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Committee for Medicinal Products for Human Use (CHMP)

Paliperidone palmitate depot suspension for injection (every 3 months) 175, 263, 350 and 525 mg product-specific bioequivalence guidance

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Start of public consultation	15 January 2024
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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 (MWP)

Bioequivalence study design	**Multiple dose study in patients.** Any dose/strength can be chosen if the test product has the same concentration of active substance as the reference for all the strengths. Single dose studies in patients are not considered feasible as the patients need to be stabilised with a 1-month depot injection before administering the 3-month depot. Single dose studies in healthy volunteers are controversial due to the safety profile and the prolonged action of this product. In addition, the need for single dose data to capture the initial release of paliperidone is limited, as patients already have steady state paliperidone plasma levels at the start of treatment with this formulation.
	cross-over or parallel
	Other critical aspects: Selection of one injection site (gluteal or deltoid muscle) to reduce variability is recommended.

	As patients are already at paliperidone steady state at study entry, study design must ensure that a new steady state has been reached at the time of PK assessment, with a negligible carry over from the previous formulation. A new steady state is estimated to be reached by the administration of dose 3.
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:** $AUC_{0-\tau}$, $C_{max,ss}$, $C_{\tau,ss}$
	90% confidence interval: 80.00– 125.00%
	To be noted: as this is an active treatment in patients, before starting the study it is essential to ascertain that the products can be regarded as comparable from a quality perspective (e.g., concentration of the suspension particle size distribution (D10, D50 and D90 as relevant), polymorphic form, *in vitro* dissolution). Additionally, as a difference in Ostwald ripening may also be relevant, re-suspendability, and particle size distribution after storage over a time period should be comparable. With regard to the dissolution method, a suitable and discriminative method should be selected. Since paliperidone palmitate has low water solubility, use of surfactant is most likely required. Undissolved API particles need to be removed during sampling e.g. by the use of an in-line filter.