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Committee for Medicinal Products for Human Use (CHMP)

Tolvaptan tablets with the dose range 7.5, 15 and 30 mg and tolvaptan tablets with the dose range 15, 30, 45, 60 and 90 mg product-specific bioequivalence guidance

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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:** Tolvaptan 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** **Background:** Since this is considered a high-risk product with a specific formulation (e.g. manufacture, excipients) of the tablets and the solid-state form of the active substance is known to be critical to the performance of the

	formulation, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, both fasted and fed state comparisons of test-to-reference formulations are required. A waiver for this fed study may be applicable if it can be shown that the products are manufactured using the same technology and if excipients that might affect the solid-state form of the active substance or the bioavailability are qualitatively the same and quantitatively similar between test and reference product.
	Strength: Highest strength applied for, for a drug with linear pharmacokinetics, in dose range 7.5 - 90 mg. **Background:** Although there are two dose ranges (7.5 - 30 mg range and 15 - 90 mg), the highest strength can be applied for the whole range, provided the requirements for biowaiver of strengths have been fulfilled for the range of strengths applied for.
	Number of studies: two single dose studies with the highest strength applied for (fasted and fed)
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables: AUC_{0-t} and C_{max}**
	90% confidence interval: 80.00– 125.00%