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Committee for Medicinal Products for Human Use (CHMP)

Memantine film-coated tablets 5, 10, 15 and 20 mg, oral solution 5 mg product-specific bioequivalence guidance*

Draft agreed by Pharmacokinetics Working Party (PKWP)	October 2013
Adoption by CHMP for release for consultation	24 October 2013
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End of consultation (deadline for comments)	15 February 2014
Agreed by Pharmacokinetics Working Party	March 2015
Adoption by CHMP	26 March 2015
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Draft revision agreed by Methodology Working Party (MWP)	3 April 2025
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* This revision relates to the addition of the salt form and strength of the oral solution

Keywords	***Bioequivalence, generics, memantine***

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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)*

BCS Classification**	**BCS Class:** ☒ **I** ☐ **III** ☐ **neither of the two** **Background:** Memantine hydrochloride is a high solubility compound with complete 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**
	Strength: For tablets 20 mg For oral solution: 5 mg (one actuation) **Background:** Highest strength to be used for a drug with linear pharmacokinetics.

	Number of studies: One single dose study with the tablets. One single dose study with the oral solution.
	Other critical aspects: A study with the oral solution may be waived if the excipients that can affect the absorption e.g. sorbitol are qualitatively the same and quantitatively similar as in the reference product.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max}
	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, at this stage it is not possible to recommend 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 seem 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).