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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

Draft

Draft Agreed by Methodology Working Party (MWP)	19 June 2024
Adopted by CHMP for release for consultation	15 July 2024
Start of public consultation	26 July 2024
End of consultation (deadline for comments)	31 October 2024

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

Keywords	*Bioequivalence, generics, tolvaptan*

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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 the specific formulation (e.g. manufacture, excipients) of the tablets 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 the products are manufactured using the same technology and if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product.
	Strength: highest strength applied for (30 mg for the 7.5 - 30 mg range, 90 mg for the 15 - 90 mg range), and provided requirements for biowaiver of strength have been fulfilled separately for each range. **Background:** Highest strength applied for, for a drug with low solubility but linear pharmacokinetics, in dose range 7.5 - 90 mg.
	Number of studies: two single dose studies (30 mg fasted and fed for the 7.5 - 30 mg dose range and 90 mg fasted and fed for the 15 - 90 mg dose range)
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%