LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Agomelatine Mylan
(agomelatine, agomelatine citric acid)

SE/H/2236/01/DC

This module reflects the scientific discussion for the approval of Agomelatine Mylan. The Public Assessment Report was written in December 2018 by the previous RMS NL after initial procedure NL/H/4018/001/DC and is attached at the end of this document. RMS transfer from NL to SE was completed 30 August 2024. For information on changes after this date please refer to the module 'Update'.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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Public Assessment Report

Scientific discussion

Agomelatine Mylan 25 mg film-coated tablets

(agomelatine)

NL/H/4018/001/DC

Date: 4 December 2018

This module reflects the scientific discussion for the approval of Agomelatine Mylan 25 mg film-coated tablets. The procedure was finalised at 26 July 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

LIST OF ABBREVIATIONS

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia

PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Agomelatine Mylan 25 mg film-coated tablets, from Mylan B.V.

The product is indicated for the treatment of major depressive episodes. Agomelatine is indicated in adults.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Valdoxan 25 mg, film-coated tablets which has been registered in the EEA by Les Laboratoires Servier since 19 February 2009 via a centralised procedure (EU/1/08/499).

The concerned member states (CMS) involved in this procedure were Czech Republic, Germany, Denmark, Estonia, Finland, France, Hungary, Ireland, Lithuania, Latvia, Poland, Portugal, Sweden and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Agomelatine Mylan is a yellow, oblong, biconvex film-coated tablet and contains agomelatine-citric acid equivalent to 25 mg of agomelatine.

The film-coated tablets are packed in OPA/Alu/PVC/Alu blisters.

The excipients are:
Tablet core - colloidal silicified dioxide, microcrystalline cellulose, mannitol, povidone 30, colloidal anhydrous silica, crospovidone, sodium stearyl fumarate, magnesium stearate and stearic acid
Tablet coating – hypromellose, macrogol, titanium dioxide (E 171), talc and iron oxide yellow (E 172).

II.2 Drug Substance

The active substance is agomelatin citric acid co-crystal. It is not a well known drug substance; it is not described in the European Pharmacopoeia (Ph.Eur.) or United States Pharmacopoeia (USP). The drug substance is a white to almost white, non-hygroscopic powder. It is freely soluble in methanol, ethanol, acetone and tetrahydrofuran, soluble in 2propanol and methylethylketone, and unstable in water (decomposition to individual components). The co-crystal of agomelatine and citric acid does not exhibit polymorphism and no other crystal form was found.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

II.2.1 Manufacturing process

Brief information about the synthesis including used solvents and reagents has been provided. This is acceptable. The information about the characterisation of the active substance is sufficient. The ASMF provided prove that the drug substance is true co-crystal and not only a mixture of two substances. Overall the manufacturing process is considered acceptable.

II.2.2 Quality control of drug substance

The active substance specification is considered adequate to control the quality and includes tests and limits for identification of the drug substance, content of related substances, sulphated ash, water content, assay, microbiological purity and residual solvents content. The specification is according to the specification of the AMSF-holder. Batch analytical data demonstrating compliance with this specification have been provided for seven production batches.

II.2.3 Stability of drug substance

Stability data on the active substance have been provided for three production batches stored at 25°C/60% RH (36 months) and at 45°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. No significant changes were observed in the tested parameters. Based on the data submitted, a retest period could be granted of 30 months.

II.3 Medicinal Product

II.3.1 Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The aim of the development was to produce a bioavailable and stable tablet dosage form of Agomelatine citric acid co-crystal. The careful selection of excipients was an important step to achieve suitable dissolution characteristics and stability of the finished tablets. The choice of the excipients was based on the originator, Valdoxan, where possible.
A pivotal bioequivalence study has been performed between the representative batch of the proposed product Agomelatine Mylan 25 mg film-coated tablets as bio (test) batch and a batch of Valdoxan 25 mg film-coated tablets as originator/reference batch.

Comparative dissolution profiles are provided of the test batch and the reference batch, complementary to the bioequivalence study. The profiles were acquired from different dissolution media at several pH's across the physiological pH range in the GI track: pH 1.2, pH 2.0 (QC dissolution medium), pH 4.5 and pH 6.8. The profiles are similar, except regarding pH = 1.2. The results of the pivotal bioequivalence study prevail.
The molecular (chemical-)physical characterisation studies of the co-crystal structure in drug substance Agomelatine citric acid co-crystal are acceptable, including the analytical techniques used. Preservation of integrity of the co-crystal structure during product manufacture and - storage structure has been confirmed, with results, including stability results. The pharmaceutical development studies are acceptable.

II.3.2 Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. It is a standard process and consists of dry granulation, roller compaction process followed by film-coating. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

II.3.3 Control of excipients

The excipients generally comply with the Ph. Eur. or the USP. The specifications are acceptable.

II.3.4 Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, identification drug substance and identification colourants, assay, uniformity of dosage units, disintegration, dissolution, impurities, microbial purity and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

II.3.5 Stability of drug product

Stability data on the product have been provided for three production batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 45°C/75% RH (6 months). The batches were stored in accordance with the ICH stability guideline. No significant changes were observed. Based on the results of a photostability study, the product can be considered light resistant. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: '*Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions*'.

II.3.6 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Agomelatine Mylan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of agomelatine are well known. The agomelatine used is, however, in the form of a co-crystal with citric acid. To verify the safety profile of different form of active substance used in comparison to originator product Valdoxan, film-coated tablets, the MAH conducted a single dose toxicity study, a repeat dose toxicity study and a genotoxicity study. From a toxicological perspective, there are no reservations about (the relatively low amount of) the citrate in the co-crystal. Citric acid is a well known endogenous substance that is common in pharmaceutical products.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Agomelatine Mylan is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Agomelatine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Agomelatine Mylan 25 mg film-coated tablets (Mylan B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Valdoxan 25 mg, filmcoated tablet (Les Laboratoires Servier, France).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

IV.2.1 Bioequivalence study

IV.2.1.1 Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 100 healthy (55 male/45 female) subjects, aged 31.7(± 0.4 SD) years. Each subject received a single dose (25 mg) of one of the 2 agomelatine formulations. The tablet was orally administered with 240 ml water after an fasting period. There were 4 dosing periods, separated by a washout period of 48 hours.

Blood samples were collected at pre-dose and at 0.25; 0.5; 0.75; 1.0; 1.25; 1.5; 1.75; 2.0; 2.25; 2.5; 2.75; 3.0; 3.5; 4.0; 5.0; 6.0; 9.0 and 12.0 hours after administration of the products.

The design of the study is acceptable. The sampling times and the wash-out period are considered sufficiently long considering the elimination half life of 1 – 2 hrs and T_{max} of 1-2 hours.

Considering the specific formulation of the test product using co-crystal form of agomelatine differs from the reference product, justification for the lack of bioequivalence study under fed conditions was provided. Agomelatine is considered a BSC class I and therefore cocrystals formation does not affect solubility. In addition, agomelatine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of agomelatine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

IV.2.1.2 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.

IV.2.1.3 Results

2 subjects were withdrawn from the study due to vomiting and personal reasons. Therefore, 98 subjects completed all four periods and were eligible for pharmacokinetic analysis.

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

Treatment N=98	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	37.205 ± 64	38.198 ± 65	26.817 ± 40	0.75 (0.25 – 4.02)
Reference	38.030 ± 69	38.768 ± 70	29.286 ± 48	0.75 (0.25 – 5.00)
*Ratio (90% CI)	1.01 0.96 – 1.05	1.01 0.97 – 1.06	0.99 0.92 – 1.07	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

IV.2.2 Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Agomelatine Mylan 25 mg film-coated tablets is considered bioequivalent with Valdoxan 25 mg, film-coated tablet.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Agomelatine Mylan.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	□ Hepatotoxic reactions □ Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)
Important potential risks	□ Suicide
Missing information	□ Use in patients with severe or moderate renal impairment □ Use in paediatric population (<18 years old) □ Use in elderly (≥75 years) □ Use during pregnancy and lactation

Additional risk minimisation measures are needed when prescribing this product. The educational material for HCPs (i.e. the Physician´s guide) should contain the following key elements:

- The need to inform patients about the potential risk of transaminases elevations, the risk of liver injury and interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin);
- The need to perform liver function tests in all patients before starting treatment and periodically thereafter around three, six (end of acute phase), twelve and twenty-four weeks (end of maintenance phase), and thereafter when clinically indicated;
- The need to perform liver function tests at the same frequency as at treatment initiation in all patients where the dosage is increased;

- Guidance in case of clinical symptoms of hepatic dysfunction;
- Guidance in case of liver function test abnormality;
- Caution should be exercised when therapy is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range);
- Caution should be exercised when therapy is prescribed for patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury;
- Contraindication in patients with hepatic impairment (i.e. cirrhosis or active liver disease);
- Contraindication in patients with transaminases exceeding 3 X upper limit of normal; Contraindication in patients receiving concomitantly potent CYP1A2 inhibitors.

The educational material for Patients (i.e. the Patient's Booklet) should contain the following key elements:

- Information about the risk of hepatic reactions and clinical signs of liver problems
- A guidance on the scheme of hepatic monitoring
- A blood tests appointments reminder

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Valdoxan. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 result of the readability user testing of the leaflet for Agomelatine 25 mg film-coated tablets may be considered satisfactory according to the recommendations on force, since 100 per cent of the interviewees found and understood properly the information requested in the leaflet. The results derived from both the first stage and second stage of confirmation prove the legibility of the leaflet since the answers to all the questions were understood in 100 per cent of the cases, found easily or very easily and only in one case an answer were found with any difficulty, obtaining no negative result, a reason why no modification of the leaflet or questionnaire were proposed after any of the testing stages. This decision was endorsed by the good results obtained at all stages.
It can therefore be said that the product leaflet for Agomelatine 25 mg film-coated tablets which has been evaluated in this readability user testing contains easy-to-find and understandable information and it thus meets the required legibility standards. The leaflet is clear and easy-to-use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Agomelatine Mylan 25 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Valdoxan 25 mg, film-coated tablet. Valdoxan 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 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 Agomelatine Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 July 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse