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Committee for Medicinal Products for Human Use (CHMP)

Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	June 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 October 2016
Agreed by Pharmacokinetics Working Party	December 2016
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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)*

Bioequivalence study design** *in case a BCS biowaiver is not feasible or applied*	**Single dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), in healthy volunteers (if feasible) or in patients stabilized on other antipsychotic medication. **Multiple dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths) in patients.
	cross-over or parallel
Analyte	☐ **parent** ☒ **metabolite** ☐ **both** **Background:** the prodrug, paliperidone palmitate, is not reliably measurable in plasma. Bioequivalence should be based on paliperidone.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**

Bioequivalence assessment	**Main pharmacokinetic variables:** **Single dose:** AUC_{0-t}, AUC_{inf}, C_{max} and T_{max} **Multiple dose:** $AUC_{0-\tau}$, $C_{max,ss}$, $C_{\tau,ss}$
	90% confidence interval: 80.00–125.00 % for AUC_{0-t}, AUC_{inf}, $C_{max,}$ $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss.}$ Comparable median and range for $T_{max.}$

* 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. $AUC\tau$ > 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.