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Committee for Medicinal Products for Human Use (CHMP)

Aprepitant, hard capsules, 80mg, 125mg, 80+125mg and powder for oral suspension 125mg product-specific bioequivalence guidance

Draft Agreed by Methodology Working Party (MWP)	21 October 2024
Adopted by CHMP for release for consultation	04 November 2024
Start of public consultation	31 January 2025
End of consultation (deadline for comments)	30 April 2025

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

Keywords	***Bioequivalence, generics, aprepitant***

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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.

B. Requirements for bioequivalence demonstration (MWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Aprepitant is a low solubility compound with limited absorption.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** **Hard capsules**: Both fed and fasting are required since it is a high-risk product with a non-standard method of manufacture **Suspension**: A fasting study is appropriate

	Strength: 125mg **Background:** For drugs with a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength.
	Number of studies: two single dose studies for hard capsules; one single dose study for suspension
Analyte	☒ **parent** ☐ **metabolite** ☐ **both** **Background:**
	☒ **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%

* 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}. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. *in vitro* dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).