11 December 2025
EMADOC-1700519818-2909554
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Melatomed and associated names

INN/active substance: melatonin

Procedure number: EMA/REF/0000303296

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Fairmed Healthcare GmbH submitted on 29 March 2024 a marketing authorisation application for Melatomed 2mg, prolonged-release tablets (and associated names) as a generic application in accordance with Article 10(1) of Directive 2001/83/EC, referring to Circadin 2 mg prolonged-release tablet (Neurim Pharmacueticals).

The application was submitted to the reference Member State (RMS) Germany and to the concerned Member States (CMS) Austria, Denmark and Sweden.

The Decentralised procedure DE/H/8092/001/DC started on 09 July 2024.

On Day 210 of the procedure, major issues on bioequivalence, raised by Sweden, remained unresolved. The procedure was hence referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by Germany on 04 June 2024. The CMDh 60-day referral procedure was initiated on 28 July 2025.

On Day 60 of the CMDh referral procedure, no agreement could be reached, with Sweden raising objections over the lack of adequate proof of bioequivalence between the generic medicinal product and the reference medicinal product, for parameters representing the shape of the plasma concentration versus time curve in the single dose studies, which was considered to be a potential serious risk to public health.

As a consequence, Germany referred the procedure to the CHMP on 07 October 2025, in accordance with Article 29(4) of Directive 2001/83/EC.

2. Scientific discussion

2.1. Introduction

Melatonin is an endogenous neurohormone that plays a key role in the regulation of circadian rhythms and the sleep-awake cycle. The applicant has submitted an application under Article 10(1) of Directive 2001/83/EC for Melatomed 2mg, prolonged-release tablets (and associated names). The reference product Circadin 2 mg prolonged-release tablet (Neurim Pharmaceuticals) was first authorised in the EU in 2007.

The proposed indication is short term treatment of primary insomnia, to be taken in the evening, about 1 to 2 hours before bedtime and after a meal.

To support this generic application and demonstrate the bioequivalence of Melatomed with the reference product, the applicant submitted three bioequivalence studies:

- ZPS-540 – Single-dose study under fasting conditions using AUC_{0-t} and C_{max} as primary parameters.
- ZPS-541 – Single-dose study under fed conditions using AUC_{0-t} and C_{max} as primary parameters.
- ZPS-542 – Multiple-dose study at steady state using AUC_{0-tau}, $C_{max(ss)}$ and C_{min} as predefined primary parameters.

All the pivotal studies were conducted during the period February-April 2015, in compliance with the relevant guidance in effect at the time, namely the "Note for guidance on modified release oral and

transdermal dosage forms: section II (pharmacokinetic and clinical evaluation) (EMA/CPMP/EWP/280/96 Corr*)". In June 2015, this guideline was replaced by the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1 (hereafter "MR guideline").

Since melatonin shows low extent of accumulation (i.e. insignificant levels at the end of the dosing interval), according to the MR guideline, a multiple dose study is not required. Instead, bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in the single dose studies under fasting and fed conditions, such as partial AUCs. Examples of partial AUC are given as an early partial AUC (0 – cut-off t) and a terminal partial AUC (cut-off t – t last), separated by a predefined cut-off time point.

In September 2025, after the submission of this application, a draft product specific bioequivalence guideline (PSBGL) for melatonin 2 mg prolonged-release tablets has been published, specifying the cut-off for the early and terminal partial AUCs, i.e. 3 hours for fasted conditions, accepting later time points for fed conditions. This draft guideline reflects recent regulatory perspectives on the demonstration of bioequivalence for melatonin 2 mg prolonged-release tablets and is open for public consultation until 31 December 2025. It has therefore not been adopted yet.

Bioequivalence of the predefined primary parameter (AUC_{0-t} and C_{max}) was demonstrated in the single dose studies under fasting and fed conditions. However, since the MR guideline was only implemented after the applicant's studies were conducted, the partial AUCs were not included as primary pharmacokinetic parameters in the single dose studies. Consequently, the applicant conducted a post-hoc analysis of partial AUCs for the fasting and fed studies, including a cut-off point of 3h for the fasting and 3.5h for the fed study, considering also the views expressed in the draft PSBGL.

In the post-hoc analysis, bioequivalence was shown for AUC_{0-3h} and AUC_{3h-t} for the single dose fasting study. However, the criteria for bioequivalence was not met for the terminal partial $AUC_{3.5-24h}$ of the single-dose study under fed conditions, which showed a wide confidence interval (90% CI 74.27-119.54%) whereas the acceptance criteria for bioequivalence would be within 80-125%. The applicant further explored alternative cut-off points in the post-hoc analysis for the fed study (3h and 4h), which likewise did not demonstrate bioequivalence.

The reference Member State considered that this had been adequately justified by the applicant, and that the bioequivalence could be considered as demonstrated. However, Sweden, as concerned Member State, concluded that bioequivalence had not been demonstrated for all required parameters included in the MR guideline. Sweden considered this to constitute a potential serious risk to public health and therefore, that was of the opinion that the application was not approvable. Overall, during the CMDh procedure an agreement could not be reached, and this issue was referred to the CHMP.

2.2. Assessment of the issues raised as a potential serious risk to public health

The CHMP asked the applicant to further substantiate that bioequivalence has been demonstrated as required for generic applications (Article 10(1)), based on the totality of pharmacokinetic data as well as the plasma concentration-time profiles under all required conditions.

As per the protocol of the single dose studies, bioequivalence was to be established for AUC_t, $AUC_{0-\infty}$ and C_{max}. CHMP noted that the MR guideline asks for the time point for truncating the partial AUC to be justified based on the PK profile and pre-specified in the study protocol. As this requirement was not in

force at the time of the studies conduct, the applicant proposed post hoc different time points as cut-off, and corresponding partial AUC calculations, to comply with the current guideline.

The applicant investigated the time point where the AUC could be divided into two equal parts, i.e. with a similar extent of exposure, which resulted in the use of cut-offs of 3 hours for the fasting study and 3.5 hours for the fed study. Indeed, due to the short half-life of melatonin, a cut-off time of half the dosage interval is not appropriate since plasma concentrations are very low at 12 hours. This would result in two unbalanced partial AUCs, with most of the exposure observed in the first half of the posology interval, and lower levels and higher variability in the terminal partial AUC, thus not reflecting the shape of the curve.

Additionally, calculations were made with cut-off points of 6, 7, 12, and 14 hours reflecting the typical duration of sleep and the circadian rhythm of endogenous melatonin. Indeed, melatonin baseline is attained nearly 8 hours post-dose, very little endogenous melatonin would be present between 08:00 h and 20:00 h. Literature data indicate that the 24-hour endogenous melatonin secretion follows a typical circadian pattern with the rise in melatonin levels at around 20:00 h, reaching peak concentration at 01:00 h, and declines at approximately 05:00 h (Gooneratne et al., 2012). During post-ingestion of prolonged release melatonin formulation, the physiologically significant melatonin concentration is achieved only up to 6 hours. The intake of a usual dose of melatonin (i.e. 1– 5 mg) usually generates a nocturnal peak within 1 hour after ingestion and returns to basal concentrations within 8 hours (Samira et al., 2023). Considering that the natural rise in endogenous melatonin occurs in the second 12-hour period of a 24-hour cycle, the administration of the study medications was performed in the morning, and the crucial first 12 hours of blood concentrations of melatonin were measured in the near-complete absence of endogenous melatonin.

The CHMP considered the different time points as cut-off justified and accepted the calculation of the corresponding partial AUCs post-hoc. Of note, whilst the draft PSBGL specifies a cut-off for the partial AUCs, it also allows for different cut-off to be used, in particular for the fed study, if it is adequately justified and characterises the shape of the plasma concentration-time curve. In that draft guideline however, it is also required that the cut-off is pre-specified in the protocol.

Under fasting conditions, bioequivalence was demonstrated for C_{max}, AUC_{0-6h}, $AUC_{0-7h,}$ AUC_{0-12h}, AUC_{0-14h} AUC_{0-24h}, $AUC_{0-\infty}$, as well as early and terminal partial AUCs (AUC_{0-3h}, AUC_{3-24h}) (Table 1). Moreover, the mean concentration-time graph demonstrated similarity in the shape of the curve (Figure 1).

Table 1. Statistical analyses for baseline-corrected melatonin (Study no ZPS-540 - fasting study)

Variable **N=28**	**Test geometric mean**	**Reference geometric mean**	**Test/ reference ratio**	**90% Confidence intervals**
AUC_{0-3} (ng.h/ml)	1.89	2.02	93.65%	87.51% – 100.23%
AUC_{3-24} (ng.h/ml)	2.18	2.35	92.58%	84.50% - 101.44%
AUC_{0-24} (ng.h/ml)	3.92	4.12	94.20%	88.60% – 100.15%
$AUC_{0-\infty}$ (ng.h/ml)	4.51	4.76	94.74%	88.18% - 101.79%
AUC_{0-6} (ng.h/ml)	2.83	3.04	92.80%	87.24% - 98.77%
AUC_{0-12} (ng.h/ml)	3.31	3.56	93.0%	87.96% - 98.24%

AUC_{0-7} (ng.h/ml)	2.99	3.19	93.6%	88.42% - 99.15%
AUC_{0-14} (ng.h/ml)	3.36	3.62	92.9%	87.26% - 98.80%
C_{max} (ng/ml)	1.22	1.15	105.8%	98.08% - 114.24%
T_{max} (h)[1]	0.75 (0.5 – 3.5)	0.75 (0.5 – 2.5)	-	-

[1]Median (range)

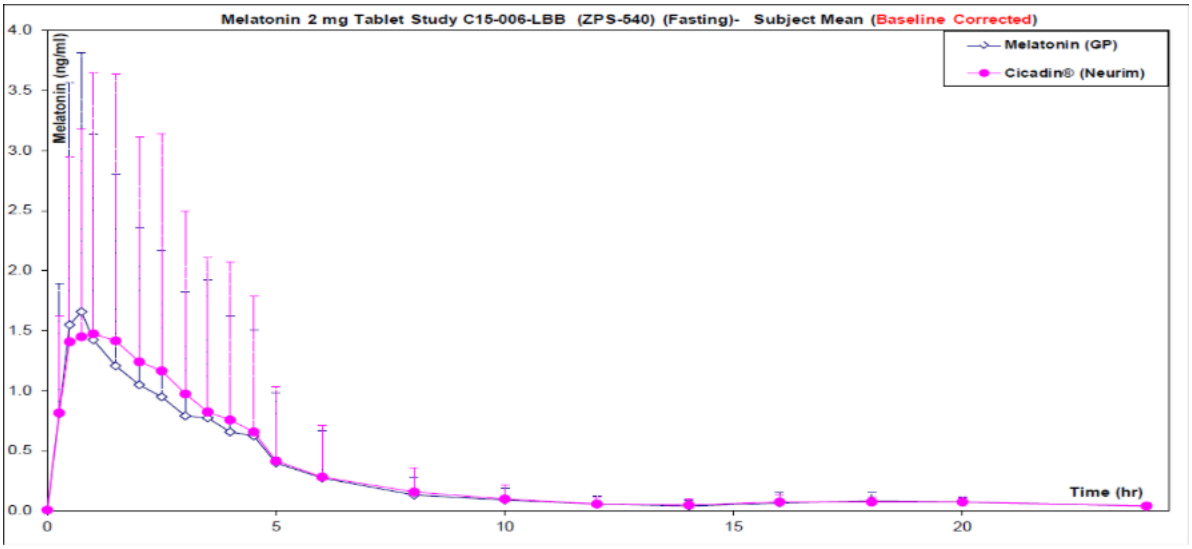

Figure 1. Mean-plasma concentration-time curve (ZPS-540 – fasting study)

Under fed conditions, bioequivalence was achieved for C_{max}, AUC_{0-6h}, AUC_{0-7h} AUC_{0-12h}, AUC_{0-14h}, AUC_{0-24h}, $AUC_{0-\infty}$, and early partial AUC ($AUC_{0-3.5h}$), while the 90% CI for the terminal partial AUC ($AUC_{3.5-24h}$) fell outside the acceptance range (i.e., 80-125%) (Table 2). Additional cut-off points of 3h and 4.5h were also explored, but these did not show bioequivalence for the terminal partial AUCs either.

Table 2. Statistical analyses for baseline- corrected melatonin (Study no ZPS-541 – fed study)

Variable N=24	Test geometric mean	Reference geometric mean	Test/ reference ratio	90% Confidence intervals
$AUC_{0-3.5}$ (ng.h/ml)	2.16	2.20	98.30%	81.68% - 118.31%
$AUC_{3.5-24}$ (ng.h/ml)	2.27	2.41	97.02%	74.27% - 119.54%
AUC_{0-24} (ng.h/ml)	5.97	5.93	100.65%	91.21% – 110.09%
$AUC_{0-\infty}$ (ng.h/ml)	6.25	6.65	93.96%	82,05% - 105.86%
AUC_{0-6} (ng.h/ml)	3.36	3.77	92.8%	90.64% - 107.84%
AUC_{0-12} (ng.h/ml)	4.16	4.21	93.0%	86.08% - 102.15%
AUC_{0-7} (ng.h/ml)	3.83	4.03	95.0%	87.38% – 103.21%
AUC_{0-14} (ng.h/ml)	3.85	3.98	96.7%	89.69% - 104.30%

C_{max} (ng.h/ml)	1.64	1.77	92.47%	84.91% - 100.04%
T_{max} (h)[1]	3.00 (0.5 – 6.0)	3.00 (0.75 – 6.0)	-	-

[1]Median (range)

The CHMP noted that the 90% CI deviation was limited to the lower bound of the confidence interval and could be explained by the low concentrations, near lower limit of quantification (LLOQ, i.e. the lowest concentration that can be reliably measured), which are associated with high intra-subject variability (~51 %), as well as lack of adequate power in the post-hoc analysis. Of note, the draft PSBGL acknowledges that fed studies may exhibit higher variability and specifies that should be taken into account in study design and interpretation. As mentioned, it could not be considered for the study design in this case, however the justifications for the deviation are considered acceptable.

The CHMP considered that since no physiologically significant concentrations (100 pg/mL) were reported approximately 6-8 hours post-administration in both fasting and fed studies, the contribution of the terminal phase partial AUC to the overall AUC post 6 hours was assumed to be negligible.

Furthermore, the mean concentration-time profile of baseline-corrected melatonin under fed condition was nearly superimposable which further depicted the closeness of the pharmacokinetic profiles of the test and reference products (Figure 2).

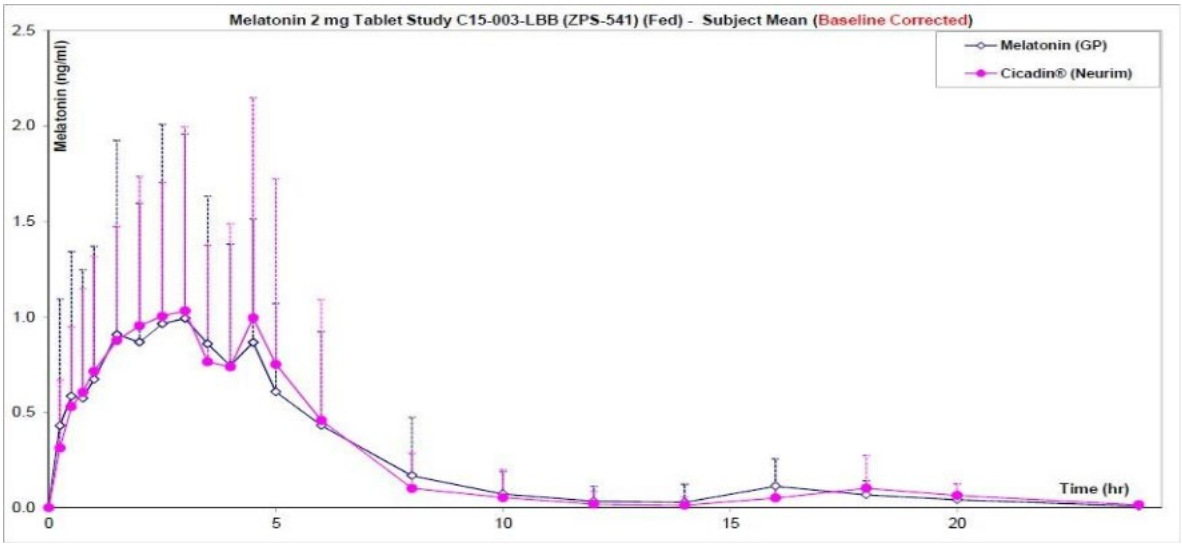

Figure 2. Mean-plasma concentration-time curve (ZPS-541 – fed study)

3. Benefit-risk balance

The CHMP was asked whether the generic medicinal product could be considered bioequivalent to the reference medicinal product, given that bioequivalence was not shown for the terminal partial AUC (3.5-24h) in the single-dose study under fed conditions.

The CHMP noted that the MR guideline asks for the time point for truncating the partial AUC to be justified based on the PK profile and pre-specified in the study protocol. In this specific case, as the studies were conducted before the MR guideline was published, different cut-offs for the partial AUCs

were selected post-hoc. Cut-off points of 3h (for fasted state) and 3.5h (for fed state) were selected so that the overall exposure could be divided into two equal partial AUCs. Additionally, cut-off points of 6, 7, 12, and 14 hours were used to reflect the typical duration of sleep and the circadian rhythm of endogenous melatonin, as well as the duration for which relevant melatonin concentrations are expected. Additionally, these cut-offs avoided late-phase intervals which present concentrations near the lower limit of quantification, for which variability of test/reference ratios is substantially inflated and non-informative.

The CHMP considered that the cut-off points for partial AUCs ensured a robust characterisation of the shape of the plasma concentration versus time curve and accepted the calculation of the corresponding partial AUCs post-hoc.

The CHMP noted that fasted state was the most sensitive condition to detect formulation differences, and that BE was conclusively shown the fasted state for all prespecified and post-hoc parameters. Further, the early partial AUCs (0-3.5; 0–6, 0–12 h) consistently met the standard acceptance criteria under both fasting and fed conditions. In addition, the visual similarity of plasma concentration–time profiles under all conditions is unquestioned.

The CHMP considered that the wide confidence interval for the late partial AUC in fed-state (despite point estimate close to unity) beyond 6h was sufficiently justified by high variability driven by very low, near-baseline concentrations in the context of a small sample size (N=24) for the post hoc analysis in the fed study.

Overall, taking into account the usual pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}), the early partial AUCs, as well as the visual similarity of plasma concentration–time profiles under all conditions, CHMP considered the applicant's justification acceptable. Therefore, bioequivalence between the test melatonin 2 mg prolonged-release tablets and Circadin 2 mg prolonged-release tablets is considered sufficiently demonstrated.

4. Grounds for Opinion

Whereas,

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as potential serious risk to public health.
- The Committee was of the view that the data provided for the usual pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}), the early partial AUCs as well as the similarity of plasma concentration–time profiles under fasting and fed conditions, adequately demonstrate bioequivalence.
- The Committee therefore considered that the provided data is sufficient to demonstrate bioequivalence between Melatomed and associated names and the reference medicinal product.

The Committee, as a consequence, considers that the benefit-risk balance of Melatomed and associated names, 2mg, prolonged-release tablets is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.

References

Gooneratne N.S., Edwards A.Y.Z., Zhou C., Cuellar N., Grander M., Barrett J.S., 'Melatonin pharmacokinetics following two different oral surge-sustained release doses in older adults', Journal of Pineal Research, Vol. 52(4), May 2012, p.437-445.

Samira A.A., Raverot V., Gal C., Guinobert I., Bardot V., Blondeau C., Claustrat B., 'Bioavailability of Melatonin after Administration of an Oral Prolonged-Release Tablet and an Immediate-Release Sublingual Spray in Healthy Male Volunteers', Drugs in R&D, Vol. 23, July 2023, p.257-265.

Appendix 1 Divergent positions

Article 29(4) of Directive 2001/83/EC

Procedure number: EMA/REF/0000303296

Melatomed and associated names

Decentralised procedure number: DE/H/8092/001/DC

Divergent statement

The following CHMP Member considers that benefit/risk balance of Melatomed and associated names is not favourable based on the following grounds:

For a generic application, bioequivalence (BE) should be demonstrated compared to the reference product. Otherwise, the benefit-risk of the generic product is negative. To demonstrate BE, requirements in relevant guidelines at the time of submission should be fulfilled and BE must be shown for all the primary PK parameters.

The applicant did not present sufficient data to show that the conditions in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) have been fulfilled, since BE was not shown for the partial AUCs in the single dose fed study (which are considered as primary parameter for demonstration of BE).

Clinical justifications cannot be taken into account for any failure to demonstrate bioequivalence within the acceptance criteria for a generic application. Further, it should also be noted that a draft PSBGL for melatonin 2 mg prolonged-release tablets has been published since the start of this procedure, clearly stating that 3 hours are reasonable cut-off and confirming that partial AUCs (early and late pAUCs) are considered as primary PK parameters. Even though the draft PSBGL is not adopted yet, this reflects the current regulatory view regarding demonstration of bioequivalence for melatonin 2 mg prolonged-release tablets.

Thus, bioequivalence has not been demonstrated and the benefit-risk is negative from the divergent CHMP members perspective.

CHMP Member expressing a divergent opinion:

- Anastasia Mountaki (Greece)
- Carolina Prieto Fernandez (Spain)
- Christophe Focke (Belgium)
- Edward Laane (Estonia)
- Elita Poplavska (Latvia)
- Jayne Crowe (Ireland)
- Kristina Dunder (Sweden)
- Selma Arapovic Dzakula (Croatia)

- Maria Grazia Evandri (Italy)
- Martine Trauffler (Luxembourg)
- Outi Mäki-Ikola (Finland)
- Peter Mol (The Netherlands)
- Beata Maria Jakline Ullrich (Hungary)
- Sol Ruiz (co-opted)