COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melatonine Biogaran 2 mg, prolonged-release tablets (melatonin)

NL/H/6364/001/DC

Date: 22 May 2026

This module reflects the scientific discussion for the approval of Melatonine Biogaran 2 mg, prolonged-release tablets. The procedure was finalised on 2 July 2025. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Biogaran 2 mg, prolonged-release tablets, from Biogaran.

The product is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Circadin 2 mg prolonged-release tablets, which has been registered in the EEA via a centralised procedure (EU/1/07/392/001-004) since 29 June 2007.

The concerned member state (CMS) involved in this procedure was Norway.

II. QUALITY ASPECTS

II.1 Introduction

Melatonine Biogaran is a white to off-white, round, biconvex prolonged-release tablet. Each tablets contains as active substance 2 mg of melatonin.

The excipients are: lactose monohydrate, calcium hydrogen phosphate dihydrate, ammonio methacrylate copolymer type B, colloidal anhydrous silica (E551), talc (E553b) and magnesium stearate (E470b).

The tablets are packed in polyvinyl chloride/polyethylene/polyvinyl dichloride (PVC/PE/PVDC) white opaque blister strips with aluminium foil backing in cardboard boxes.

II.2 Drug Substance

The active substance is melatonin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to slightly yellowish powder which is slightly soluble in water, soluble in acetone, ethyl acetate and methanol. It appears not to exhibit polymorphism and no chiral centres are present.

Two CEP procedures are 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
Two CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification has been established in-house by the MAH. The specification is based on the specification from the CEP holders, with additional tests for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches per manufacturer.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the two CEPs (and has been granted by the EDQM).

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 main development studies were formulation trials, manufacturing process optimisation trials and comparative dissolution studies with the innovator product. In general, the pharmaceutical development of the product has been adequately performed. The development of the QC dissolution method is acceptable. The test product used in the bioequivalence studies are acceptable in view of composition, manufacture, batch size and assay. *In vitro* dissolution profiles of test and reference product are comparable. Dissolution profiles in presence of alcohol have been performed, the results show no dose dumping and results comparable to the reference product.

Manufacturing process
The drug product is prepared by direct compression. Due to the low drug-load and the pharmaceutical form, the process is a non-standard manufacturing process. The in-process controls are acceptable. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients used are Ph.Eur. quality. Relevant functionality related characteristics and limits are included in the specification of several excipients. 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, dimensions, identity, water content, uniformity of dosage units by content uniformity, assay, related substances, dissolution, friability, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. The MAH concludes that the risk for presence of nitrosamine impurities in the drug product can be considered negligible, which is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three validation batches 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 batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability study results indicate that the drug product should be protected from light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are 'Do not store above 30°C. Store in the original package in order to protect from light'.

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

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Melatonine Biogaran 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)

At the time of the approval of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. Then the conclusion for this medicinal product was: since Melatonine Biogaran is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

On 1 april 2026, an updated ERA was approved through variation NL/H/6364/001/IB/001). See the list of 'Steps taken after finalisation of the initial procedure' at the end of this PAR and the supplementary Annex.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Circadin which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the two pivotal bioequivalence studies, which is are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Melatonine Biogaran (Biogara, France) was compared with the pharmacokinetic profile of the reference product Circadin (RAD Neurim Pharmaceuticals EEC SARL, France).

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

The rate of melatonin absorption and Cmax following melatonin 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (T_{max} = 3.0 h versus T_{max} = 0.75 h) and lower peak plasma concentration in the fed state (C_{max} = 1020pg/mL versus C_{max} = 1176 pg/mL).

Bioequivalence studies

Study 1: 2022a/S-21-653

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fasted conditions in 90 healthy male subjects, aged 19 – 44 years. Each subject received a single dose (2 mg) of one of the two melatonin formulations. The tablet was orally administered with 150 mL water after an overnight fast of at least 10 hours. There were two groups with two dosing periods, separated by a washout period of 3 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 0.75, 0.83, 1, 1.25, 1.33, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable.

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

90 subjects enrolled in the study. One subject was withdrawn during period II due to an adverse event (cannula pain). 89 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of melatonin, 2 mg under fasted conditions.

Treatment N= 89	**AUC_{0-3}** (ng.h/mL)	**AUC_{3-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	5.5 ± 3.6	5.2 ± 3.7	11.0 ± 7.2	2.8	1.0 (0.3 – 3.0)
Reference	5.3 ± 3.4	5.0 ± 3.5	10.4 ± 6.7	2.7	0.9 (0.3 – 3.0)
***Ratio (90% CI)**	1.04 (0.98 – 1.11)	1.05 (0.98 – 1.11)	1.05 (0.99 – 1.15)	1.07 (0.99 – 1.15)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-3/3-t}$	Area under the plasma concentration-time curve from time zero to 3 hours/ 3 hours to the last measurable plasma concentration / to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: 2022b/S-21-652

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fed conditions in 90 healthy male subjects, aged 26 – 44 years. Each subject received a single dose (2 mg) of one of the two melatonin formulations. The tablet was orally administered with 150 mL water after a high-fat, high-calorie meal (180.2 Kcal protein, 581 Kcal fat, 1013.5 Kcal energy). There were two groups with two dosing periods, separated by a washout period of 3 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.33, 4, 6, 8, 12, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable.

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

90 subjects enrolled in the study. 90 subjects were eligible for pharmacokinetic analysis.

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

Treatment N= 89	**AUC_{0-3} (ng.h/mL)**	**$AUC_{3-tlast}$ (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3.3 ± 2.0	6.3 ± 4.0	9.8 ± 5.3	2.3 ± 1.2	2.5 (0.5 – 8.0)
Reference	3.7 ± 2.2	5.8 ± 3.5	9.6 ± 5.0	2.3 ± 1.2	2.4 (0.5 – 8.0)
***Ratio (90% CI)**	0.92 (0.82 – 1.03)	1.07 (0.98 – 1.17)	1.01 (0.93 – 1.09)	0.99 (0.90 – 1.09)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-3/3-t}$	Area under the plasma concentration-time curve from time zero to 3 hours/ 3 hours to the last measurable plasma concentration / to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies 1 and 2:

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 studies Melatonine Biogaran is considered bioequivalent with Circadin.

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 Biogaran. At the time of approval, the most recent version of the RMP was version 0.2 dated 12 December 2024.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	Confusion Hallucinations Dyspnoea
Missing information	Use in pregnancy/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 Circadin. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies 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 language used for the purpose of user testing the PL was English.

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 Biogaran 2 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Circadin 2 mg prolonged-release tablets. Circadin 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 Biogaran with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 July 2025.

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
NL/H/6364/001 /IB/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Environmental Risk Assessment	No	28-11-2025	Refused	Phase I ERA was found not acceptable
NL/H/6364/001 /IB/002	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Environmental Risk Assessment	No	1-4-2026	Approved	See Annex 1

ANNEX 1 – Submission of Updated Environmental Risk Assessment (NL/H/6364/001/IB/002)

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the type IB variation for Melatonine Biogaran 2 mg (melatonin 2 mg), as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over, for the following proposed changes: update Environmental Risk Assessment

is approvable.

II. EXECUTIVE SUMMARY

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

Environmental Risk Assessment (ERA)

Melatonin is a naturally occurring substance which is synthesised in the human body in the brain, retina and pineal gland. As such no studies concerning the environmental risk of melatonin are necessary in accordance with the current guidance on environmental risk assessment.

Although there were no ERA data available from the reference product, it is clearly stated in the EPAR of Slenyto (2025) that melatonin is a naturally occurring substance.

It is agreed that since the active substance is naturally occurring, the use of Melatonin Biogaran is unlikely to have a significant effect on environmental levels. The justification is acceptable.

Conclusion

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, melatonin is not expected to pose a risk to the environment.

III.3 Clinical aspects

N/A

III.4 Product Information

N/A

IV. OVERALL CONCLUSION

The MAH submitted sufficient justification for the updated ERA variation to be approved.

REFERENCES

EPAR Slenyto (2025)
Assessment report Slenyto International non-proprietary name: melatonin
https://www.ema.europa.eu/en/documents/variation-report/slenyto-h-c-004425-ii-0028-eparassessment-report-variation_en.pdf