17 February 2025
EMA/339228/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on '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' (EMA/CHMP/254395/2024)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Coripharma ehf.
2	Norwegian Medical Products Agency

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. General comments – overview – N/A

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 1 Section "Bioequivalence study design - Background"	2	**Comment:** It is true that the manufacturing method/excipients of tolvaptan tablets can be critical to the performance of the formulation. It is however difficult for the reader to understand why this is important, and thereby judge if any specific generic product is at risk. The importance of manufacturing principle and excipients is that an amorphous state of tolvaptan is obtained and maintained throughout shelf life. **Proposed change:** Add "and the solid state form of the active substance" between "[...] tablets" and "is known [...]"	Accepted Comment acknowledged, proposed modification of the text has been implemented.
Line 5 Section "Bioequivalence study design - Background"	2	**Comment:** The applicant normally does not have access to the necessary details of the reference product. The authorities may know that two products are manufactured using the same technology by accessing the respective dossiers, but the applicant must somehow show that this is true, based on, for example, their	Accepted Comment acknowledged, proposed modification of the text has been implemented.

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		thorough examination of the reference product (including analysis of solid state form). **Proposed change:** Add "it can be shown that" between "[...] applicable if" and "the products [...]"	
Line 6 Section "Bioequivalence study design - Background"	2	**Comment:** Active substance solid state is a CQA in these products (in terms of bioequivalence), and should be addressed in pharmaceutical development and the control strategy. **Proposed change:** Add "active substance solid state or" between "[... affect] and [bioavailability [...]	Accepted Comment acknowledged, proposed modification of the text has been implemented.
Line Bioequivalence study design - Strength "Strength: highest strength applied for (30	1	**Comment:** The Jinarc European public assessment report (PAR) states that the 15 mg and 30 mg strengths, which are the same for Jinarc and Samsca, are dose proportional with regard to the active substance and excipients, and that the 45 mg and 90 mg strengths of tablets were designed to be quantitatively proportional with the 60 mg tablets. Furthermore, the originator	Not accepted In the Jinarc and Samsca SmPC, no warning is included not to switch between the different non-dose proportional strengths. This is based on the range of BE studies that was provided as summarised in the comment. The additional bioequivalence studies were

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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"		demonstrated bioequivalence of the 60 mg tablet to the 15 mg (1×60 mg vs 4×15 mg) and 30 mg (1×60 mg vs 2×30 mg) tablet strengths and between 30 mg and 90 mg tablets (3×30 mg vs 1×90 mg), all under fasting conditions –which was considered acceptable and appropriate –thereby bridging the 2 series. The additional strength of 7.5 mg for Samsca was approved in Europe in 2017, however, no PAR was published and therefore no data available in the public domain on the bioequivalence demonstration of this strength to the higher strengths. From the information on the qualitative and quantitative composition of strengths in the Samsca summary of product characteristics (SmPC), it can be concluded that the 7.5 mg strength is not proportional to other strengths. Given the above, and the fact that pharmacokinetics of tolvaptan are linear across the range of 7.5-90 mg, the basis for considering the strength series of 15-90 mg and 7.5-30 mg separately, and requiring studies at the 30 mg strength against Samsca has not been provided in the PSBGL. **Proposed change:** Include basis for the requirement, e.g. in Background.	needed because of non-dose proportional composition of the different dose ranges for Jinarc and Samsca. As a general principle in generic applications, in case the different strengths of the test product are dose-proportional, and provided all other requirements for biowaiver of strength have been fulfilled, the outcome of a BE study may be extrapolated to other strengths. This is stated in the current text of the PSBGL, '*the highest strength can be applied for the whole range, provided the requirements for the biowaiver of strengths have been fulfilled for the range of strengths applied for'*. Therefore, the current text already explicitly states that additional studies may be needed when different strengths are not dose-proportional, as was the situation for Jinarc and Samsca. Conclusion: No change needed.
Line	1	**Comment:**	Accepted

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Bioequivalence study design - Strength „...and provided requirements for biowaiver of strength have been fulfilled separately for each range.“		This presentation appears to be unique to the tolvaptan PSBGL, no such statement is included in other PSBGLs. Does this indicate that the waiver described under the section on bracketing approach in the Guideline on the Investigation of Bioequivalence for immediate release solid oral dosage forms (see quotation below) does not apply – specifically for tolvaptan, or generally for all products with special formulation characteristics? „Where bioequivalence assessment is needed both in fasting and in fed state and at two strengths due to nonlinear absorption or deviation from proportional composition, it may be sufficient to assess bioequivalence in both fasting and fed state at only one of the strengths. Waiver of either the fasting or the fed study at the other strength(s) may be justified based on previous knowledge and/or pharmacokinetic data from the study conducted at the strength tested in both fasted and fed state. The condition selected (fasting or fed) to test the other strength(s) should be the one which is most sensitive to detect a difference between products.“ **Proposed change:** Clarify the intent of and rationale for this text.	The text has been changed to indicate that the highest dose can be used in support of either dose range.