EMA/344082/2010

Evaluation of Medicines for Human Use

Assessment report

Ribavirin Three Rivers

International Nonproprietary Name: ribavirin

Procedure No. EMEA/H/C/001185

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

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1 Background information on the procedure

1.1. Submission of the dossier

The applicant Three Rivers Global Pharma Limited submitted on 8 May 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ribavirin Three Rivers 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.

A - Centralised / Article 10(1) / Generic application.

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 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**

☐ 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**
- Bioavailability study number(s): **S08-0152**

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Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

1.1.1. Licensing status:

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

An application was filed in for Ribavirin Capsules (iQur Pharmaceuticals Ltd) in the following countries: Denmark, Germany, Greece, France, Ireland, Italy and Poland but it was refused on 24 July 2008.

The Rapporteur appointed by the CHMP was Ian Hudson.

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 8 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.
- 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 25 September 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2009.
- During the CHMP meeting on 15-18 February 2010 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During the meeting on 15-18 March 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 Three Rivers on 18 March 2010.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 10 June 2010.

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2. Scientific discussion

2.1. Introduction

Ribavirin Three Rivers 200 mg Hard Capsule is a generic medicinal product containing ribavirin as the 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 the Ribavirin Three Rivers and with the reference product Rebetol were submitted to support the application.

The indication for Ribavirin Three Rivers is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.

The therapeutic indication of Rebetol is:
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.

The therapeutic indication of Ribavirin Three Rivers is:
Ribavirin Three Rivers is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with interferon alfa-2b (adults, children (3 years of age and older) and adolescents). Ribavirin monotherapy must not be used. There is no safety or efficacy information on the use of Ribavirin with other forms of interferon (i.e., not alfa-2b).

2.2. Quality aspects

2.2.1. Introduction

Ribavirin Three Rivers is presented as hard capsules containing 200 mg of ribavirin as active substance. The excipients used in the preparation of the capsules are well known excipients such as croscarmellose sodium, lactose monohydrate, microcrystalline cellulose and povidone. The capsule shell contains gelatine and titanium dioxide (E171). The capsule shell imprint contains shellac, propylene glycol, concentrated ammonia solution and colouring agents (Yellow iron oxide E172, Indigotine E132 and Titanium dioxide E171).

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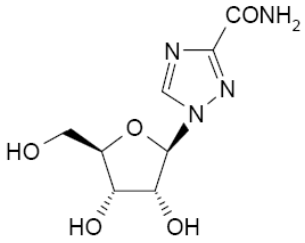
Ribavirin Three Rivers hard capsules are packaged in high-density polyethylene (HDPE) bottle, closed with a child-resistant (CR) polypropylene (PP) screw cap.

2.2.2. Active substance

The active substance in this product is Ribavirin (INN) or 1-ß-D-Ribofuranosyl-1*H*-1,2,4-triazole-3 – carboxamide (Chemical Name) and has the following structure:



Ribavirin is a white to off-white powder with lumps, soluble in water, slightly soluble in anhydrous ethanol and insoluble in ether and chloroform. It has a specific rotation between -33.5 to -37.0° (USP 28) or -33 to -37° (Ph. Eur. 5), pH value in water 4.0 – 6.5, Melting Point Onset 169 ± 2°C.

The API exhibits polymorphism, with two forms, one melting at 170°C and one melting at 180°C. The polymorphic form manufactured in this EDMF is the low melting point one.

Ribavirin contains four chiral centers in the sugar portion of the molecule. Thus, there are 16 possible stereoisomers. Ribavirin is synthesized as a single isomer (ß-D-isomer) by the current synthetic route.

2.2.2.1. Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure. A three step synthesis involving coupling step (formation of ribavirin ester), ammonolysis (formation of crude ribavirin) and re-crystallisation (formation of ribavirin) has been well described. Controls of critical steps and intermediates are sufficient to ensure quality of the final compound.

The active substance has been characterised using Infra-red (IR), Nuclear Magnetic Resonance (NMR), Ultra-violet (UV) and Mass Spectrometry (MS) techniques. The active substance exhibits two polymorphic forms. Based on the analysis melting points (by DSC), X-ray powder diffraction patterns, and IR spectra it can be concluded that the ASMF Holder produces Ribavirin a single polymorphic form (lower melting point only). In addition, it has been demonstrated that the polymorphic form remains stable and no change occurs over time.

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

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2.2.2.2. Specification

The drug substance specification includes tests for physical appearance, identification (IR), specific rotation, loss of drying, pH, sulphated ash, heavy metals, related substances (HPLC), assay (HPLC), 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 polymorph testing (by melting point) and residual solvents. Full method validation data was provided for the non compendial (in-house) analytical methods.

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 drug substance.

Data on three commercial batches of ribavirin have been provided by the ASMF Holder and the requirements in the drug substance specification were met.

2.2.2.3. Stability

Stability data has been provided from three batches of material stored at ICH long term conditions Three commercial batches have been stored under ICH long term conditions (up to 24 months at 25˚C/65%RH). The data demonstrates that the API is stable. No adverse stability trends are observed.

The parameters tested during stabilities studies are Identification, pH, Specific Rotation, Loss on Drying, HPLC Related Substances (Impurity F, Any other impurity, and Total), and Assay. The acceptance criteria and analytical procedures are the unchanged from those performed at release.

The stability studies confirmed the proposed re-test period with the storage condition statement "Store in the original containers".

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

The aim of the pharmaceutical development was to obtain hard capsules, containing quantitatively and qualitatively the same drug substance as the reference medicinal product, Rebetol 200mg capsules and to be bioequivalent.

The manufacturing process for Ribavirin Capsules has undergone very little change since this product was developed as a generic version of an already approved drug in the U.S. market. The original (pilot-scale) manufacturing process was developed simultaneously with the formulation development. Upon

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identification of a formulation that provided the necessary dissolution and other desired properties, the same process was utilized for the manufacture of the original (pilot-scale) batch.

During the optimization and scale up of the manufacturing process the following processes were validated and optimized: Wet Granulation, Extrusion/Spheronization, Pellet Drying and Sieving, Encapsulation, Packaging and Labeling

The excipients used in the drug product are the same as those in the reference product Rebetol 200mg capsules with the exception of the use of povidone in the proposed product and magnesium stearate in Rebetol and the use of different printing inks. The applicant states that compatibility with all other excipients can be justified on the basis of Rebetol and the stability data generated on the finished product is sufficient to indirectly demonstrate compatibility with povidone and the printing ink. This is acceptable.

The excipients used in the manufacture of Ribavirin Capsules are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, and purified water. These excipients are controlled using the PhEur specifications. Satisfactory certificates of analysis have been provided.

The primary container closure system for Ribavirin Capsules is a high density polyethylene bottle with a child-resistant, polypropylene induction-seal screw cap. The applicant propose a 100ml bottle for the 84 pack size and a 250ml bottle for the 112,140 and 168 pack sizes.

2.2.3.2. Adventitious agents

Only lactose monohydrate and hard gelatin capsules are of human or animal origin. Valid PhEur Certificates of Suitability for the bovine gelatin used to make the capsules are provided and the lactose monohydrate that was used to manufacture the capsules is from bovine milk from cows in the USA. Based on this information, the excipients used to manufacture capsules do not pose a TSE risk.

2.2.3.3. Manufacture of the product

The manufacturing process involves wet granulation, followed by extrusion and drying to produce pellets, which are encapsulated into capsules

Validation of the manufacturing process of Ribavirin Capsules was performed using three consecutive full-scale production batches. The critical steps in the manufacturing process to be monitored were identified as: granulation, extrusion, spheronization, drying, pellet sifting, and capsule filling. These steps were identified as critical because they directly or indirectly affect the quality attributes of the pellet and capsule content uniformity and capsule dissolution.

The validation data demonstrate that the manufacturing process is robust and reproducible and ensure that the product has the quality, purity, strength, and identity that it purports. The manufacturing process has been suitably validated.

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2.2.3.4. 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), assay (HPLC), impurities and degradation products (HPLC), microbial limits (Ph Eur) and water content. Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

Full details of all analytical methods have been provided.

Batch analysis data on key parameters are provided from six commercial scale batches of Ribavirin Capsules according to the European specification. Batches met the proposed specification limits. Results showed that tablets can be manufactured reproducibly according to the finished product specifications.

2.2.3.5. Stability of the product

Stability studies were carried out for three batches under ICH conditions of 25ºC/60%RH (long term, 36 months) in the proposed 100ml bottles and 40ºC/75%RH (accelerated, 6 months) in the 250ml bottles. Bracketing studies in 10ml containers containing 100 capsules and 1300ml containers containing 1000 capsules have also been conducted, for which complete long-term (36 months) and accelerated (6 months) stability data in are available. The data shows no adverse stability trends and all specifications are met.

In addition, two stability studies have been completed on Ribavirin Capsules stored in bulk containers (Sanitainers and 2-mil LDPE Bag/Fiber Drums), which showed no adverse stability trends.

Photostability studies in accordance with ICH requirements have been conducted. The drug product was found not be light sensitive.

The stability parameters and specifications for Ribavirin Capsules are identical to that proposed for batch release except that only stability-indicating parameters are retained (i.e., the Identification and Uniformity of Dosage Units (weight variation) tests are omitted on stability).

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have 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.

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2.3. Non-clinical aspects

Ribavirin is an approved product of long-established use. Its pharmacology, pharmacokinetic and toxicology profiles are well understood and well documented.
The applicant has provided an acceptable summary of the pharmacology, pharmacokinetics and toxicology of ribavirin based on published literature. No further studies are required and the applicant has adequately justified why no such data was provided.

The impurity profiles of both the drug substance and medicinal product are compliant with the Ph. Eur. Monograph and ICH guidance and are acceptable.

A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of these generic products onto the market is unlikely to result in an increase in the combined sales of all ribavirin-containing products, which in turn is unlikely to increase exposure of the environment to ribavirin.

2.4. Clinical aspects

Introduction

This application concerns a generic medicinal product that contains a single strength of 200 mg ribavirin in a hard capsule. Pharmacokinetic properties as well as clinical efficacy and safety have been well demonstrated for the reference product Rebetol.
To support the marketing authorisation application, the applicant had conducted two bioequivalence studies with the EU reference product under fasting and fed condition. Furthermore, the applicant presented two additional bioequivalence studies conducted with the US reference product under fasting and fed condition. Detailed assessment of the US studies has not been included in the CHMP assessment report.

No CHMP scientific advice was sought for the development programme, neither was scientific recommendation given by Member States.

GCP

All bioequivalence studies were complying with GCP, as claimed by the applicant.
A routine inspection was carried out for the bioequivalence studies performed with the EU reference product (M1ER07001 and M1ER07002) since the clinical/analytical sites used in these trials had not been previously inspected by the European Medicines Agency.
No critical findings were observed at either the Clinical Laboratory or the Clinical Facility. The overall compliance with GCP and GLP was deemed to be satisfactory for the studies reviewed and the data submitted in the application is acceptable.

Clinical studies

To support the application, the applicant has submitted four bioequivalence studies conducted under fed or fasting conditions with either the EU or the US reference product. These studies are summarized in table 1 below. Studies M1ER07001 and M1ER07002 are further described in the relevant sections.

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Table 1: Summary of Bioequivalence studies

Study Ref. No.	Study Objective	Study Design	Treatments	Subjects
M1ER07001 (EU)	To assess the relative bioavailability of Ribavirin 200 mg capsules by Three Rivers Pharmaceuticals, LLC. compared to that of Rebetol Capsules by Schering Plough under fasting conditions	Open label, two period, Two treatment, Two sequence, single dose, two-way crossover study with at least a 5 week washout period	3 x 200 mg Ribavirin capsules 3 x 200 mg Rebetol capsules	3 M and 40 F enrolled. 3 M and 35 F completed Healthy volunteers 45 years (27 - 55)
M1ER07002 (EU)	To assess the Relative bioavailability of Ribavirin 200 mg capsules by Three Rivers Pharmaceuticals, LLC. compared to that of Rebetol Capsules by Schering Plough under fed conditions	Open label, two period, two treatment, two sequence, Single dose, two-way crossover study with at least a 5 week washout period	3 x 200 mg Ribavirin capsules 3 x 200 mg Rebetol capsules	42 M and 42 F enrolled. 0 M and 36 F completed Healthy volunteers 46 years (25 - 55)
11612C (US)	To compare the ribavirin plasma levels after administration of Ribavirin 200 mg capsules compared 200 mg Rebetol Capsules (fasted conditions)	Randomised, open label, Two treatment crossover study	3 x 200 mg Ribavirin capsules 3 x 200 mg Rebetol capsules	40 F enrolled 36F completed Healthy volunteers 44.87 years (29-55)
11620A (US)	To compare ribavirin plasma levels after administration of ribavirin capsules with those after administration of Rebetol 200 mg Capsules (fasted conditions)	Randomized, open label, Two treatment crossover	3 x 200 mg Ribavirin capsules 3 x 200 mg Rebetol capsules	18F enrolled 14F completed Healthy volunteers 40 years (19-54)

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2.4.1. Pharmacokinetics

Study M1ER07001 - Bioequivalence study with the EU reference product under fasting conditions

Methods

Study design

Study M1ER07001 was a single dose, randomised, open-label, two-period, crossover bioequivalence study conducted under fasting conditions.

Each of the study subjects received three 200 mg capsules of ribavirin (600 mg as a single dose) of the test or the reference product according to the randomisation schedule in period 1 and 2. Subjects were housed at the clinical facility the night before drug administration and remained at the clinical facility until the 24 hour blood sample collection. Subjects were fasted for at least 10 hours prior to administration of study drug which was administered with 240 mL water. Washout period was 5 weeks between the period 1 and 2.

Blood samples were collected prior to dosing (0 hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 14, 24, 36, 48, and 72 hours post dosing. Nineteen blood samples (approximately 114 ml) were collected over the course of each study period. All samples were cooled by an ice bath until processed. Samples were processed within 60 min after the withdrawal.

The study was conducted at the clinical trial site of the Allied Research International – Cetero Research, Florida, USA. Clinical part of the study was undertaken from 5 March 2008 (first dosing) to 9 April 2008 (second dosing).

The study protocol (dated 14 February 2008) was conditionally approved by the Ethics Committee of the Florida Institutional Review Board Services on 19 February 2008. Unconditional approval was then obtained on 27 February 2008. However, the study protocol and informed consent were amended several times. Changes included a modification in the end of study procedures from 24 h to 72 h in period 2 and the inclusion of a statement that the drug was FDA approved as requested by Sponsor. The final protocol was approved on 12 March 2008 and the revised consent form was approved on 7 April 2008.

The final study report was dated 10 October 2008.

Test and reference products

The test and reference product used in study M1ER07001 were as follow:

Test Product: Ribavirin (Ribasphere) 200 mg capsules
Manufactured by: Three Rivers Pharmaceuticals LLS, USA
Batch No.: A30438Z
Expiry date: July 2010

Reference Product: Rebetol 200 mg capsules
Manufactured by: Schering-Plough Ltd, UK
Batch No.: 7RCJA40A02
Expiry date: May 2009

Population studied

44 subjects were to be enrolled, but 43 subjects were actually dosed, one subject was excluded due to non-compliance with age. The study population was comprised of healthy surgically sterile male and/or postmenopausal or surgically sterile female volunteers under fasting conditions. 3 men and 40 women were enrolled.

The mean age of subjects was 45 years, with the range of 27 to 55 years. Inclusion and exclusion criteria presented were acceptable for the product and for this type of study.

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Table 2: Summary of the demographic data (study M1ER07001)

Parameters	Subject Age (years)	Subject Height (cm)	Subject Weight (kg)	Subject BMI (kg/m^2)
Min	27	148.5	51.7	22.3
Max	55	180.0	87.8	30.0
Mean	45	160.3	68.7	26.6
SD	7	7.6	9.4	2.3

Analytical methods

Analytical part of the bioequivalence study was conducted at the BA Research Co. – Cetero Research in Canada from 23 April 2008 to 9 May 2008. The analysis was performed by a LC/MS/MS system. The positive ions were measured using ElectroSpray Ionisation technique in MRM mode.

Study samples were analysed in a total of 22 analytical sequences, including 2 repeats. Within-study accuracy and precision was within the acceptance range, 98% to 101% and 2.0% to 6.6%, respectively, based on the back-calculated concentrations of quality control (QC) samples and calibration curve samples. Calibration curve ranged from 20.0 ng/ml to 2000.0 ng/ml.

The specificity of the assay was documented during sample analysis by assaying pre-dose samples from period 1. During validation plasma from 8 donors was evaluated and no significant interfering peaks were observed at the retention times of ribavirin. Matrix effect was also studied. Dilution integrity by factor 10 and analyte stability at various storage conditions were shown. The long term stability at three concentrations was established and covered the actual sample storage period. Recovery for sample preparation with acetonitrile was determined.

The analytical method was validated according to the FDA Guidance on the Bioanalytical Method Validation. Within-study validation was shown based on the back-calculated concentrations of the quality control samples and calibration curve samples.

Pharmacokinetic Variables

Pharmacokinetic parameters C_{max}, AUC_{0-t}, T_{max}, were determined. These parameters for each individual were tabulated and graphically presented. Non-compartmental analysis and the linear trapezoidal method were used to calculate AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-72}/ $AUC_{0-\infty}$, Kel, $t_{1/2}$, as well as ln-transformed $AUC_{0-\infty}$ were also calculated for information purposes only. For the calculation of Kel the R2 had to be >0.8000.

Actual blood collection times were used for pharmacokinetic calculations. All values below the lower limit of quantitation (BLQ) were considered as zero during the pharmacokinetic and statistical analysis.

Statistical methods

The primary pharmacokinetic parameters were C_{max} and AUC_{0-72} transformed to their natural logarithms. AUC_{0-72} was chosen as the appropriate parameter for bioequivalence because ribavirin has a long terminal half-life estimated to be greater than 200 hours. Therefore the truncated AUC was deemed to be the appropriate bioequivalence parameter.

A SAS® program and the generalized linear model of the analysis of variance with sequence, subject within sequence, period and treatment effects was used to calculate the least square means for the parameters AUC_{0-72} and C_{max} using ln-transformed data. Ratios of least-squares means and 90% confidence intervals for the difference between formulation least-squares means were calculated for the C_{max} and AUC_{0-72}.

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Results

38 out of 43 subjects enrolled completed the study. Among the 5 dropouts of the study, one subject was tested positive for cotinine and one subject was tested positive for pregnancy. Therefore, they were withdrawn prior to Period 2 dosing. Also, three subjects did not show for Period 2 dosing. The subject who had a positive pregnancy test was later found to have an abnormal cystic ovarian mass and pregnancy was excluded.

None of the pre-dose samples contained detectable levels of ribavirin. For period 2, for most of the study subjects an interfering peak was detected at the retention time of ribavirin, but all these samples were quantified less than the LLOQ and were reported as zero.

None of the first post-dose samples was reported as a C_{max}. The ratio of AUC_{0-t} / $AUC_{0-\infty}$ ranged from 55% to 82%. Since ribavirin has long elimination half life, AUC_{0-t} was chosen as a primary pharmacokinetic parameter according to the study protocol. Pharmacokinetics parameters of the 38 subjects who completed the clinical part are presented in tables 3 and 4 below.

Table 3: Summary of individual and mean pharmacokinetic parameters of Ribavirin

Parameter	Test		Reference	
	Mean[a] (SD)	[Min – Max]	Mean[a] (SD)	[Min – Max]
AUC_{0-72} (ng·h/mL)	13954.9932 (4570.2466)	[7076.5225 – 26759.5014]	13719.5792 (3906.8492)	[5613.0531– 22771.3775]
C_{max} (ng/mL)	927.5763 (431.88129)	[338.5000 – 2147.0000]	903.8789 (404.2928)	[401.3000 – 1914.0000]
T_{max} (h)	1.50[b]	[1.00 – 4.00]	1.50[b]	[0.70 – 4.00]

[a] Arithmetic mean

[b] Median

Table 4: Summary of the statistical analysis for Ribavirin Ln-transformed data

Parameter	Geometric Mean of Test	Geometric Mean of Reference	Ratio of Geometric Means Test/Reference	90% Confidence Interval Lower – Upper
AUC_{0-72} (ng·h/mL)	13289.549	13195.754	1.007	0.953 – 1.065
C_{max} (ng/mL)	844.086	836.655	1.009	0.936 –1.088

The point estimates and their 90% confidence intervals for AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} were all contained within the usual Bioequivalence acceptance range of 0.80 to 1.25. The 90% CI for $AUC_{0-\infty}$ was 94.66-106.96.

Safety data

There were 14 non-serious (mild or moderate) adverse events and one serious adverse event during the conduct of the study. The serious adverse event detected was considered unlikely related to the drug by the investigator. All adverse events were followed until resolution with the exception of one serious adverse event (abnormal cystic ovarian neoplasm) which is being followed up.

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Study M1ER07002 - Bioequivalence study with the EU reference product under fed conditions

Methods

Study design

Study M1ER07002 was a single dose, randomised, open-label, two-period, crossover bioequivalence study conducted under fed conditions.

Each of the study subjects received three 200 mg capsules of ribavirin (600 mg as a single dose) of the test or the reference product according to the randomisation schedule in period 1 and 2. The randomization scheme was computer generated using SAS version 9.1. According to the study report, 600 mg dose was selected to represent a usual therapeutic dose.

Subjects were housed at the clinical facility the night before drug administration and remained at the clinical facility until the 24 hour blood sample collection. Subjects were fasted for at least 10 hours prior to administration of standardised high-fat breakfast in period 1 and 2. Study drug was administered after receiving the breakfast with 240 mL water. The standardized breakfast was received 30 minutes prior to dosing and consisted of eight ounces of whole milk, two eggs fried in butter, two strips of bacon, two slices of toast with butter, and four ounces of hash brown potatoes.

Washout period was 5 weeks between the period 1 and 2.

Blood samples were collected prior to dosing (0 hour) and after dose administration at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 14, 24, 36, 48, and 72 hours post dosing. Nineteen blood samples (approximately 114 ml) were collected over the course of each study period. All samples were cooled by an ice bath until processed. Samples were processed within 60 min after the withdrawal.

This study was conducted at the clinical trial site of the Allied Research International – Cetero Research, Florida, USA. The clinical part of the study was undertaken from 15 March 2008 (first dosing) to 19 April 2008 (second dosing).

The amended final study protocol and revised consent (dated 10 March 2008) was approved by the Ethics Committee of the Florida Institutional Review Board Services on 12 March 2008. Subsequent changes were made in the consent form including the addition of a statement that the drug was FDA approved. A revised consent form dated 7 April 2008 was approved and used for the second period. The final study report was dated 9 October 2008.

Test and reference products

The test and reference product used in study M1ER07002 were identical to the study products used in study M1ER07001.

Population studied

44 subjects were to be enrolled, but 43 subjects were actually dosed. The study population comprised of healthy surgically sterile male and/or postmenopausal or surgically sterile female volunteers under fasting conditions. One man and 42 women were enrolled. Seven of the enrolled women were younger than 40 years of age.

The mean age of subjects was 46 years, with the range of 25 to 55 years. Inclusion and exclusion criteria presented were acceptable for the product and for this type of study.

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Table 5: Summary of the demographic data (study M1ER07002)

Parameters	Subject Age (years)	Subject Height (cm)	Subject Weight (kg)	Subject BMI (kg/m^2)
Min	25	143.0	45.4	20.1
Max	55	173.5	82.7	29.8
Mean	46	158.5	65.3	25.9
SD	8	6.9	9.1	2.9

Analytical methods

The analytical part of the bioequivalence study was conducted at the BA Research Cor – Cetero Research, Canada from 5 May 2008 to 21 May 2008. The analysis was performed using the same methods as used in study M1ER07001.

Study samples were analysed in a total of 20 analytical sequences. Within-study accuracy and precision was within the acceptance range, 97% to 101% and 1.2% to 5.2%, respectively, based on the back-calculated concentrations of quality control (QC) samples and calibration curve samples. Calibration curve ranged from 20.0 ng/ml to 2000.0 ng/ml.

The method validations are described within the M1ER07001 study section.

Pharmacokinetic Variables

Pharmacokinetic variables used in study M1ER07002 were identical to those used in the fasted study M1ER07001.

Statistical methods

Statistical methods used in study M1ER07002 were identical to those used in the fasted study M1ER07001.

Results

36 out of 43 subjects enrolled completed the study. One subject experienced an adverse event in period 1 and was therefore withdrawn. One subject tested positive for cotinine and one subject with a positive pregnancy test were withdrawn before period 2. Four of the subjects voluntarily withdrew prior to period 2 (due to a family emergency).

One subject did not complete breakfast before drug administration in period 1 (98% consumed). Pharmacokinetic analysis including and excluding this subject were provided.

None of the pre-dose samples contained detectable levels of ribavirin. For period 2, most of the study subjects had an interfering peak which was detected at the retention time of ribavirin, but all these samples were quantified less than the LLOQ and were reported as zero.

None of the first post-dose samples was reported as a C_{max}. The ratio of AUC_{0-t} /$AUC_{0-\infty}$ ranged from 56% to 70% after test. Since ribavirin has long elimination half life, AUC_{0-t} was chosen as a primary PK parameter according to the study protocol.

Pharmacokinetics parameters of the subjects who completed the clinical part are presented in tables 6 and 7 below.

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Table 6: Summary of individual and mean pharmacokinetic parameters of Ribavirin (untransformed data)

Parameter	Test			Reference		
	n	Mean[a] (SD)	[Min – Max]	n	Mean[a] (SD)	[Min – Max]
AUC_{0-72} (ng·h/mL)	33	19874.4383 (5245.8690)	[9547.2275 – 33162.1000]	35	19738.1305 (5962.9728)	[6282.0235 – 32855.5563]
C_{max} (ng/mL)	35	1264.56 (416.88)	[476.00 – 2216.00]	35	1229.78 (508.91)	[488.90 – 2764.00]
T_{max} (h)	35	3.50[b]	[2.50 – 4.09]	35	3.50[b]	[2.00 – 4.00]

[a] Arithmetic mean
[b] Median

Table 7: Summary of the statistical analysis for Ribavirin Ln-transformed data

Parameter	Geometric Mean of Test	Geometric Mean of Reference	Ratio of Geometric Means Test/Reference	90% Confidence Interval Lower – Upper
AUC_{0-72} (ng·h/mL)	19194.4750	18880.8990	1.017	0.9803 – 1.0543
C_{max} (ng/mL)	1197.9007	1141.1407	1.050	1.0071 – 1.0942

Similar results were obtained in the secondary analysis which included data from the subject who did not complete the breakfast. For ribavirin, the Test/Reference ratios of geometric means were 1.015 (90% CI 0.9795 – 1.0513) for AUC_{0-72}, and 1.041 (90% CI 0.9973 – 1.0860) for C_{max}.
The point estimates and their 90% CI for $AUC_{0-\infty}$ were also within the acceptance range (98.89, 106.41) (analysis included the subject who did not complete breakfast).

In conclusion, the point estimates and the 90% CIs for AUC_{0-72} and C_{max} were contained within the conventional defined acceptance range of 0.80 to 1.25.

Safety data
There were 38 non-serious adverse events during the conduct of the study. There was one serious adverse event which was not considered related to the drug by the Investigator. One subject had a positive pregnancy test before period 2 with unknown outcome or follow up.

Conclusions

Based on the presented bioequivalence studies Ribavirin Three Rivers 200 mg capsule is considered bioequivalent with Rebetol 200 mg capsule.

2.4.2. Pharmacodynamics

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

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2.4.3. Additional data

The applicant also provided results of two further Bioequivalence studies with the US reference product. Description of these two studies is provided in Table 1.

2.4.4. Post marketing experience

Although the same medicinal product has been approved in Turkey in December 2006 and in the USA in April 2004, no post-marketing data have been presented in the dossier by the applicant.

2.5. Pharmacovigilance

2.5.1. PSUR

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

2.5.2. 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.

2.5.3. Risk management plan

The applicant has submitted a justification for not submitting a Risk Management Plan as this is a generic application. This was considered acceptable in principle. However, any additional risk minimisation measures that might be put in place for the reference product will also have to be implemented for this generic product

2.6. Discussion on Clinical aspects

Two bioequivalence studies were conducted to support this generic application. A single-dose two-period crossover study under fasting and under fed condition with the test and the EU reference product were submitted. The bioequivalence study under fed conditions was considered as a pivotal study for this application since, according to the SmPC of the reference product Rebetol, ribavirin should be administered with food.
In both studies, bioequivalence of the two products was demonstrated with the standard bioequivalence criteria 0.8-1.25.
600 mg dose (3 x 200 mg tablet) was selected for the bioequivalence study on the grounds that the 600 mg represents the dose used in clinical practice. As ribavirin has a linear pharmacokinetics and is highly soluble, the choice of 600 mg dose was acceptable.
Washout period was sufficient for the analytical method used. No detectable levels of ribavirin was seen in pre-dose samples from period 2, although interfering peaks less than LLOQ were seen for almost all subjects.

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C_{max} and AUC_t were selected as primary pharmacokinetic parameters. Ribavirin accumulates in red blood cells (60:1 compared with plasma), and extremely long elimination is attributable to the redistribution from the cellular compartment. Ribavirin is highly soluble and is absorbed quickly with T_{max} around 1 to 2 h. On these grounds it could be concluded that the blood collections time (72 h) was sufficient to entirely cover the absorption phase. 90% CI for the AUC_{inf} fell also within the standard 0.8-12.5 range.
Finally, the SmPC of this generic product is in line with the one of the reference product. As requested, the applicant has removed information on the patented indications. However, safety information, details of adverse events and warning and information about these indications have been retained in the product information.

2.7. Recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality data. From a non clinical perspective the applicant provided an adequate summary of the current scientific knowledge related to ribavirin based on published literature. In addition, the impurity profiles of the test and reference products were compared, and the absence of an environmental risk assessment was adequately justified.
Regarding clinical data, an appropriate summary of the pharmacokinetics, pharmacodynamics, efficacy and safety of ribavirin for treatment of chronic hepatitis C was provided. The application was based on two single dose bioequivalence studies between Ribavirin Three Rivers and the EU reference product conducted under fed and fasting conditions. Standard statistical methods were used for the calculation of pharmacokinetic parameters and bioequivalence. Analytical method used was validated and within-study accuracy and precision was demonstrated. In both studies, bioequivalence was shown.
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. However, any additional risk minimisation measures that might be put in place for the reference product will also have to be implemented for this generic product.

Recommendation

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

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