16 February 2026
EMA/32320/2026
Committee for Medicinal products for Human Use (CHMP)/Methodology Working Party
European Medicines Agency

# Overview of comments received on 'Melatonin prolonged release tablets 2 mg product-specific bioequivalence guidance' (EMA/CHMP/226444/2025)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | Vit Perlik, Marina Fertek: BioBridges Conference |

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# 1. General comments – overview

| Stakeholder no. | General comment | Outcome |
|---|---|---|
| 1 | The melatonin prolonged-release (PR) tablets PSG is generally welcome as it sheds light into the comparative pharmacokinetic description of endogenous substance melatonin, for the purpose of bioequivalence demonstration. The main positives, among others, are clarification of the study design, i.e. single-dose studies are sufficient, sampling for 12h during the daytime, and rational position regarding base-line adjustment, which is not needed if the study is performed during the day, when endogenous melatonin plasma concentration is negligible. | Accepted. |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| Table (Main pharmacokinetic variables) | 1 | **Comments:**<br><br>The current draft proposes partial AUC0-3h and AUC3h-t. We suggest setting the cut-off time separately for fasting and fed conditions and setting the pAUC cut-off time at 2 or 2.333 h for fed conditions. The rationale for this proposal is given below.<br><br>In order to describe "the shape of the plasma concentration versus time curve" of the modified-release formulation, pAUCs are mandated by the modified release guideline. The major purpose of this requirement should be considered, which is to evaluate the onset and the prolonged absorption phase from the test and reference formulations.<br><br>Melatonin is a compound with substantial first pass metabolism. It is mainly metabolized by cytochrome P450 CYP1A1, CYP1A2 and potentially CYP2C19. Low oral bioavailability in the range 10 - 20% of exogenous melatonin has repeatedly been shown (Circadin PAR). In addition, melatonin PR products pose flip-flop kinetics. The elimination half-life (t1/2) in humans of around 40 - 50 minutes was reported for intravenously administered melatonin (Zetner 2021, Andersen 2016a and Andersen 2016b). Plasma elimination t1/2 for | Not accepted.<br><br>Administration of melatonin PR tablets with food results in a delayed tmax (3 hours versus 0.75 hours). For this reason, it would seem counter-intuitive to have an earlier cut-off for the fed study compared to the fasted study. Based on available data, a cut-off of 3 hours results in two approximately equal partial AUCs for the reference product (both in the fasted and in the fed state, although tmax is later in the fed state) and this is thus considered a reasonable cut-off to characterise the shape of the plasma-concentration time curve and to determine both partialAUCs reliably. A cut-off of 2 or 2.33 hours would also result in reasonable partial AUC values (each partialAUC providing 30%-70% of AUC0-t); thus such a cut-off could be acceptable if prespecified and justified. However, in the product-specific guideline, we prefer to keep the same cut-off for the fasted, and for the fed studies (3 hours). |

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| | | immediate-release product reported in Circadin PAR was around 40 - 50 minutes. In contrast, the t1/2 of 3,5 - 4 h has been reported under fasting conditions (Circadin PAR) and t1/2 of 2,333 h under fed conditions (recently approved product) in case of PR products, representing in fact the absorption half-life due to the flip-flop kinetics of PR products.<br><br>Thus, it is critical to set the pAUCs appropriately and distinguish exogenous factors such as potential formulation differences from endogenous factors e.g. gastric emptying (acknowledged also by the modified release guideline as the gastric emptying of single unit dosage forms that do not disintegrate in the stomach may be prolonged and highly erratic, leading to different GIT transit/absorption times) or pronounced intra subject variability due to metabolism of the active substance (Faber 2005). To simplify, later the cut-off time for pAUC is from the point where half of the drug is absorbed, higher the bias that would be introduced to terminal pAUCs, and consequently the bioequivalence assessment. This is due to lower concentrations observed towards the end of the sampling with predominant effects of higher variability associated with metabolism and elimination. Therefore, it is suggested to set the cut-off time individually for fasting (3 h, as proposed) and fed conditions and add the pAUC cut-off time at 2 or 2.333 h for fed conditions. The justification should be | |

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| | | associated rather with absorption half-life of 2.333h representing exactly 50% of drug absorbed or t1/2 obtained in the respective bioequivalence study for reference product, and thus fulfilling the objective of the plasma concentration shape comparison evaluating the onset and the prolonged absorption phase in equivalent portions.<br><br>**References:**<br>Andersen LP, Werner MU, Rosenkilde MM, Harpsøe NG, Fuglsang H, Rosenberg J, Gögenur I. Pharmacokinetics of oral and intravenous melatonin in healthy volunteers. BMC Pharmacol Toxicol. 2016a Feb 19;17:8. doi: 10.1186/s40360-016-0052-2. PMID: 26893170; PMCID: PMC4759723.<br><br>Andersen LP, Werner MU, Rosenkilde MM, Fenger AQ, Petersen MC, Rosenberg J, Gögenur I. Pharmacokinetics of high-dose intravenous melatonin in humans. J Clin Pharmacol. 2016b Mar;56(3):324-9. doi: 10.1002/jcph.592. Epub 2015 Sep 14. PMID: 26184078.<br><br>Circadin PAR: https://www.ema.europa.eu/en/medicines/human/EPAR/circadin#assessment-history | |

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| | | Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? Basic Clin Pharmacol Toxicol. 2005 Sep;97(3):125-34. doi: 10.1111/j.1742-7843.2005.pto_973160.x. PMID: 16128905.<br><br>Zetner D, Andersen LPK, Alder R, Jessen ML, Tolstrup A, Rosenberg J. Pharmacokinetics and Safety of Intravenous, Intravesical, Rectal, Transdermal, and Vaginal Melatonin in Healthy Female Volunteers: A Cross-Over Study. Pharmacology. 2021;106(3-4):169-176. doi: 10.1159/000510252. Epub 2020 Sep 16. PMID: 32937627.<br><br>Proposed change: Test in all locations proposed for the injection. | |
| Table (background/ justification of the main pharmacokinetic variables) | 1 | **Comments:**<br>We also suggest amendments to the section "Background/justification" of the draft guideline. For rationale, please see the comment to Main pharmacokinetic variables<br><br>**Proposed change:**<br>Partial AUCs should be prespecified and included as primary PK variables. The cut-off time should be set individually for fasting (3 h) and fed conditions (2 or 2.33 h). The justification is based on the absorption half-life representing exactly 50% of drug absorbed | Not accepted. See above. |

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| | | or t1/2 obtained in the respective bioequivalence study for the reference product, and thus fulfilling the objective of the plasma concentration shape comparison evaluating the onset and the prolonged absorption phase in equivalent portions. A different cut-off may be used, 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. | |