CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ribavirine ratiopharm 200 and 400 mg, film-coated tablets ratiopharm Nederland B.V., the Netherlands

ribavirin

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2092/001-002/DC
Registration number in the Netherlands: RVG 108116, 108119

3 November 2011

Pharmacotherapeutic group:	antiinfectives for systemic use; nucleosides and nucleotides excl. reverse transcriptase inhibitors
ATC code:	J05AB04
Route of administration:	oral
Therapeutic indication:	chronic hepatitis C virus (HCV) infection in adults, children 3 years of age and older and adolescents as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	20 October 2011
Concerned Member States:	Decentralised procedure with CZ, DE, ES, HU, LU, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) (200 mg), 10(3) (400 mg)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ribavirine ratiopharm 200 mg and 400 mg, film-coated tablets from ratiopharm Nederland B.V. The date of authorisation was on 20 October 2011 in the Netherlands.

The product is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults, children 3 years of age and older and adolescents and must only be used as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b. Ribavirine ratiopharm must not be used as monotherapy.

There is no safety or efficacy information on the use of Ribavirin ratiopharm with other forms of interferon (i.e. not alfa-2b).

A comprehensive description of the indications and posology is given in the SPC. Refer to section 4.1 and 4.4 of the approved SPC for more details on treatment of naïve patients, previously treated patients, as well as use in children 3 years of age and older and adolescents.

Ribavirin is a synthetic nucleoside analogue which has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b exerts its effects against HCV is unknown. Oral formulations of ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on eliminating hepatitis virus (HCV-RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Rebetol 200 mg hard capsules which has been registered in the EEA by Schering-Plough Europe through centralised procedure EU/1/99/107/001-003 since 7 May 1999.

The marketing authorisation for the 200 mg is granted based on article 10(1) of Directive 2001/83/EC. Ribavirine ratiopharm 200 mg is an immediate-release oral pharmaceutical form (film-coated tablet) as well as the innovator (hard capsule), and as such these two formulations are considered one and the same pharmaceutical form. The application for the 400 mg strength is based on article 10(3), hybrid application (different strength).

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the 200 mg product is compared with the pharmacokinetic profile of the reference product Rebetol 200 mg capsules, as registered in the EEA and obtained from Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products. No paediatric development programme has been submitted as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ribavirin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white crystalline powder, and is freely soluble in water. Ribavirin shows polymorphism. Requirements for the polymorphic form used are included in de CEP.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is based on the applicable Ph.Eur. 7.2 monograph and CEP requirements. Appropriate additional requirements have been laid down. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Ribavirin ratiopharm 200 mg is an oval, biconvex, ivory film-coated tablet of 14 mm length and 7 mm width.
Ribavirin ratiopharm 400 mg is an oval, biconvex, yellow film-coated tablet of 18 mm length and 9 mm width.

The film-coated tablets are packed in blisters consisting of white polyvinyl chloride (PVC)/aluminium (ALU) or white polyvinylidene chloride (PVDC)/aluminium (ALU) or in tablet containers consisting of high density polyethylene (HDPE) with a polypropylen (PP) screw cap.

The excipients are: microcrystalline cellulose, croscarmellose sodium, pregelatinised maize starch, colloidal anhydrous silicia, talc, magnesium stearate, hypromellose, macrogol 6000, titanium dioxide, iron oxide yellow.

The tablets are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the choice of the granulation approach, comparative dissolution studies and optimisation of the manufacturing process.
Bioequivalence studies were performed with the 200 mg tablet. The batch used in the bioequivalence studies has the same composition and is manufactured the same way as the future commercial batches. Dissolution profiles of the 200 mg and 400 mg products were demonstrated to be comparable to the innovator's dissolution profile. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process is divided in the following steps: mixing, wet granulation, drying, lubrication, compression and packaging. Satisfactory in-process controls have been specified. Validation studies on two batches of both strengths have been performed.
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur., except for iron oxide which complies with in-house specifications in accordance with Directive 2008/128/EC. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, hardness, disintegration time, loss on drying, identification of ribavirin, identification of colourants, assay, uniformity of dosage units, related substances, residual solvents, dissolution, and microbiological quality. The release and end shelf-life specification are identical, except for water content and a specified impurity. The drug product specification is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site has been provided on two pilot-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided two pilot-scale batches of both strengths stored at 25°C/60% RH (18 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVDC-Alu blisters, PVC-Alu blisters and HDPE bottles (different sizes). No relevant changes were observed. Photostability studies demonstrated that protection from light is not necessary.
Based on the stability data provided, a shelf life of 24 months without special storage conditions was granted.
Stability data has been provided demonstrating that the product remains stable for 8 weeks following first opening of the tablet container, when stored at 25°C/60%RH.

Several commitments have been made with regard to the drug product; these can be found on page 7 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Rebetol, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ribavirin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ribavirin is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ribavirine ratiopharm 200 mg film-coated tablets (ratiopharm Nederland B.V., NL) compared with the pharmacokinetic profile of the reference product Rebetol 200 mg capsules, hard (Schering-Plough, Germany) sourced in Belgium.

The choice of the reference product
The choice of the reference product in the bioequivalence study is acceptable, as the innovator produt has been authorised through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 58 healthy male and female subjects, aged 31-54 years. Each subject received a single dose (200 mg) of one of the 2 ribavirin formulations. The products administered with 240 ml water 30 min after start of intake of a standard breakfast. A subsequent fasting period was applied for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 56 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject was withdrawn due to requirement of concomitant drug therapy to treat an adverse event and one subject elected to withdraw to consult a physician in regards to adverse event. Fifty-six subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ribavirin

Treatment N=56	**AUC_{0-72}**** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6791 ± 1888	--	674 ± 216	1.75 (1.5 – 3.0)	--
Reference	6942 ± 1700	--	668 ± 160	1.75 (1.0 – 4.0)	--
***Ratio (90% CI)**	0.97 (0.94-1.00)	--	0.99 (0.94-1.04)	--	--

CV (%)	10	--	15	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*
*** n = 55 : for one subject the 36, 48 and 72 h samples were not available*

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of ribavirin under fed conditions, it can be concluded that Ribavirin 200 mg film-coated tablets and Rebetol 200 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

As recommended in the SPC, ribavirin should be taken with food as the bioavailability of ribavirin is increased by co-administration of a high fat meal. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fed conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 400 mg strength
The results obtained for the 200 mg tablets can be extrapolated to the 400 mg tablet, as:
- the formulations are dose proportional
- the formulations are manufactured by the same manufacturer and manufacturing process
- ribavirin shows linear pharmacokinetics over the therapeutic dose range of 200-1200 mg
- and dissolution data have been submitted showing comparable dissolution at three different pH values.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Ribavirin was first approved in 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ribavirin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Rebetol.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each.
The traceability of the information in the PIL was tested thoroughly. Comprehensibility and applicability testing could however be improved. Overall, readability of the PIL has been demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ribavirine ratiopharm 200 mg and 400 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Rebetol 200 mg, hard capules. Rebetol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ribavirine ratiopharm 200 mg and 400 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 6 July 2011. Ribavirine ratiopharm 200 mg and 400 mg, film-coated tablets were authorised in the Netherlands on 20 October 2011.

The date for the first renewal will be: 6 July 2016

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH to revise the release and end of shelf life limits for total impurities based on batch analytical data and stability data of production scale batches, if required. If it is necessary to revise the specifications the updated specifications will be submitted upon availability.
- The MAH committed to place the first three production batches of each strength on long-term stability studies throughout the proposed shelf life and on accelerated studies for 6 months.
- The MAH committed to perform full stability testing for the HDPE bottles if a significant change occurs.
- The MAH committed to subject a batch of each strength toward the end of its shelf life to in-use stability testing. The data will be submitted upon availability.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached