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Committee for Medicinal Products for Human Use (CHMP)

Paliperidone prolonged-release tablet 1.5 mg, 3 mg, 6 mg, 9 mg and 12 mg product-specific bioequivalence guidance

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†This revision clarifies the dose requirements for the single dose fed and multiple dose fasting studies in the bioequivalence study design section of the guideline.

Keywords	***Bioequivalence, generics, paliperidone***

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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 (PKWP)*

BE Study design**	**Single dose fasting:** All strengths or bracketing approach, healthy volunteers. **Single dose fed:** 12 mg, healthy volunteers. A study with a lower strength may be acceptable if the test product has the same release mechanism as the originator. **Multiple dose fasting:** 6 mg, healthy volunteers. **Background:** Single dose (fasting and fed) and multiple dose studies are required for prolonged release formulations with accumulation. Single dose fasting studies on all strengths are necessary for a prolonged release single unit formulation, which can be administered with or without food according to the SmPC. Because of the potential for poor tolerability of higher doses following repeated dose administration, the multiple dose study in healthy volunteers can be conducted with 6 mg strength.
	cross-over
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**

	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** **Single dose:** AUC_{0-t}, AUC_{0-inf}, and C_{max} **Multiple dose:** $AUC_{0-\tau}$, $C_{max,ss}$, and $C_{\tau,ss}$
	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}, $C_{\tau,ss}$, and partial AUC. If high intra-individual variability (CV_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.

** For prolonged release formulations: If a single-dose study with the highest strength has shown that there is low risk of accumulation (i.e. AUC_{τ} > 90% of AUC_{inf}), the multiple-dose study may be waived. If low degree of accumulation is expected, the applicants might follow respective guideline recommendations.