COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melatonine Clinigen 3 mg, film-coated tablets

(melatonin)

NL/H/4422/001/DC

Date: 11 June 2019

This module reflects the scientific discussion for the approval of Melatonine Clinigen 3 mg, film-coated tablets. The procedure was finalised at 13 March 2019. 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 Melatonine Clinigen 3 mg, film-coated tablets, from Clinigen Healthcare B.V.

The product is indicated for short-term treatment of jet-lag in adults.

Melatonin is a hormone produced by the pineal gland during the night in response to light/dark information received by the retina. The plasma concentration of melatonin exhibits a circadian pattern, rising in the evening with dim light (Dim Light Melatonin Onset (DLMO)), increases progressively to reach maximal values in the middle of the night and then decreases progressively to reach minimal values in the morning. This endogenous melatonin rhythm may be disturbed by flying over several time zones. Exogenous melatonin may help re-entrain the natural cycle.

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 Bio-Melatonin 3 mg film-coated tablets which has been registered in Hungary by Pharma Nord Aps since 22 July 2003 national procedure under Article 10(a) of EU Directive 2001/83/EC. As no registration of Bio-Melatonin film-coated tablets has been granted in the Netherlands, the Hungarian product is used as European Reference Product.

The concerned member state (CMS) involved in this procedure was the United Kingdom.

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

Scientific advice

Scientific advice has been given by the reference member state prior to the submission of the application concerning the indication. The reference product has been registered with the indications sleep disturbance caused by jetlag or shift work in adults. Recently these indications have been assessed by the RMS in an other procedure, and the indication "sleep disturbance originating from shift work in adults" has been rejected at national level. The indication short term use in adults suffering from jet lag has been considered acceptable. From a regulatory point of view a generic application with a restricted indication is fully acceptable. The MAH has complied with the RMS's request to restrict the indication to short-term treatment of jet-lag in adults.

II. QUALITY ASPECTS

II.1 Introduction

Melatonine Clinigen is a off-white, round, biconvex, film-coated tablet and contains 3 mg of melatonin.

The film-coated tablet are packed in of PVC/PVdC-Aluminium blisters.

The excipients are:
Tablet core -microcrystalline cellulose, maltodextrin, colloidal anhydrous silica and magnesium stearate
Tablet coating - hypromellose , lactose monohydrate , titanium dioxide and macrogol 4000

II.2 Drug Substance

The active substance is melatonin, an established active substance described in the British Pharmacopoeia (BP). Melatonin is a ivory to beige, crystalline powder. It is slightly soluble in water, soluble in acetone, ethyl acetate and methanol. The active substance does not exhibit polymorphism and does not show isomerism.

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.

Manufacturing process
The manufacturing process is described in sufficient detail. No class-I solvents or heavy metal catalysts are used in the synthesis. Melatonin has been adequately characterised and acceptable specifications for the starting material and other solvents and reagents used in the manufacturing process have been adopted.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the BP ant the specifications of the ASMF-holder. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for an appropriate amount of batches stored at 25°C/60% RH (up to 60 months) and at 40°C/75% RH (6 months) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months without specific storage conditions.

II.3 Medicinal Product

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 explained. The development focussed on preliminary formulation trials, maltodextrin effect on drug release and design of experiments.

Two bioequivalence studies (one pilot and one pivotal) have been performed using the test product Melatonine Clinigen 3 mg, film-coated tablets versus the reference product Bio-melatonin 3 mg, film-coated tablets. Dissolution profiles of the test, reference product and commercial scale batches have been provided in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 and as per QC method. All profiles showed similar dissolution profiles.

Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process consists of sieving, blending, compression, coating and has been validated according to relevant European guidelines. It Is considered a non-standard process due to low content of the active substance (2%). Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

Excipients are tested according to the Ph.Eur, except for the coating. Functionality-related characteristics of several excipients have been discussed and tests included in the specifications when relevant. These specifications are acceptable.

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, identification of the active substance, assay, average mass, uniformity of dosage units, resistance to crushing, dissolution, disintegration, loss on drying, related compounds and microbial contamination. The latter is not routinely performed which is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life specifications are identical except for average mass, uniformity of dosage units, resistance to crushing. 0.1 N HCl is medium for routine dissolution testing with an acceptance criterion of NLT 85% (Q) in 30 minutes. Compliance via release and stability data that this limit can be met are provided. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production batches stored at 25°C/60% RH (18 months), 30°C/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. A photostability study showed that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 18 months when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

TSE/BSE statements are provided for lactose monohydrate. It has been adequately justified that the excipients does not pose a BSE risk. No other animal-derived materials are used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Melatonine Clinigen 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 Ecotoxicity/environmental risk assessment (ERA)

Since Melatonine Clinigen 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Bio-Melatonin which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Melatonin 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 one pilot and one pivotal bioequivalence study, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Melatonine Clinigen 3 mg film-coated tablets (Clinigen Healthcare B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Bio-Melatonin (Pharma Nord Aps, Hungary).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The MAH performed a pilot study and a pivotal study. The MAH pooled the data of both studies to show bioequivalence between the test and reference product and therefore both studies are described in detail.

Bioequivalence studies

Bioequivalence study I – pilot study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 12 healthy male subjects, aged 19-43 years. Each subject received a single dose (3 mg) of one of the 2 melatonin formulations. The tablet was orally administered with 240 ml water after 10 hours fasting prior to dosing. There were 2 dosing periods, separated by a washout period of 3 days.

Blood samples were collected pre-dose and at 0.083, 0.167, 0.250, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, and 6 hours after administration of the products.

The design of the study is acceptable.

Melatonin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substance. 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.

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
All 12 subjects completed the study and were eligible for pharmacokinetic analysis.

In Table 1 the pharmacokinetic parameters of melatonin baseline uncorrected data are summarised.

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

Treatment N=12	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	8159 ± 7745	--	5055 ± 4389	0.47 (0.333 – 0.667)
Reference	7262 ± 4832	--	4821 ± 3113	0.51 (0.250 – 1.50)
***Ratio (90% CI)**	1.06 (0.90 – 1.25)	--	1.00 (0.84 – 1.18)	--

$AUC_{0-\infty}$ 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*

In Table 2 the pharmacokinetic parameters of melatonin baseline corrected data are summarised.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of melatonin baseline corrected under fasted conditions.

Treatment N=12	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	8137 ± 7247	8227 ± 7823	5051 ± 4389	0.50 (0.333-0.667)
Reference	7247 ± 4840	7348 ± 4889	4818 ± 3113	0.34 (0.250-1.5)
***Ratio (90% CI)**	1.06 (0.90 – 1.25)	1.06 (0.90 – 1.24)	1.00 (0.84 – 1.18)	--

$AUC_{0-\infty}$ 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*

Based on the data of 12 subjects, the 90% confidence intervals of Cmax and AUC0-t are within the acceptance ranges 80.00-125.00%.

Bioequivalence study II – pivotal study

Design

A single-dose, randomised, three-period, two-treatment, three-sequence, partial replicate, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 20-42 years. Each subject received a single dose (3 mg) of one of the 2 melatonin formulations. The tablet was orally administered with 240 ml water after 10 hours fasting prior to dosing. There were 3 dosing periods, separated by a washout period of 6 days.

Blood samples were collected pre-dose and at 0.083, 0.167, 0.250, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, and 6 hours after administration of the products.

The design of the study is acceptable.

Melatonin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of the active substance. 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.

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 from the study due to emesis, two subjects due to medical grounds and one subject withdrew on his own accord. Therefore, 56 subjects received one dose of both test and reference product and were eligible for pharmacokinetic analysis.

In Table 3 the pharmacokinetic parameters for the baseline uncorrected data are summarised.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of melatonin baseline uncorrected under fasted conditions.

Treatment N=56	**AUC_{0-t}** (pg.h/ml)	**$AUC_{0-\infty}$** (pg.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	7898 ± 7896	--	5747 ± 6367	0.55 (0.25-1.25)

Reference	8411 ± 7604	--	6318 ± 5807	0.55 (0.167-1.5)
***Ratio (90% CI)**	0.89 (0.80 – 0.99)	--	0.83 (0.73 – 0.93)	--
$AUC_{0-\infty}$ 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*

In Table 4 the pharmacokinetic parameters for the baseline corrected data are summarised.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of melatonin baseline corrected under fasted conditions.

Treatment N=56	**AUC_{0-t} (pg.h/ml)**	**$AUC_{0-\infty}$ (pg.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	7891 ± 7898	7966 ± 7937	5746 ± 6368	0.50 (0.25-1.25)
Reference	8398 ± 7611	8470 ± 7639	6316 ± 5809	0.50 (0.167-1.5)
***Ratio (90% CI)**	0.89 (0.80 – 0.99)	0.90 (0.80 – 0.99)	0.83 (0.73 – 0.93)	--
$AUC_{0-\infty}$ 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*

Based on the data of 56 subjects, the 90% confidence intervals of Cmax and AUC0-t are not within the acceptance ranges 80.00%-125.00%. The Cmax is within the widened 90% confidence interval of 72.97 to 137.04% based on the intra-subject variability of 43.5% for the Reference product.

Conclusion: Bioequivalence is shown for Cmax using the widened confidence interval, but is not shown for AUC0-t between the test and reference product as the 90% CI is not within 80–125%.

<u>Pooling pharmacokinetics pilot and pivotal study</u>

The MAH performed a pooled analysis of the pilot and pivotal studies, focussing on the analysis of the baseline corrected pharmacokinetic parameters as the primary analysis. It may however be noted that the statistical analyses for the baseline corrected and uncorrected data were highly similar.

The bioequivalence guideline describes the following on pooling: "*If for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be*

considered as a whole. The existence of a study which demonstrates bioequivalence does not mean that those which do not can be ignored. The MAH should thoroughly discuss the results and justify the claim that bioequivalence has been demonstrated. Alternatively, when relevant, a combined analysis of all studies can be provided in addition to the individual study analyses."
The MAH explained that sampling schemes, calculation methods of PK parameters and bioanalytical methods were the same in both studies and based on these considerations pooling of data is allowed.

For the pooling an ANOVA has been performed using factors Study, Seq(Study), Subject(Study*Seq), Period(Study), Formulation*Study and Formulation. This ANOVA model has been used for all PK parameters (ln(Cmax), ln(AUC0-t), ln(AUC0-inf)). The results showed that Formulation*Study was found to be statistically non-significant for all PK parameters (p-value > 0.05). This is further support for pooling of the studies.
Since the term Formulation*Study was found to be statistically non-significant for all ln-transformed PK parameters, the statistical analysis has also been performed by dropping the term "Formulation*Study" and keeping the factors Study, Seq(Study), Subject(Study*Seq), Period(Study) and Formulation.

The results of the final ANOVA model for the pooled data for melatonin (baseline corrected data) are summarised below.

Table 5. Relative bioavailability results for melatonin (Baseline corrected data; N=68 [N=56 subjects from pivotal study and N=12 subjects from pilot study])

Parameters	Ratio (T/R)%	90% Confidence Interval	Acceptance Criteria
lnC_{max}	84.8	0.76 – 0.95	0.73 – 1.37*
lnAUC_{0-t}	91.3	0.83 - 1.01	0.80 – 1.25
ln$AUC_{0-\infty}$	91.6	0.83 – 1.01	--
$AUC_{0-\infty}$ 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			

*Based on the intra-subject CV of Cmax for the reference product (43.3%, being > 30%) in the pivotal BE study, the acceptance range for Cmax was allowed to be widened to 72.97–137.04% as per criteria set in the protocol and the bioequivalence guidance.

Conclusion on bioequivalence studies
Based on the submitted bioequivalence studies Melatonine Clinigen is considered bioequivalent with Bio-Melatonin.

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 Melatonine Clinigen.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	- Off-label use in paediatric patients with sleep disorders
Missing information	- Use in individuals with autoimmune diseases - Use in patients with renal or hepatic impairment - Fertility, pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Bio-melatonin. 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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Melatonine Clinigen 3 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Bio-Melatonin 3 mg film-coated tablets. Bio-Melatonin 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 Melatonine Clinigen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 March 2019.

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