European Medicines Agency

Doc. Ref.: EMEA/424700/2009

Medicinal product no longer authorised

CHMP ASSESSMENT REPORT
FOR

RIBAVIRIN TEVA PHARMA B.V.

International Nonproprietary Name:
ribavirin

Procedure No. EMEA/H/C/1064

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

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TABLE OF CONTENTS

Page

Medicinal product no longer authorised

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 1 September 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ribavirin Teva Pharma BV, 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'.

Ribavirin Teva Pharma BV 200 mg film-coated tablets:

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/1/99/107/005**
  - Bioavailability study numbers: **S08-0152**

Ribavirin Teva Pharma BV 400 mg film-coated tablets

The legal basis for this application refers to Article 10(3).

- *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:

Medicinal product no longer authorised

- 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/1/99/107/005**

■ Difference(s) compared to the reference medicinal product:

- ☐ changes in the active substance(s)
- ☐ change in therapeutic indications
- ☐ change in pharmaceutical form
- ☒ change in strength (quantitative change to the active substance)
- ☐ change in route of administration
- ☐ bioequivalence cannot be demonstrated through

The Rapporteur appointed by the CHMP and the evaluation teams was:
Rapporteur: 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 the applicant after authorisation.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 1 September 2008.
- The procedure started on 24 September 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2008.
- During the meeting on 19-22 January 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 23 January 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 February 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 April 2009.
- During the meeting on 20-23 April 2009, 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 Pharma B.V. on 23 April 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 April 2009.

Medicinal product no longer authorised

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Ribavirin Teva Pharma B.V. 200 mg and 400 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. The application for 400 mg tablets was submitted under the Article 10(3) of Directive 2001/83/EC i.e. hybrid application (change in strength).

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. A single dose bioequivalence study with the Ribavirin Teva Pharma B.V. and with the reference product Rebetol was submitted to support the application.

The indication proposed for Ribavirin Teva Pharma B.V. 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

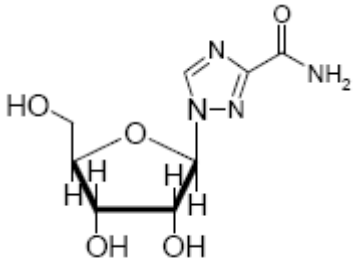
Ribavirin Teva Pharma B.V. is presented as film-coated tablets containing 200 mg or 400 mg of ribavirin (active substance). The 200 mg film-coated tablets are light pink to pink, debossed with “93” on one side and “7232” on the other. The 400 mg film-coated tablets are light pink to pink, debossed with “R” on one side and “400” on the other. The excipients used in the preparation of Ribavirin Teva Pharma B.V. are well known excipients used in tablets preparations such as calcium hydrogen phosphate dehydrate, croscarmellose sodium, povidone and magnesium stearate (present in the tablet core) and Opadry II 85F23470 (coating agent) which is composed of polyvinyl alcohol – partly hydrolysed, macrogol, titanium dioxide, talc, and red, yellow and black iron oxide.

Ribavirin Teva Pharma B.V. film-coated tablets are packaged in polyvinyl chloride / polyethylene / polyvinyl acetate (PVC/PE/PVAc) 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:

Medicinal product no longer authorised



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 drug substance specification includes tests for physical appearance and solubility, identification (IR), specific rotation, loss on drying, pH, sulphated ash, heavy metals, related substances (HPLC), assay (HPLC), bulk and tapped density, particle size distribution, polymorphism, 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.

Medicinal product no longer authorised

In general analytical methods proposed are suitable to control the quality of the drug 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 drug product manufacturer. All batches represented full scale production and complied with the requirements in the drug 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 immediate release tablets, containing quantitatively and qualitatively the same drug substance as the reference medicinal product, Rebetol 200mg capsules and to be bioequivalent.

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

Compositions of Ribavirin Teva Pharma B.V. film-coated tablets and the reference medicinal product are similar. Ribavirin Teva Pharma B.V. film-coated tablets contain calcium hydrogen phosphate, croscarmellose sodium, povidone and magnesium stearate. The reference medicinal product was authorised through the centralised procedure and therefore the qualitative and quantitative composition of the active substance [ribavirin] and the excipients [microcrystalline cellulose, lactose, croscarmellose and magnesium stearate] is identical in all Member States. The formulation of Ribavirin Teva Pharma B.V. film-coated tablets differs, namely by the inclusion of calcium hydrogen phosphate anhydrous and povidone product compared to lactose monohydrate and microcrystalline cellulose in reference medicinal product.

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 highly soluble in all cases.

An impurity comparison of Ribavirin Teva Pharma B.V. drug 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, Ribavirin Teva Pharma B.V. film-coated tablets and the reference medicinal product showed levels of impurities to be under the reporting limit.

Since the application concerned two strengths of 200 mg and 400 mg film-coated tablets, the bioequivalence was demonstrated between Ribavirin Teva Pharma B.V. 200 mg film-coated tablets

Medicinal product no longer authorised

and Rebetol 200 mg capsules, and biowaiver for a bioequivalence study with the 400 mg strength was claimed. The biowaiver could be applied since:

- both strengths are manufactured by the same manufacturer and process,
- the drug input has been shown to be linear over the therapeutic dose range following single doses of 200-1200 mg ribavirin,
- the qualitative composition of the strengths is the same,
- the ratio between amounts of active substance and excipients is the same,
- the dissolution profiles were similar for both strengths of Ribavirin Teva Pharma B.V. 200 mg and 400 mg film-coated tablets and the tablets are rapidly dissolved products (more than 85% of the labelled amount dissolved after 15 minutes).

The drug product manufacturing process development was also performed. Details were provided for experimental batches manufactured to establish optimum manufacturing conditions. To obtain immediate release tablets, which were essentially similar to the reference product, a formulating strategy was undertaken in order to optimise the manufacturing process with respect to:

- use of existing production equipment technology,
- choice of wet granulation as the appropriate process
- formulation of a product which meets the in-house specification,
- use of blister packs which meet the European market patient pack initiative.

The tablet formulations are based on Ribavirin Teva capsule formulation, which has already been authorised via centralised procedure. Essentially, the objective of preliminary formulation studies was to select adequate excipient grades and manufacturing conditions in order to develop capsules and later on tablets that exhibit acceptable physical and chemical characteristics. Wet granulation was selected as the conventional method of converting powders into granules having a suitable flow and cohesive properties for both encapsulation and tabletting. Developmental work therefore commenced with details for the capsule formulation and then progressed onto the tablets.

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

The second set of experiments performed on 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 granulation process was carried out in exactly the same way as for the capsules, following which the tablets were compressed. Following scale up a sticking phenomenon was observed. To resolve the amount of povidone was increased to obtain a final blend with better characteristics. No sticking phenomen was observed during the compression of the tablets at the high speed. However, when compressed at the lower speed, a slight sticking phenomenon was observed. The slight sticking problem was overcome by increasing the quantity of the lubricant, magnesium stearate

- Adventitious Agents

None of the excipients used in the drug product are of animal origin. Magnesium stearate used in the formulation is of vegetal origin.

Manufacture of the Product

The manufacturing process is sufficiently described with granulation and tabletting 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 dry granulate is milled; (4) Final blending, (5) Compression – the mix is pressed according to product specification; (6) Coating - the film coating suspension is sprayed over the tablets cores and (6) Packaging – film-coated tablets are packed.

Medicinal product no longer authorised

The critical steps in the manufacturing process are granulation and tabletting. 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.

As part of the discussion on the in-process controls, process validation data were provided for pilot scale batches of each tablet strength. In addition the validation protocol has been provided and the applicant committed that full process validation will be performed on three consecutive commercial scale batches.

- Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identification (HPLC and UV), dissolution, uniformity of dosage units (by mass variation), thickness, friability of uncoated tablets, resistance to crushing of tablets, assay, impurities and degradation products (HPLC), microbial limits, water content and identification of colour.

Full details of all analytical methods have been 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. As part of method validation, stress studies (light, heat, acid/base hydrolysis and oxidation) were performed to provide an indication of the stability-indicating properties and specificity of the HPLC method. Results confirmed that all impurities are adequately controlled.

Batch analysis data was provided on one pilot scale and one commercial scale batches of 200 mg strength and on two pilot scale batches of 400 mg strength. Batches met the proposed specification limits. Results showed that tablets 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 stored under long term conditions met all the proposed specification limits; appearance of tablets did not change, ribavirin assay values did not change significantly, dissolution values were within specification, values for degradants met the proposed specification limits.

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 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.

Medicinal product no longer authorised

2.3 Non-Clinical aspects

No new nonclinical data were submitted in support of this application. 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. The nonclinical aspects of the SPC are in line with the SPC of the reference product. No further studies were required and the applicant has justified why no such data were provided.

The impurity profile of the product compared with that of the reference product was adequately discussed and no further studies were warranted. The absence of an environmental risk assessment was justified by the fact that the medicinal product will be prescribed interchangeably with other similar products already marketed in Europe. It is assumed that the introduction is unlikely to result in any significant increase in the combined sales for ribavirin-containing products hence will not have an adverse impact on the environment. This justification was considered acceptable.

2.4 Clinical Aspects

Introduction

This is an abridged application for film-coated tablets containing 200 mg and 400 mg ribavirin. To support the marketing authorisation application the applicant conducted a single dose bioequivalence study with crossover design conducted under fed conditions using the 200 mg strength. This study was the pivotal study for the assessment. For the 400 mg strength the applicant applied for a biowaiver.

The relevant clinical data on pharmacokinetics, pharmacodynamics, efficacy and safety of the active substance ribavirin and respective formulations have been summarised by the applicant based on published literature. The proposed SPC of the product is in line with the one of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the Note for Guidance on the 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 S08-0152 was conducted outside the community and was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant requested a biowaiver for the conduct of a bioequivalence study with the 400 mg strength based on the following justification related to the comparison of the 200 mg strength and the 400 mg strength as well as characteristics of the active substance.

As detailed under “Quality aspects”, both strengths are manufactured by the same manufacturer and process, have the same qualitative composition as well as the same ratio between amounts of active substance and excipients. Furthermore, the dissolution profiles are similar for both strengths of the film-coated tablets and the tablets are rapidly dissolving products (more than 85% of the labelled amount dissolved after 15 minutes).

From a pharmacokinetic point of view, it has been shown for ribavirin that the drug input is linear over the therapeutic dose range following single doses of 200-1200 mg.

Medicinal product no longer authorised

A bioequivalence study was conducted with the 200 mg strength. Based on the above information and taking into account the criteria laid out in the applicable Note for Guidance, the CHMP considered that a bioequivalence study with the 400 mg strength is not necessary.

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 S08-0152

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	Crossover	One (test) tablet and One (reference) capsule formulation, 200 mg, Oral	34 enrolled (30 completed)	Healthy Subjects	Single dose

Pharmacokinetics

- Methods

STUDY DESIGN

Study S08-0152 was a single dose, randomised, open-label, two-period, two-sequence, crossover 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 randomisation scheme was computer generated and treatment sequences were randomly assigned to each subject number.

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 and were no allowed additional food for 4 hours after dosing. 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, 36, 48, 72 and 96 hours. Twenty-two blood samples (approximately 130 ml) were collected over the course of the study period.

The washout period between the study periods was five weeks.

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

Medicinal product no longer authorised

Test Product: Ribavirin 200 mg film-coated tablet
Manufactured by: TEVA Pharmaceutical Industries Ltd
Batch No.: K-39307
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.: 7RCJA18A02
Expiry date: February 2009

POPULATION(S) STUDIED

34 healthy, male (27) and post-menopausal female (7), non-smoking subjects were enrolled and randomised to receive either test or reference product according to the dosing randomisation schedule. According to the study protocol 36 subjects had to be enrolled, due to the lack of eligible subjects 34 were finally enrolled. The mean demographic data of all enrolled 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 consume grapefruit, Seville oranges and pomelo containing products for 14 days prior to period I dosing and throughout the study, alcoholic beverages and caffeine containing beverages were not allowed 48 hours prior to each dose. 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 7 days prior to dosing. Female subjects did not use hormone replacement therapy for a period of 6 months prior to dosing.

30 subjects completed the clinical part of the study in its entirety, had plasma samples analysed for ribavirin and were included in the statistical analysis.

Table 2: Summary of Mean Demographic Data (±SD) for enrolled subjects (n=34)

	All Subjects (N=34)	**Male Subjects (N=27)**	**Female Subjects (N=7)**
Age	32.5 (±10.3)	29.4 (±8.7)	44.1 (±8.7)
Weight (lbs.)	174.2 (±26.1)	179.3 (±25.1)	154.7 (±21.6)
Height (inches)	68.8 (±3.4)	69.8 (±2.7)	64.9 (±3.1)
BMI (kg/m^2)	25.9 (±2.8)	25.8 (±2.7)	25.9 (±3.6)

ANALYTICAL METHODS

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

Within-study accuracy and precision was within the acceptance range.

The bioanalytical method was considered adequately validated.

PHARMACOKINETIC VARIABLES

Pharmacokinetic parameters C_{max}, AUC_{0-96} and T_{max} 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_{0-96}. Actual blood collection times were used for PK calculations.

STATISTICAL METHODS

Medicinal product no longer authorised

Pharmacokinetic and statistical analyses were performed for ribavirin plasma data. Data was analysed if the subject completed the study. Analyte concentration values from subjects who withdraw consent or are dropped from the study were reported, but they were not to be included in the pharmacokinetic and statistical analysis.

Subjects who exhibited pre-dose levels higher than 5% of C_{max} were excluded from the statistical analysis. Subjects that exhibit non-zero pre-dose levels < 5% of C_{max} were included in the statistical analysis with no baseline correction.

Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantitated) may have been used if pharmacokinetic parameters could be estimated using the remaining data points. Otherwise, concentration data from these subjects were excluded from the final analysis. The exclusion was to be conducted prior to sample analysis. The statistical analysis should be performed on all data from all subjects in the final data set.

Analyses of variance (ANOVA) were performed on the ln-transformed pharmacokinetic parameters AUC_{0-96} and C_{max}. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. 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_{0-96} and C_{max} using ln-transformed data. The geometric mean values were reported.

Statistical analyses were considered appropriate for a two-period crossover design to assess the bioequivalence of the two products.

- Results

34 subjects were enrolled and were dosed in period I. 30 subjects were dosed in period II; these subjects completed the study, had plasma samples analysed for ribavirin and were included in the statistical analysis. Of the four subjects who discontinued the study after period I, two withdrew their consent after period I due to personal reasons. Two subjects were dropped after period I by the investigator/sponsor due to too many missing return blood draws:

- One subject did not come back for 36, 72, and 96 hour draws on period I. It was judged that there were not enough data points to calculate the AUC to 96 hours.
- One subject did not come back for the 48, 72, and 96 hour draws in period I. It was judged that there were not enough data points to calculate the AUC to 96 hours.

All pre-dose samples collected in period II after the administration of test and reference product contained detectable levels of ribavirin. Reported plasma levels of ribavirin were below 10 ng/mL, mostly below 5 ng/mL, which is less than 5% of corresponding C_{max}.

The pharmacokinetic parameters obtained in the 30 subjects who completed the clinical part of the study in its entirety are summarised in Table 3. The results of the statistical analysis for ln-transformed data are displayed in Table 4.

Medicinal product no longer authorised

Table 3 Pharmacokinetic parameters of study S08-0152 (non-transformed values)

	Test			Reference		
	N	**Mean***	**SD****	**N**	**Mean***	**SD****
AUC_{0-96} [ng*h/ml]	30	6048.902	1343.191	30	6407.033	1478.900
C_{max} [ng*ml]	30	582.133	170.044	30	538.343	139.018
T_{max} [h]	30	1.783	0.709	30	2.325	0.496

AUC_{0-96} area under the plasma concentration-time curve from time zero to 96 hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
* arithmetic mean; for t_{max} median
** standard deviation, for t_{max} range

Table 4 Statistical analysis of study S08-0152 (ln-transformed data)

Parameter	**Least Square Mean**		**Geometric Mean**		**Ratio of geometric means (%)**	**90% CI***		**CV (%)**
	Test	**Reference**	**Test**	**Reference**		**Lower**	**Upper**	
AUC_{0-96}	8.69	8.74	5917.18	6254.50	94.6	91.3	98.0	8.1
C_{max}	6.32	6.25	554.94	520.56	07	98.8	115	17.3

* 90% confidence intervals based on ln transformed values.

The 90% confidence intervals for the ratio of geometric means of AUC_{0-96} and C_{max} (ln-transformed data) are within the limits of 80% to 125%.

Safety data

Five subjects experienced a total of seven adverse events over the course of the study. Adverse events were mild to moderate in severity. No serious adverse events were reported. Following administration of the test product one adverse event was reported, which was swelling – left ankle. The adverse events reported following administration of the reference product were abnormal white blood cell count (lost to follow up), abnormal urinalysis, headache, loss of appetite, and injured right hand.

- Conclusions

Based on the presented bioequivalence study Ribavirin Teva Pharma B.V. 200 mg film-coated tablets is considered bioequivalent with Rebetol 200 mg hard capsules. The results of study S08-0152 with the 200 mg formulation can be extrapolated to the 400 mg strengths, according to conditions in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), section 5.4.

Pharmacodynamics

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

Post marketing experience

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

Medicinal product no longer authorised

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.

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 crossover design under fed conditions was conducted with the 200 mg strength. Overall the bioequivalence study design was adequate considering the pharmacokinetic properties of ribavirin.

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 test and reference product were administered according to the randomisation scheme in two-sequence, two-period crossover design. Washout period between study periods was 5 weeks. All study subjects after administration of test and reference product had detectable levels of ribavirin in pre-dose samples collected in period II, indicating a carryover from period I. The plasma ribavirin levels in period II pre-dose samples were however below 10 ng/mL, mostly <5 ng/mL, which is approximately 1% of the corresponding C_{max} and is therefore acceptable.

The bioequivalence 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 30%. A bioequivalence study under fed conditions is therefore acceptable.

Ribavirin has an elimination half-life of 80 hours due to the extensive distribution into non-plasma compartments. Elimination from red blood cells has been reported to occur with a half-life of 40 days. The bioanalytical method had the lower limit of quantification adequate for the purpose. Ribavirin plasma levels were determined at various time points for up to 96 hours post dose. Ribavirin concentrations were measurable at the last time point 96 hours post dose.

The bioequivalence conclusion was based on the C_{max} and AUC_{0-96}, 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.

The Applicant applied for a biowaiver for the conduct of a bioequivalence study with the 400 mg strength. The justification is sufficient as all criteria for biowaiver according to the applicable CHMP guideline are fulfilled.

Medicinal product no longer authorised

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. The pivotal basis of this application was a bioequivalence between the test product (200 mg strength) and the reference product. This study was a two sequence, cross-over study in fed state; the overall design as well as the bioanalytical methods are considered adequate. The statistical analysis of the pharmacokinetic data from this study showed that the target parameters $AUC_{0\text{-}96\ h}$ and C_{max} (ln-transformed data) were within the acceptance limits of 0.8-1.25. Therefore, bioequivalence has been shown. For the 400-mg strength the biowaiver concept is deemed acceptable and a specific bioequivalence study is not needed.

Overall, 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 Pharma B.V. 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 granting of the marketing authorisation.

Medicinal product no longer authorised