Annex II

Scientific conclusions

Scientific conclusions

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, including two single dose studies under fasted and fed conditions. All the pivotal studies were conducted before the coming into force of the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1 (hereafter “MR guideline”). In line with this guideline, bioequivalence should 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 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.

Overall summary of the scientific evaluation by the CHMP

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 was 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 in 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.

Grounds for the CHMP 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_{inf} 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.