EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2021
EMA/CHMP/559889/2021
Committee for Medicinal Products for Human Use (CHMP)

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

Draft Agreed by Pharmacokinetics Working Party (PKWP)	7 October 2021
Adopted by CHMP for release for consultation	16 December 2021
Start of public consultation	17 December 2021
End of consultation (deadline for comments)	31 March 2022
Agreed by Pharmacokinetics Working Party	
Adopted by CHMP	
Date for coming into effect	

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

Keywords	***Bioequivalence, generics, liposomal amphotericin B***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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

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** **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}, partial AUCs (e.g. *liposomal amphotericin B*: AUC_{0-10h} and $AUC_{10-tlast}$; *non-liposomal amphotericin B*: AUC_{0-24h} and $AUC_{24-tlast}$) **Background/justification:** AUC_{0-t} and C_{max} are considered insufficient to fully characterize distribution and elimination processes of liposomes, which release the active substance over a longer period of time.
	90% confidence interval: 80.00–125.00%
	To be noted: Proving equivalent efficacy and safety of a liposomal formulation developed to be similar to an innovator product is considered a totality of evidence approach, which, in addition to the pharmacokinetic study, also takes account of quality and non-clinical comparison, and a clinical therapeutic equivalence study, where appropriate.

* 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.