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Committee for Medicinal Products for Human Use (CHMP)

Liposomal amphotericin B powder for dispersion for infusion 50 mg product-specific bioequivalence guidance

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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)*

The current recommendations for product specific guidance for liposomal amphotericin should be read and followed in line with the Reflection paper on the data requirements for intravenous liposomal products developed to be similar to a liposomal product (EMA/CHMP/806058/2009/Rev. 02). Demonstration of equivalent efficacy and safety of a liposomal formulation developed with reference to an innovator product is considered a multi-disciplinary approach that in addition to the pharmacokinetic study, it also takes account of quality and non-clinical comparison, and a clinical therapeutic equivalence study, where appropriate.

Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over:** Given the long terminal elimination half-life of non-liposomal amphotericin B, a parallel design study could be considered.
	healthy volunteers
	Strength: 3 mg/kg infused over 2 hours **Background:** 3 mg/kg is the usual starting dose and a sensitive dose in the clinical dose range.

	Number of studies: one
	Other critical aspects: An infusion time of 2 hours is recommended to lower the risk of infusion-related reactions. Premedication, as appropriate, may also be given.
Analyte	☐ **total drug** ☒ **liposomal drug** ☒ **non-liposomal drug** **Background:** Liposomal and non-liposomal amphotericin B are both considered relevant to conclude on bioequivalence as they best reflect the biopharmaceutical quality of the proposed product.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, $AUC_{0-\infty}$, C_{max} for liposomal and non-liposomal amphotericin B and partial AUCs for liposomal amphotericin B (e.g. AUC_{0-10h} and $AUC_{10-tlast}$) **Background/justification:** AUC_{0-t} and C_{max} are considered insufficient to fully characterise distribution and elimination processes of liposomes, which release the active substance over a longer period of time.
	90% confidence interval acceptance limits: 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 (CV_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.