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Committee for Medicinal Products for Human Use (CHMP)

Melatonin prolonged release tablets 2 mg product-specific bioequivalence guidance

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Adopted by CHMP for release for consultation	14 July 2025
Start of public consultation	25 September 2025
End of consultation (deadline for comments)	31 December 2025

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support

Keywords	***Bioequivalence, generics, melatonin***

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Melatonin prolonged-release tablets 2 mg product-specific bioequivalence guidance

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (MWP)*

Bioequivalence study design	**Single dose fasting:** 2 mg, healthy volunteers. **Single dose fed:** 2 mg, healthy volunteers. **Background:** 2 mg is the only available strength. Both fasted and fed single-dose study are needed since this is a prolonged-release formulation. It is not relevant to perform a multiple dose study since there is no accumulation.
	cross-over
	Other critical aspects: A sampling time of 12 hours is considered sufficient. Melatonin is an endogenous substance that fluctuates due to circadian rhythm. Since day-time base-line melatonin values are generally low compared to the concentration values obtained with the 2 mg prolonged-release formulation, base-line correction is not considered necessary provided that the tablet is administered in the morning (e.g., at 8 a.m.).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**

	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** Single dose (fasted and fed study): AUC_{0-t}, AUC_{0-inf}, C_{max} and partial AUCs: AUC_{0-3h} and $AUC_{3h-t.}$ **Background/justification:** Partial AUCs should be included as primary PK variables. A cut-off of 3 hours results in two approximately equal partial AUCs for both the fasted and the fed study and is thus a reasonable cut-off to characterise the shape of the plasma-concentration time curve and to determine the partial AUCs reliably. A different cut-off may be used, in particular for the fed study, if it is pre-specified in the protocol, adequately justified and characterises the shape of the plasma concentration-time curve. The variability may be higher in the fed study, which should be considered in the design of the study.
	90% confidence interval: 80.00– 125.00%

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max} and $_{partial}$ AUC. If high intra-individual variability (CVi_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.