

**Direction de l'Evaluation  
des Médicaments et des Produits Biologiques**

# **PUBLIC ASSESSMENT REPORT**

## **Scientific Discussion**

**RILMENIDINE WINTHROP**  
**1 mg**  
**Tablet**  
**(Rilmenidine)**

**FR/H/462/01/MR**

**Applicant: SANOFI AVENTIS**

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| <b>Date of the PAR: February 2011</b> |
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## Information about the initial procedure:

|                                |                       |
|--------------------------------|-----------------------|
| <b>Application/Legal Basis</b> | <b>Generic 10 (1)</b> |
| <b>Active substance</b>        | <b>Rilmenidine</b>    |
| <b>Pharmaceutical form</b>     | <b>Tablet</b>         |
| <b>Strength</b>                | <b>1 mg</b>           |
| <b>Applicant</b>               | <b>SANOFI AVENTIS</b> |
| <b>EU-Procedure number</b>     | <b>FR/H/462/01/MR</b> |
| <b>End of procedure</b>        | <b>30.08.2010</b>     |

### 1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for Rilmenidine Winthrop on 14<sup>th</sup> April 2006.

Rilmenidine is indicated in the treatment of arterial hypertension.

A comprehensive description of the indication and doses is given in the SPC.

This application is a Mutual Recognition Procedure (MRP) with France acting as Reference Member State (RMS), and involved Lithuania and Slovakia as Concerned Member State (CMS).

This application is submitted in accordance with Art 10 (1) “generic application” according to Directive 2001/83/EC. The product is claimed to be essentially similar to Hyperium 1 mg tablets that was first authorised in France on April 23<sup>rd</sup> 1987 to Les laboratoires Servier.

No new preclinical or clinical studies were conducted, which is acceptable for this kind of application.

One bioequivalence study is submitted to show the bioequivalence between Rilmenidine phosphate 1mg and Hyperium 1 mg.

During this Mutual recognition Procedure (MRP), no potential serious risk to public health concern was raised on the quality, non-clinical, clinical and safety data.

The procedure was ended positively on 30<sup>th</sup> August 2010.

### 2. QUALITY ASPECTS

#### 2.1 Introduction

Rilmenidine Winthrop 1 mg tablet are of similar shape and colour to the reference product Hyperium from Laboratoires Servier Industrie: round, biconvex and white 6 mm diameter tablet.

The following excipients compose the formulation: microcrystalline silicified cellulose, crospovidone, stearic acid, talc and anhydrous colloidal silica.

They are packed in Alu/Alu blisters made of Aluminium foil CFF and Aluminium foil coated with a heat seal lacquer.

#### 2.2 Drug substance

The drug substance Rilmenidine dihydrogen phosphate is described in the Eur. Ph. The Applicant has provided full details of the manufacture into an ASMF application. Satisfactory scientific data have been provided.

Rilmenidine dihydrogen phosphate is a white or almost white powder freely soluble in water.

The specifications of Rilmenidine Dihydrogen Phosphate comply with the requirements of the specific monograph of Eur. Ph. current edition completed by an addition test for residual solvent. In-house method has been suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

## **2.3 Medicinal product**

Rilmenidine Winthrop 1 mg Tablet is formulated using excipients described in the current Ph Eur. except microcrystalline silicified cellulose which is adequately tested by in-house monograph.

All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The development is sufficiently described in accordance with the relevant European guidelines.

Comparative *in vitro* dissolution profiles and impurities profiles of the generic product and the reference product support the essentially similar character. Furthermore, the medicinal product was tested for bioequivalence *versus* the reference medicinal product Hyperium 1 mg and exhibited the same bioavailability.

The manufacturing process has been sufficiently described and critical steps identified.

Results from the process validation studies which was carried out on two pilot scale batches, one semi-industrial scale batch and three industrial scale batches, confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Batch analysis results of each validation batches are presented and comply with specifications.

Analytical methods are satisfactory described and validated according to ICH guidelines.

The container closure system of the medicinal product is a blister made of Aluminium foil CFF and aluminium foil coated with a heat seal lacquer.

Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 3 years at a temperature not higher than 30°C.

## **3. NON-CLINICAL ASPECTS**

### **3.1 Discussion on the non-clinical aspects**

Since this product is a generic application of a widely used and well known substance based on a full application with regard to preclinical data, no further data have been submitted or are considered necessary, which is adequate. Pharmacodynamic, pharmacokinetic and toxicological properties of rilmenidine are well known.

No modification of section 5.3. Preclinical Safety Data of the SPC was necessary; the initial Applicant's proposal was endorsed by the RMS and all CMS.

#### Environmental risk

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

## **4. CLINICAL ASPECTS**

### **4.1 Introduction**

Since this is a generic application, no further clinical studies are required and the applicant provides none. The clinical overview provides an adequate summary of the clinical data of rilmenidine. The report is an overview of the published literature regarding clinical pharmacodynamics, pharmacokinetics, efficacy and safety aspects of orally administered rilmenidine.

From a clinical point of view, there are no objections to approval of Rilmenidine Winthrop 1 mg tablet.

### **4.2 Discussion on the clinical aspects**

Rilmenidine is a centrally acting antihypertensive that appears to act through stimulation of central imidazoline receptors and also has alpha2-adrenoceptor agonist activity. It has general properties similar to those of clonidine, but is reported to cause less sedation and central adverse effects. Thus, rilmenidine, the first antihypertensive with selectivity for brainstem and renal I1 imidazoline receptors, allows to lower blood pressure by a central action without the drawbacks of the side effects of earlier central agents. Rilmenidine dihydrogen phosphate (or dihydrogenophosphate) is a white or almost white powder. Rilmenidine is an oxazoline rather than an imidazoline and, though less potent than clonidine, has a 30-fold greater selectivity than clonidine for imidazoline receptors over 2-adrenoreceptors.

Rilmenidine phosphate 1.5 mg is equivalent to about 1 mg of rilmenidine. The dose is 1 mg daily, as a single dose by mouth; this may be increased if necessary, after 1 month, to 2 mg daily in divided doses.

#### **Pharmacovigilance System (PV system)**

As described, the *PV System* adequately covers all the requested information, including: i) the qualified person responsible for pharmacovigilance (including the backup procedure to apply in the absence of the EUQP), ii) the documented procedures; iii) databases; iv) training and v) the documentation (including the locations of the different types of pharmacovigilance source documents, and archiving arrangements).

#### **Risk Management Plan (RMP)**

In view of the existing knowledge and experience with the active substance rilmenidine, the available data and the known risk benefit profile, a specific RMP is not justified. Routine Pharmacovigilance with adequate Pharmacovigilance System as described and completed by the applicant are sufficient to adequately follow up the safety profile of rilmenidine.

### **4.3 Pharmacokinetics**

A study to compare the bioavailability of two Rilmenidine Phosphate 1 mg Tablet products under fasting conditions has been conducted. The study was designed according to an open label, laboratory-blind, single dose, randomised, two-period cross-over in healthy male and female subjects.

After an overnight fast of 10 hours the subjects received the study drug, of either test or reference product, a washout period of 7 days was maintained between the two dosing days. A total of 25 healthy adult subjects satisfied all inclusion and none of the exclusion criteria were enrolled in the study. In accordance with the protocol only the first 24 completers were included in the statistical analysis.

Test product: Rilmenidine phosphate 1mg tablet manufactured by Delpharm, France,

Reference product: Hyperieum 1mg tablet, manufactured by Serviers Industrie, France.

Relevant pharmacokinetic parameters were estimated using non compartmental analysis (NCA) The pharmacokinetic parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub> and T<sub>max</sub> were either observed or calculated.

AUC was calculated by the trapezoidal rule. C<sub>max</sub> and T<sub>max</sub> were directly estimated from the individual concentrations versus time profiles.

## RESULTS

**Table1.** Pharmacokinetic parameters (non-transformed values; geometric mean  $\pm$  SD, t<sub>max</sub> median, range) for **rilmenidine** (n=24).

| Treatment                                                                                                                                                                                                                                                                                                                     | AUC <sub>0-t</sub><br>ng/ml/h | AUC <sub>0-∞</sub><br>ng/ml/h | C <sub>max</sub><br>ng/ml | t <sub>max</sub><br>h |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|---------------------------|-----------------------|
| Test                                                                                                                                                                                                                                                                                                                          | 31.6 9.06                     | 35.1 9.18                     | 3.97 0.69                 | 1.33<br>[0.5-2.33]    |
| Reference                                                                                                                                                                                                                                                                                                                     | 30.5 8.22                     | 34.0 8.73                     | 3.73 0.66                 | 1.33<br>[0.5-3.0]     |
| *Ratio<br>[90% CI]                                                                                                                                                                                                                                                                                                            | 103%<br>[96.1 ; 111]          | 103%<br>[96.7 ; 110]          | 107%<br>[101 ; 112]       | NS                    |
| Intra-subject<br>CV (%)                                                                                                                                                                                                                                                                                                       | 15%                           | 13%                           | 10%                       |                       |
| AUC <sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity<br>AUC <sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours<br>C <sub>max</sub> maximum plasma concentration<br>T <sub>max</sub> time for maximum concentration<br>T <sub>1/2</sub> half-life |                               |                               |                           |                       |

The conventional CI for Log transformed AUC<sub>t</sub>, AUC<sub>inf</sub> and C<sub>max</sub> are within the [80; 125]% acceptance range. No significant difference in T<sub>max</sub> was evidenced by the non parametric test. Therefore, the BE of the test and reference drug products could be concluded.

## 5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Satisfactory chemical-pharmaceutical documentation has been provided, assuring consistent and sufficient quality of the product.

Considering the extensive knowledge on the preclinical and clinical data for rilmenidine, and given human experience, it can be stated that the rilmenidine tablets do not raise any new pre-clinical or clinical concerns.

Based on the submitted bioequivalence studies, the rilmenidine tablets are considered bioequivalent with the reference product.

In conclusion, the Concerned Member States mutually recognised the French marketing authorisation; all issues being solved for the marketing authorisation of Rilmenidine Winthrop 1mg tablet.

There was no discussion in the CMDh.

The following post-approval commitment was made during the procedure regarding quality: to provide additional data on impurity profile of the drug substance Rilmenidine dihydrogen phosphate.

The current SPC, Package Leaflet (PL) and labelling are in the agreed template.

### User consultation

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 language used for the purpose of user testing the PL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The testing method included 24 participants and was done in 3 stages. The pilot phase included 4 participants and was followed by 2 testing rounds including each one 10 participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.