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Committee for Medicinal Products for Human Use (CHMP)

Azacitidine powder for suspension for injection 25 mg/ml product-specific bioequivalence guidance

Draft

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Adopted by CHMP for release for consultation	4 December 2023
Start of public consultation	15 January 2024
End of consultation (deadline for comments)	30 April 2024

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	***Bioequivalence, generics, azacitidine***

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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	**Single dose:** Patients, initial therapeutic dose of 75 mg/m^2 of body surface area. **Background:** In principle, suspensions for injection are not waived from the in vivo demonstration of bioequivalence. However, in this case a waiver based on in vitro similarity might be applicable if certain conditions are met, taking into account that the suspension becomes a solution at body temperature (see below).
	cross-over study where test and reference are administered on two consecutive days during a cycle of treatment
	Other critical aspects: azacitidine should be injected subcutaneously into the upper arm, thigh, or abdomen. The study can be conducted in one site of injection only.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**

	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** C_{max} and AUC_{0-t}.
	90% confidence interval: 80.00–125.00%
Waiver of bioequivalence study	A waiver of in vivo bioequivalence study may be granted, if the test product has: • The same qualitative and quantitative composition in active substance as the reference product. • The same qualitative and very similar quantitative composition in excipients as the reference product. • Similar crystal morphology of the drug substance immediately prior to use as documented by microphotographs (e.g. optical and scanning electron microscopy). • Equivalent particle size distribution as demonstrated by showing average equivalence for D_{10}, D_{50}, D_{90} and span within an acceptance range of 15% for the ratio of geometric means between test and reference products (i.e., 85.00–117.64%). • Equivalent physicochemical properties: viscosity, osmolality and pH. • Equivalent "time to clear solution" after reconstitution between test and reference products, where the product after reconstitution is maintained at e.g. 34, 35, 36 and 37ºC to determine the time required to obtain a clear solution at each of those temperatures. At least 3 batches of the test and reference product should be included in the comparability studies. More batches may be needed in case of higher variability of the reference product results. The choice of statistical methods and acceptance criteria should be justified. An acceptance range of ±10% is generally acceptable for the comparison of in vitro tests.

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* 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 (CVi_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.