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Committee for Medicinal Products for Human Use (CHMP)

Vortioxetine hydrobromide immediate release tablets 5 mg, 10 mg, 15 mg, and 20 mg; vortioxetine lactate oral drops solution 20 mg/ml product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	October 2016
Adopted by CHMP for release for consultation	15 December 2016
Start of public consultation	22 December 2016
End of consultation (deadline for comments)	31 March 2017
Agreed by Pharmacokinetics Working Party	April 2017
Adopted by CHMP	22 June 2017
Date of coming into effect	1 January 2018
Draft revision agreed by Methodology Working Party (MWP)	3 April 2025
Adopted by CHMP	10 June 2025
Date of coming into effect	1 January 2026

* This revision relates to the deletion of the reference to low solubility in accordance with the ICH M13A guideline

Keywords	***Bioequivalence, generics, vortioxetine***

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

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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:** Vortioxetine hydrobromide may be considered a low solubility compound. The available data on solubility does not allow the BCS classification of vortioxetine lactate. Vortioxetine can be considered a 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**

	Strength: 20 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics.
	Number of studies: One single dose study for each dosage form.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** $AUC_{0\text{-}72h}$ 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, 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).