under the reporting limit.

A single-dose, randomised, one-period, open-label study under fed conditions was conducted to compare the relative bioavailability of Ribavirin Teva 200mg capsules to that of the reference medicinal product - Rebetol 200mg capsules. Data obtained conclude that the 90% confidence intervals of the relative mean AUC_t, $AUC_{inf\ and}$ C_{max} of the test to reference product are within the 80-125% range. Results therefore show the two products to be bioequivalent under fed conditions.

The medicinal product manufacturing process development was also performed. Details were provided for experimental batches manufactured to establish optimum manufacturing conditions. Wet granulation was selected as the conventional method of converting powders into granules having a suitable flow and cohesive properties.

The first set of experiments compared the effect of different percentages of the disintegrant on the dissolution profile of different sizes of capsules. Experiments also allowed establishing an appropriate concentration of disintegrant in the formulation.

The second set of experiments performed on a larger scale batches, examined the effect of a batch size on the physical properties and chemical results (dissolution profile). The study re-examined batches with different quantities of disintegrant in the formulation.

The scale-up batch formula was manufactured to optimise the manufacturing steps. The granulate was dried, milled and blended together with the lubricant to obtain the final blend for encapsulation. This scale-up batch details were selected and used to make the pilot batches.

- Adventitious Agents

Among excipients used in the medicinal product only gelatin (component of the capsule shell) are of animal origin and Ph Eur TSE Certificates of Suitability were provided for this excipient.

Magnesium stearate used in the formulation is of vegetal origin.

- Manufacture of the Product

The manufacturing process is sufficiently described with granulation and encapsulation being defined as the critical steps. A flow diagram and detailed description of the manufacturing process have been provided.

Briefly, the manufacturing process involves (1) Premixing, (2) Granulation, (3) Drying and milling – the granulate is dried and then milled, (4) Final blending, (5) Capsule filling – the mix is filled into the capsules and (6) Packaging.

The critical steps in the manufacturing process are granulation and encapsulation. The homogeneity of the final blend was examined by testing for uniformity of blend during the validation procedure for two batches, one of pilot scale and one of commercial scale. Results clearly showed that the granulate is homogenous and the manufacturing process suitably controlled.

At the time of submission only validation protocol was provided. This is acceptable as according to CPMP/QWP/848/96, Note for Guidance on Process Validation, "it is recognised that, at the time of submission, process validation data may not always be available. Nevertheless it is essential that valid manufacturing processes are always utilised". The in-process control parameters were verified during the manufacture of pilot batches.
Also the applicant committed to perform validation on the first three production scale batches.

- Product Specification

The product specification is standard for capsules and contains tests with suitable limits for appearance, identification (HPLC and UV), dissolution, uniformity of dosage units, assay, impurities and degradation products (HPLC), microbial limits, water content and identification of colour.

Full details of all analytical methods are provided. All non pharmacopoeial methods have been satisfactory validated. The HPLC method for assay, dissolution and impurity/degradant products has been suitably validated with respect to specificity, precision, linearity, accuracy, detection limit, quantitation limit, robustness, stability of sample and standard solution.

The proposed dissolution limits is tighter than that proposed in the Ph Eur. The proposed limits for individual degradation products is in line with the qualification and identification threshold in the ICH Q3B (R2) Impurities in New Drug Products and is well justified by real time data.

Batch analysis data was provided on one pilot scale and one commercial scale batches, made using different batches of the active substance. Batches met the proposed specification limits. Results showed that capsules can be manufactured reproducibly according to the finished product specifications.

- Stability of the Product

Stability studies were carried out under ICH conditions of 25ºC/60%RH (long term, 12 months), 30ºC/65%RH (intermediate, 3 months) and 40ºC/75%RH (accelerated, 6 months).

Batches tested under long term conditions met all the proposed specifications; appearance of capsules did not change, ribavirin assay values did not change significantly, dissolution values were within specification, values for degradants met the proposed specifications.

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

In summary the stability data provided support the proposed shelf-life and storage conditions.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and medicinal 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 issue which has no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measure after the opinion, within an agreed time-frame.

- **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.

- **Clinical Aspects**

Introduction

This application concerns a generic medicinal product that contains a single strength of 200 mg ribavirin in a hard capsule. The proposed SPC of the generic product is in line with the one of the reference product. To support the marketing authorisation application the applicant had conducted a single dose bioequivalence study with parallel design under fed conditions (study R07-1285). This study was the pivotal study for the assessment.

Scientific advice was not 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

The pivotal study was complying with GCP, as claimed by the applicant. The applicant has provided a statement to the effect that clinical trial R07-1285 was 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 one bioequivalence study; the details of this study are summarised in table 1.

Table 1 Summary of study R07-1285

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	Randomized, parallel	Two capsule formulations, 200 mg, Oral	88(82 completed)	Healthy Male Subjects	Single dose

Pharmacokinetics

- Methods

Study design

Study R07-1285 was a single dose, randomised, open-label, one-period, parallel design bioequivalence study conducted under fed conditions.

Subjects were housed at the clinical facility on the day prior to drug administration and remained at the clinical facility until the 24 hour blood sample collection. The randomization scheme was computer generated and the subjects were randomized prior to study drug administration.

Dosing occurred 30 minutes after the initiation of a standardised high-fat breakfast, consisting of two eggs cooked in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and 240 mL of whole milk. Subjects were required to consume the entire breakfast prior to drug administration. No fluid, except that given with drug administration, was allowed from one hour prior to dose administration to one hour following dose administration. Study drug was administered with 240 ml water.

Blood samples were collected within 90 minutes prior to dosing (0-hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8, 12, 24, 48, 96, 144, 216, 288, 432, 576, and 720 hours. Twenty-six blood samples (approximately 156 ml) were collected over the course of the study period.

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

The test and reference product used in study R07-1285 were as follows:

Test product: Ribavirin 200 mg capsules
Manufactured by: TEVA Pharmaceutical Industries Ltd
Batch No.: K-39306
Batch size: 130 000
Manufacturing date: 23 September 2007

Reference product: Rebetol 200 mg capsules, marketed in the UK
Manufactured by: Schering-Plough Ltd
Batch No.: 6RCJA38A06
Expiry date: May 2008

Population(s) studied

88 healthy male non-smoking subjects were enrolled and received either test or reference product according to the dosing randomisation schedule. Study groups were balanced with respect to age. The mean age of subjects was 25 years, with the range of 18 to 52 years. Subjects were mainly white. The demographics of the subjects are summarised in table 2.

Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study. Subjects were not allowed to use prescription medications for a period of 14 days prior to dosing. Over-the-counter medications were restricted for a period of seven days prior to dosing.

87 subjects completed the clinical portion of the study in its entirety. The plasma samples from 87 subjects were assayed for ribavirin. There were 87 sets of data for ribavirin for this study.

Table 2 Demographics of participants in study R07-1285

Demographic Data – All Subjects by Treatment				
Characteristic	**Variable**	**All**	**Test**	**Reference**
Age	N	88	44	44
	Mean	25.4	23.2	27.6
	(SD)	8.4	5.7	10.0
BMI (kg/m^2)	N	88	44	44
	Mean	25.5	25.4	25.6
	(SD)	2.8	2.7	2.9
Height (cm)	N	88	44	44
	Mean	178.2	178.5	177.9
	(SD)	6.3	6.4	6.2
Weight (kg)	N	88	44	44
	Mean	81.0	81.2	81.1
	(SD)	11.1	11.3	11.1
Gender	N	88	44	44
	Males	100%	100%	100%
	Females	0%	0%	0%
Race	N	88	44	44
	Asian	2.27%	2.27%	2.27%
	American Indian	1.14%	2.27%	0%
	Alaskan Native	5.68%	4.55%	6.82%
	Black or African	89.77%	90.91%	88.64%
	American	1.14%	0%	2.27%
	White			
	White, Asian			

Test: Ribavirin 200 mg Capsules EU (Batch No.: K-39306)
Reference: REBETOL® 200 mg hard capsules (Batch No.: 6RCJA38A06)

Analytical methods

The analysis of plasma samples using a LC/MS/MS method.

With the initial method, study samples were analysed in a total of 36 analytical sequences, within-study accuracy and precision was within the acceptance range, 95% to 105% and 4.2% to 14.2%, respectively.

At the completion of the sample analysis of the samples from study R07-1285, it was observed that the assay range may not have had a sufficient lower limit of quantitation as most samples past 48 hours were below level of quantitation. The samples were then subsequently re-analysed using a different analytical method with a lower limit of quantitation .

Both analytical methods were adequately validated.

Pharmacokinetic Variables

Pharmacokinetic (PK) parameters C_{max}, AUC_{0-t}, AUC_{0-inf}, 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}. A standard pharmacokinetic approach was used to calculate the elimination rate constant, $T_{1/2}$ and AUC_{0-inf}. The target blood collection times were used in the pharmacokinetic calculations, except for cases where the deviations were greater than ±2 min, the actual times of collection were used.

Statistical methods

Statistical analyses were performed for ribavirin plasma concentration data. Analyses of variance (ANOVA) were performed on the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, and C_{max}. The ANOVA model containing a factor for treatment was utilized in comparing the effects between the treatment products. BMI (20-23, 24-26, 27-30) and gender were to be used as covariates in the ANOVA model. Interactions between treatment and covariates were examined and ruled out as appropriate. Each ANOVA included a calculation of least-squares means, the difference between adjusted formulation means, and the standard error associated with this difference.

Ratios of least-squares means and 90% confidence intervals for the difference between drug formulation least-squares means were calculated for the parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} using ln-transformed data. The geometric mean values were reported. All data were analysed using SAS software.

Statistical analyses appropriate for a one-period parallel design were performed to assess the bioequivalence of the two products.

- Results

Plasma samples from all subjects who completed the study according to the protocol (n=87) were analysed and used in the statistical analysis. One randomised subject withdrew consent after study hour 144 blood draw due to schedule conflict, and is therefore not included in the analysed data set.

None of the pre-dose samples contained detectable levels of ribavirin, which is expected from a parallel design. None of the C_{max} values were detected in the first post-dose sample.

The elimination of ribavirin from plasma appeared to be polyphasic for most of the subjects. The terminal elimination rate constants were estimated from the plasma ribavirin data for all subjects using the plasma concentrations of the terminal elimination phase, determined from the plasma concentration *versus* time plots (log scale). There were multiple cases where the terminal elimination phase of ribavirin was not well characterized, i.e. non-linear after log-transformation. No values for AUC_{0-inf} or $T_{1/2}$ were reported for these cases.

The 90% confidence intervals for the ratios of the geometric means of AUC_{0-t}, AUC_{0-inf} and C_{max} (ln-transformed data) were within the limits of 0.8-1.25.

The CHMP noted however that the AUC_{0-t} was less than 80% of the AUC extrapolated to infinity for most of the study subjects; individual values were reported in a range of 60% to 90%. On the other hand, none of the last blood samples collected at 576-hours and at 720-hours post-dose contained measurable levels of ribavirin indicating that the blood collection time was sufficient using the current analytical method. Therefore, the sensitivity of the employed analytical method was questioned. In response to this issue the applicant presented the results from re-analysed study samples using an analytical method with lower limit of quantification, in which case all study subjects had detectable levels of ribavirin at 720 hours post-dose. The area extrapolated from AUC_{0-t} to infinity was less than 10% of the AUC_{0-inf} for most of the subjects. Except in one case the terminal elimination phase in all

profiles from reanalysed samples was linear after log-transformation of the data allowing the determination of $AUC_{0\text{-}inf}$ and $T_{1/2}$

The pharmacokinetic parameters obtained with the test product and the reference product using the improved analytical method are presented in table 3.

Table 3 Pharmacokinetic parameters (non-transformed values)

	Test			Reference		
	N	**Mean***	**SD****	**N**	**Mean***	**SD****
$AUC_{0\text{-}t}$ [ng*h/ml]	44	12999.37	2684.03	43	12656.91	3239.53
$AUC_{0\text{-}inf}$ [ng*h/ml]	44	15437.94	3316.07	42	15122.58	3820.65
C_{max} [ng*ml]	44	551.18	126.39	43	560.46	117.37
T_{max} [h]	44	2	1-4	43	2	1.25-4
$T_{1/2}$ [h]	44	315.0	70.88	42	320.95	51.81

$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{0\text{-}inf}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life
* arithmetic mean; for t_{max} median
** standard deviation, for t_{max} range

According to the statistical analysis plan, the BMI and gender were covariates in the ANOVA model. Due to the fact that all subjects in this study were male, the gender covariate was not included. The interaction between treatment and BMI was performed and there was no significant interaction (α = 0.05). As BMI was not a stratification factor in this study, additional analyses not including this covariate were requested. The data showed that the 90% confidence intervals are very similar whether or not a covariate for BMI is included in the model leading to the same conclusions.

The results of the statistical analysis of the ln-transformed data obtained with the new analytical method and not using BMI as covariate are presented in table 4.

Table 4 Statistical analysis of (ln-transformed data)

Parameter	**Least Square Mean**		**Geometric Mean**		**Ratio of geometric means (%)**	**90% CI***		**CV (%)**
	Test	**Reference**	**Test**	**Reference**		**Lower**	**Upper**	
$AUC_{0\text{-}t}$	9.45	9.41	12720.6	12277.1	104	95.4	113	23.5
$AUC_{0\text{-}inf}$	9.62	9.59	15090.3	14668.7	103	94.6	112	23.7
C_{max}	6.28	6.29	535.9	541.9	99	90.3	108	26.0

* 90% confidence intervals based on ln transformed values.

The 90%confidence intervals for the ratios of the geometric means of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} (ln-transformed data) were within the limits of 0.8-1.25.

Safety data

13 subjects experienced a total of 25 adverse events over the course of the study. Adverse events were mild to moderate in severity. No serious adverse events were reported. A total of 9 adverse events were reported following the oral administration of the test product, the most commonly reported

events were abdominal pain, reported by 2/44 (4.55%) subjects and nasopharyngitis, reported by 2/44 (4.55%) subjects. A total of 16 adverse events were reported following the oral administration of the reference product, the most commonly reported events were headache, which was reported by 2/44 (4.55%) subjects, and pharyngo-laryngeal pain, also reported by 2/44 (4.55%) subjects. There were no clinically significant changes in the clinical laboratory measurements over the course of the study.

- Conclusions

Based on the presented bioequivalence study Ribavirin Teva 200 mg hard capsules are considered bioequivalent with Rebetol 200 mg hard capsules.

Pharmacodynamics

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

Additional data

Study 02105

In response to questions raised by the CHMP regarding the conduct of the study under fed conditions as well as the composition of the meal used in study R07-1285, the applicant provided as supportive data the report of another bioequivalence study conducted under fasting conditions (study 02105). The qualitative and quantitative formulations of the test product were the same in this study however the formulation used a different source of the active substance therefore the Applicant considered this study as supporting data only.

This was a randomised, single dose, two-way cross over study in 24 healthy volunteers (of which 21 successfully completed) in the fasted state. The wash-out period between doses was 42 days. Blood samples were collected over 96 hours post dose. Summary data is provided in table 5.

Table 5 Summary data from study 02105

Pharmacokinetic Parameters

Parameters		Test (Ribavirin (A)) Mean	±	SD	CV (%)	Reference (Rebetol® (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	7012.04	±	1530.27	21.82	7006.95	±	1562.93	22.31
AUC_{0-96h}	(ng·h/mL)	7012.04	±	1530.27	21.82	7006.95	±	1562.93	22.31
C_{max}	(ng/mL)	506.14	±	155.76	30.77	507.14	±	155.10	30.58
T_{max}	(h)	1.50	±	0.83	-	1.25	±	0.50	-
K_{el}	(h^{-1})	0.0138	±	0.0030	21.89	0.0133	±	0.0026	19.79
$T_{½ el}$	(h)	52.74	±	11.68	22.14	54.28	±	12.28	22.63

For T_{max}, medians and interquartile ranges are presented instead of means and SD

Ribavirin (A) vs Rebetol® (B)

	AUC_{0-t}	AUC_{0-96h}	C_{max}
Ratio[1]	100.11%	100.11%	98.87%
90 % Geometric C.I.[2]	95.61 % to 104.81 %	95.61 % to 104.81 %	90.89 % to 107.56 %
Intra-Subject CV	8.62 %	8.62 %	15.86 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Ribavirin (A)} - \text{Rebetol® (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

Bioequivalence under fasting conditions was demonstrated. In order to bridge the two bioavailability studies comparative in vitro dissolution was provided on the two biobatches.

Post marketing experience

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

- **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.

The applicant should ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

Discussion on Clinical aspects

A single dose bioequivalence study in parallel design under fed conditions was conducted to support the marketing authorisation application for a generic product containing 200 mg ribavirin.

The standard daily dose of ribavirin in adults is 800 mg to 1400 mg depending on the body weight in two divided doses. Ribavirin has linear pharmacokinetics after a single dose administration in a dose range of 200 mg to 1200 mg. The bioequivalence study was conducted in healthy volunteers and ribavirin dosing may cause significant side effects. On the grounds of safety of study subjects and linear pharmacokinetics of ribavirin, the 200 mg dose selected for the bioequivalence study is acceptable.

A parallel design was used in the pivotal bioequivalence study. Due to the long elimination half-life of ribavirin (80 hours), the parallel design is acceptable and is in line with the applicable guideline.

The study was conducted under fed conditions (high-fat high-calorie meal). The SmPC of the reference product recommends drug intake with food to maximise absorption, the dose could be subsequently reduced based on the individual tolerance. It is known that food increases AUC and C_{max} of ribavirin by 70%. Therefore, it is appropriate to conduct the bioequivalence study under fed conditions in line with applicable guidelines. As supportive data the applicant submitted a single dose bioequivalence study in a crossover design under fasted conditions, which also demonstrated bioequivalence under fasting conditions.

Initial pharmacokinetic analysis revealed that the AUC_{0-t} was less than 80% of the AUC extrapolated to infinity for most of the study subjects, individual values ranged from 60% to 90%. However, none of the last blood samples collected at 576 hours and at 720 hours post-dose contained measurable levels of ribavirin. A re-analyses of study samples was performed using an improved analytical assay and the applicant provided a respective statistical analysis for the bioequivalence conclusion.

Based on the available data it is concluded that bioequivalence of the two products has been demonstrated.

- **Overall conclusions, benefit/risk assessment and recommendation**

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

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