10 June 2025
EMA/188397/2025/Rev. 1*
Committee for Medicinal Products for Human Use (CHMP)

Zonisamide hard capsules 25, 50 and 100 mg, orodispersible tablets 25, 50, 100 and 300 mg product-specific bioequivalence guidance**

Draft agreed by Pharmacokinetics Working Party (PKWP)	April 2015
Adoption by CHMP for release for consultation	25 June 2015
Start of public consultation	15 July 2015
End of consultation (deadline for comments)	1 November 2015
Agreed by Pharmacokinetics Working Party	23 February 2016
Adoption by CHMP	1 April 2016
Date for coming into effect	1 November 2016
Draft revision agreed by Methodology Working Party (MWP)	3 April 2024
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
** This guideline was previously published as part of a "compilation of individual product-specific guidance on demonstration of bioequivalence Rev.3 EMA/CHMP/736403/2014"

Keywords	***Bioequivalence, generics, zonisamide***

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

Zonisamide hard capsules 25, 50 and 100 mg, orodispersible tablets 25, 50, 100 and 300 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 (MWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Zonisamide is a compound with complete absorption, but not highly soluble according to the BCS criteria. Thus, a BCS biowaiver is not applicable.
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: 100 mg for the hard capsules 300 mg for the orodispersible tablets

	Background: Highest strength to be used for a drug with linear pharmacokinetics.
	Number of studies: One single dose study for each dosage form.
	Other critical aspects: Intake without water for the orodispersible tablets.
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, 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 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).