EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2013
EMA/CHMP/461787/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ribavirin Teva Pharma BV

International non-proprietary name: RIBAVIRIN

Procedure No. EMEA/H/C/001064/II/0010

Note

Variation 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. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Teva Pharma B.V. submitted to the European Medicines Agency on 5 February 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Ribavirin Teva Pharma BV	RIBAVIRIN	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	II

Submission of a repeat bioequivalence study performed in response to the article 20 CHMP referral opinion in order to lift the suspension of the marketing authorisation.

The requested variation did not propose amendments to the product information.

Rapporteur: Ian Hudson

1.2. Steps taken for the assessment

Submission date:	5 February 2013
Start of procedure:	19 February 2013
Rapporteur's preliminary assessment report circulated on:	7 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	26 March 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	09 April 2013
CHMP opinion:	25 April 2013

2. Scientific discussion

2.1. Introduction

Ribavirin is a purine nucleoside analogue which is active against a number of DNA and RNA viruses. There are several 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 Teva Pharma is indicated for the treatment of chronic hepatitis C (HCV) virus infection in adults, children 3 years of age and older and adolescents and must only be used as part of a combination regimen with interferon alfa-2b.

Ribavirin Teva Pharma BV 200 and 400 mg tablets (EMEA/H/C/1064) was authorised via the centralised procedure in 2009 under article 10(1) of directive 2001/83/EC. The application was supported by a single pivotal bioequivalence study, conducted to determine bioequivalence with the EU reference product Rebetol (study S08-0152). The samples for this study were analysed at Cetero Research facilities in Houston (Texas).

Following an inspection of Cetero Research facilities in Houston (Texas), the US Food and Drug Administration (FDA) raised major concerns about the conduct of bio-analytical studies in the period April 2005 to June 2010. In November 2011 the EMA notified the concerned Marketing Authorisation Holders that bio-analytical studies conducted by Cetero Research in that period in support of marketing authorisation applications may need to be repeated or confirmed. The issue was subsequently assessed in an Article 20 referral procedure, and based on the CHMP scientific assessment (opinion adopted on 20 September 2012), the EC decided to suspend the marketing authorisation of Ribavirin Teva Pharma BV, as of 06 December 2012. The MAH was also requested to not release further batches of the medicinal product until the results of a new bioequivalence study are available.

The Annex II of the Article 20 Opinion "Conditions for lifting the suspension" specified that, in order to lift the suspension, the MAH should provide adequate and satisfactory data confirming the bioequivalence of their product with the reference product within one year of the Commission decision. Accordingly, the MAH repeated the pivotal study (S08-0152) which had supported the initial MAA for Ribavirin Teva Pharma BV 200 and 400 mg tablets.

This application has been submitted as a type II variation (classification C.I.z) to provide the clinical study report for the repeat bioequivalence study performed in response to the Article 20 CHMP referral opinion. Study P12-1093 (S12-0222) was a relative bioavailability study of Ribavirin Teva Pharma BV 200 mg tablets versus Rebetol 200 mg capsules under fed conditions.

2.2. Quality aspects

Study P12-1093 (S12-0222): A Relative Bioavailability Study of Ribavirin Teva Pharma B.V. 200 mg Tablets Versus Rebetol 200 mg Capsules Under Fed Conditions

Test and reference product

Test Product	Ribavirin 200 mg tablets, Teva Pharmaceutical Industries Ltd
Dose	1 x 200 mg
Administration	Oral
Lot number	R53009
Biobatch size	not provided
Manufacturing date	06/2012

Reference Product	Rebetol 200 mg capsules, Merck Sharp & Dohme Limited (MSD), UK
Dose	1 x 200 mg
Administration	Oral
Batch number	2RCJA14A03
Expiry Date	02/2014

Certificates of analysis (CoAs) of both the test and reference product as tested by Teva/MSD are provided. Impurities are below the reporting threshold for the test product and not reported for the reference product.

During the procedure MAH was asked to confirm that the test product was manufactured according to the approved manufacturing method and at a batch size of at least 100,000 tablets or 1/10 of the commercial scale and complies with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/QWP/1401/98). The MAH confirmed that the batch size of the test product used in the bioequivalence study was a commercial scale batch and was manufactured to the approved manufacturing method.

In vitro dissolution

During the procedure the MAH was requested to provide in vitro dissolution data, in line with the Guideline on the Investigation of Bioequivalence (CPMP/QWP/1401/98). While the CHMP recognised that this was initially demonstrated for the batches used in the disregarded bioequivalence study, acceptable data should also be provided for the biobatches used in the new bioequivalence study.

In response to this request the MAH has performed comparative in vitro dissolution testing of the test product batch R53009 against the reference product batch 2RCJA14A03 used in the bioequivalence study S12-0222 in pH 1.2, 4.5 and 6.8 and the media used for product release (water). The dissolution method used was the same method that is currently registered for routine quality control (QC) batch release.

Data are presented for the two batches used in the bioequivalence study P12-1093 (S12-0222). Dissolution data are also provided in tabulated form (n=12). Drug release is >85 % in 15 minutes in all pH media including the QC medium (water), so that, in line with guideline (CPMP/QWP/1401/98), F2 values do not need to be calculated. Release is comparable between the various dissolution media (water, 0.1N HCl and in buffered medium at pH 4.5 and 6.8) and the two formulations. At pH 6.8 ca. 5% difference in release is observed; however, as both products dissolve completely after 10 minutes this difference is not considered to be significant. Relative standard deviation (RSD) is not more than (NMT) 6.5% for each time point. The dissolution profiles are supportive of the bioequivalence claims and the in vivo data.

Biowaiver

No data were provided in the initially submitted variation dossier. The CHMP noted that a biowaiver was approved for the 400 mg strength as part of the initial assessment. However, as the initial bioequivalence study was not accepted, the MAH was requested to demonstrate comparative dissolution with the new 200 mg tablet biobatch (batch no. R53009) in line with the Guideline on the Investigation of Bioequivalence (CPMP/QWP/1401/98), and to provide the justification for a biowaiver for the 400 mg strength tablets supported by comparative dissolution data using the biobatch.

In their response the MAH provided the justification for a biowaiver for the 400 mg strength tablet that was included with the initial marketing authorisation application, as well as comparative in vitro dissolution data of the test product R53009 used in the repeated bioequivalence study S12-0222 and batches of 400 mg strength of Ribavirin Teva Pharma B.V. tablets, at pH 1.2, 4.5 and 6.8 and the media used for product release (water). The dissolution method used was the same method that is currently registered for routine QC batch release.

Data are presented for the bio-batch used in BE study P12-1093 (S12-0222), batch R53009 (200 mg) and various batches of the 400 mg strength: K-39308 (pilot scale; water, pH 6.8, 0.1 N HCl), R54003 (commercial scale; water) and R54001 (commercial scale; pH 4.5). It is not clear why three batches of the 400 mg strength were used for the various media instead of one batch for all media; however, considering that all 400 mg batches fulfil the conditions for the strength waiver (same qualitative and proportional quantitative composition, same manufacturing process) this may be accepted. Dissolution data are also provided in tabulated form (n=12). Drug release is >85 % in 15 minutes, so that F2 values do not need to be calculated. Release is comparable between the various dissolution media (water, 0.1N HCl and in buffered medium at pH 4.5 and 6.8) and the two strengths, and it is further noted that the three 400 mg batches show similar release curves between the different media as expected based on the information provided on the 200 mg strength (biobatch). RSD is NMT 9.55 % for each time point. The dissolution profiles are supportive of the strength waiver which may be accepted from a quality point of view.

2.3. Clinical Pharmacology aspects

2.3.1. Methods – analysis of data submitted

A single bioequivalence study was submitted in support of this application, study P12-1093 (S12-0222). The study was performed at the PRACS Institute.

Study title

An open-label, single dose, randomised, 2-way crossover bioequivalence study of Ribavirin Teva 200 mg tablets versus Rebetol 200 mg capsules following a single dose in healthy subjects under fed conditions.

Study design

A randomised, single dose, open-label, two-treatment, two-period, two-sequence, crossover bioequivalence study in healthy, adult male and female subjects under fed conditions.

Population studied and clinical part of the study

Thirty healthy, non-smoking male and female volunteers aged 18 years and older were entered in the study. Subjects' body mass indices (BMI) were within 18.5 and 30 kg/m^2. All subjects were randomly assigned to one of the two sequences in a balanced manner. The drug randomisation scheme was computer-generated and was provided.

Assuming a 25% intra-subject variability for C_{max} of ribavirin, and a difference between the treatment means of 5% or less, the necessary sample size for a 80% probability of the 90% confidence interval (CI) of the treatment means ratio to be within the conventional limits was estimated to be 28 subjects. Two extra subjects were included in the study to account for potential dropouts.

Thirty healthy adult subjects were thus enrolled in the study, and 27 subjects completed the clinical portion of the study in its entirety. Plasma concentration data from 27 of 30 subjects were used in the final statistical analysis for ribavirin. Data from Subjects 004, 010 and 016 were excluded from the final ribavirin analysis. Subject 004 was dropped from the study because they did not show up for Period II check-in. Subject 010 was discontinued by the clinical research organisation (CRO) due to a protocol violation (smoked past cut-off date). Subject 016 elected to withdraw from the study during Period I due to an adverse event (conjunctivitis).

Subjects fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration. During each period, and 30 minutes after a standardised high-fat high-calorie meal, each subject received one of the following: one tablet of Ribavirin Teva 200 mg or one capsule of Rebetol, 200 mg, MSD, taken with 240 ml of water. Standardised meals were provided to subjects at 4 hours and 10 hours after drug administration in each period. Blood samples were collected within 90 minutes prior to each subject's scheduled dose time (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, 3.5, 4, 5, 6, 8, 12, and 24 hours while subjects were confined to the clinic. Subjects returned to the clinic for blood samples at 36, 48 and 72 hours post-dose. The wash-out between period 1 and 2 was 35 days. The actual time of sample collection was documented.

The investigator states that the study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki and ICH Guidance on Good Clinical Practice. In addition, it is stated that the study was carried out in accordance with the ethical requirements of Directive 2001/20/EC.

The bioanalytical method used in the study was a LC-MS/MS method which was validated in 2012.

Pharmacokinetic variables and statistical methods

Pharmacokinetic parameters for ribavirin plasma concentration were calculated with SAS using standard non-compartmental approaches. Since ribavirin exhibits a long terminal elimination half-life, a truncated design at 72 hours was used.

Descriptive statistics were estimated for the pharmacokinetic parameters in each treatment. Analysis of variance (ANOVA) was applied to log-transformed AUC_{0-72h} 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. A 10% level of significance was used to test the sequence effect.

Bioequivalence was to be declared if the test/reference ratios of geometric means of C_{max} and AUC_{0-72h}, and their 90% CIs, were all contained in the interval 80.00 to 125.00%.

For the statistical analysis, subject sample values below the lower limit of quantification (BLQ) were reported as zero. For pharmacokinetics (PK) calculations, BLQ values were treated as zero when occurring at the beginning of the concentration profile. BLQ values were treated as missing when occurring at the end of the concentration profile or between two detectable concentration values.

2.3.2. Results

The results of study S12-0222 are summarised in figure 1 and table 3 below. The test/reference ratio of the geometric means of C_{max} and AUC_{0-72h} and their 90% CIs were all contained in the interval 80.00 to 125.00%.

Figure 1. Mean plasma concentrations (0-72 hours) for Ribavirin (n=27)

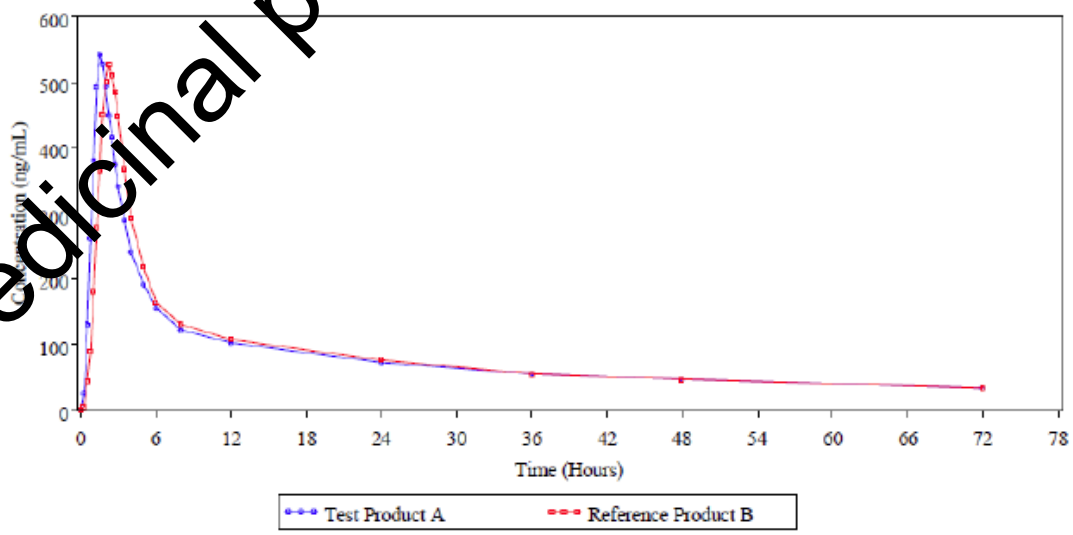

Table 3. Geometric means, ratio of means, and 90% confidence intervals of ln-transformed ribavirin data for test product A versus reference product B (n=27)

Parameter	Geometric Means*		% Ratio	90% CI (Lower Limit, Upper Limit)
	Test Product A: Ribavirin 200 mg Tablets	Reference Product B: Rebetol 200 mg Capsules		
AUC_{0-72} (ng·hr/mL)	5748.42	5892.03	97.56	(93.96, 101.31)
C_{max} (ng/mL)	633.33	605.50	104.60	(98.08, 111.54)

* Geometric means are based on the exponential of least squares means of ln-transformed values.

2.3.3. Discussion

Study design and conduct aspects:

Ribavirin is an immediate-release formulation. According to the SmPC, the product should be taken with food. A single-dose bioequivalence study in the fed state is appropriate.

The strength tested is the strength of the reference product and the same as the recommended dose and is acceptable. Upon request, the MAH confirmed that the batch size of test product used in the bioequivalence study was a commercial scale batch and was manufactured to the approved manufacturing method, and thus complies with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/QWP/1404/98). Also upon request, the MAH has provided the results of dissolution tests with the batches of the test and reference products used in the study, which also demonstrate compliance with the above guideline. The MAH has also provided a justification for a biowaiver for the 400 mg strength tablets supported by comparative in vitro dissolution data; these data were in compliance with the above guideline and the biowaiver for the 400 mg strength was accepted by the CHMP.

The reference product used in the bioequivalence study is acceptable. The design of the study and the population chosen are appropriate. Inclusion and exclusion criteria were presented and are acceptable. The randomisation scheme was provided. The sampling period and sampling scheme seem adequate to estimate PK parameter of an immediate release formulation. Considering the elimination half-life of ribavirin, the washout period of 35 days is expected to be long enough to avoid any carry-over effects.

There were several protocol deviations relating to the sample time and documentation failures for the time of placement of the blood samples into the freezer. Deviations from the scheduled sampling time were accounted for in the pharmacokinetic calculations since the actual sampling times were used. The investigator considers that the protocol violations described do not have a significant impact on the results.

Ribavirin plasma concentrations were measured using a validated bioanalytical method and according to the bioanalytical laboratory's SOP.

The pharmacokinetic variables follow the current European standard and are appropriate for this study. The statistical methods are adequately described. The protocol specified 80.00-125.00% as criteria for bioequivalence in line with the bioequivalence guideline. The data evaluation follows regulatory standards.

However, the MAH chose to truncate the AUC at 72h instead of using AUC_{0-t}. Ribavirin is a drug with a long plasma concentration half-life and a truncated AUC is in line with the revised bioequivalence guideline (CPMP/QWP/1401/98), which states that AUC_{0-72h} may be used as the absorption phase has been covered by 72 h for immediate release formulations.

Clinical pharmacology aspects:

The statistical analysis of the pharmacokinetic results of study S12-0222 demonstrates that the point estimates of the test/reference ratio of geometric means for ln-transformed AUC_{0-72h} and C_{max} and their

90% CIs were all contained within the acceptance interval of 80.00% to 125.00% defined in the Guideline on the Investigation of Bioequivalence (CPMP/QWP/1401/98).

There were no subjects with a positive plasma concentration at the beginning of period 2, the washout period was sufficient.

There was just one missing sample. The number of repeated samples was low (<1%), and the reasons given for repeating were appropriate.

2.4. Clinical Safety aspects

2.4.1. Methods – analysis of data submitted

Subjects who successfully completed the study were exposed once to the Ribavirin Teva Pharma BV 200 mg tablet and once to the Rebetol 200 mg capsule for a total of 400 mg of drug exposure throughout study conduct.

2.4.2. Results

Six subjects reported a total of 12 adverse events (AEs) across all treatments over the course of the study. The AEs were mild to severe in intensity. A total of 3 mild and 1 severe AEs were reported by subjects after they received the Ribavirin 200 mg tablet. A total of 7 mild and 1 moderate AEs were reported by subjects after they received the Rebetol 200 mg capsule. No serious adverse events (SAEs) were reported over the course of this study. Subject 016 elected to withdraw due to the AE of conjunctivitis infective.

Overall, the most common AE reported was diarrhoea. Diarrhoea was reported on at least one occasion in 2 (2/30) subjects (6.7%) and was considered by the Investigator to have a reasonable possibility of relationship to the treatment.

2.4.3. Discussion

Overall, Ribavirin Teva Pharma BV was well tolerated as a single oral dose of 200 mg (1 × 200 mg tablet) administered to healthy adult subjects under fed conditions.

3. Overall conclusion and impact on the benefit/risk balance

On 16 July 2012 the EC initiated a referral procedure under Article 20 of Regulation (EC) No 726/200 for Ribavirin Teva Pharma BV, due to concerns regarding the reliability and correctness of data for studies conducted at the Cetero research facilities in Houston (Texas, USA), which included the critical pivotal bioequivalence study submitted in support of the marketing authorisation of this medicinal product. In the referral procedure, the CHMP concluded that the available data gave rise to serious doubts as to the evidence of the bioequivalence of Ribavirin Teva Pharma BV with the EU reference product and that the benefit-risk balance of Ribavirin Teva Pharma BV cannot be considered to be positive under normal conditions of use. The CHMP thus recommended the suspension of the marketing authorisation. For the suspension to be lifted, the MAH for Ribavirin Teva Pharma BV was requested to provide adequate and satisfactory data confirming the bioequivalence of their product with the reference product.

Accordingly, with this type II variation and in order to lift the MA suspension, the MAH has submitted the clinical study report for a repeat bioequivalence study conducted to confirm bioequivalence of their product with the EU reference product.

The MAH has conducted a standard bioequivalence study with a two-period, two-sequence crossover design, which was in line with the relevant Guideline and GCP requirements, and which the CHMP considered adequate to address the bioequivalence of an immediate-release oral formulation. A single-dose study in fed subjects was appropriate as the SmPC states that ribavirin should be taken with

food. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ribavirin Teva Pharma BV (200 mg tablets) met the protocol-defined criteria for bioequivalence when compared with the reference formulation Rebetol of MSD, administered as a single dose under fed conditions. Bioequivalence of the two formulations can thus be accepted. Clinical criteria for the biowaiver are fulfilled and upon request the MAH also provided confirmation that pharmaceutical criteria for the biowaiver are met.

The MAH has thus, as requested in the Conditions for lifting the suspension annexed to the Article 20 referral opinion, provided adequate and satisfactory data confirming the bioequivalence of Ribavirin Teva Pharma BV with the reference product.

The CHMP is therefore of the opinion that

- the benefit-risk balance of Ribavirin Teva Pharma BV can be considered positive under normal conditions of use
- the particulars supporting the application as provided in Article 10 of Directive 2001/83/EC can be considered correct

and therefore recommends the lifting of the suspension of the marketing authorisation.

Furthermore, the CHMP considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds: this variation was submitted to lift the suspension of the marketing authorisation.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	II

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