

Reply Letter – to Urso et al “Comment on: Comparative dissolution profiles of two anti-emetic delayed release dosage forms of doxylamine and pyridoxine: Xonvea® tablets vs. Cariban® capsules”

Dear Editor,

We thank Urso et al¹ for their comments on our article. Their first concern is whether Cariban® has been wrongly defined as “delayed-release” while the product is formulated as an extended-release formulation. We want to confirm that there is a typo in the title of our article². However, Cariban® is entitled as a modified-release hard capsule product throughout the rest of the article. This is consistent with its approved Summary of Product Characteristics (SmPC)³.

Indeed, in our article², these two pyridoxine/doxylamine fixed-dose combination products are described as drug products with slight differences in their release characteristics. However, both share the same functional polymer [methacrylic acid-ethyl acrylate copolymer (1:1)].

We want to point out that no reference regarding Cariban® potential acid degradation can be found in our article². It is only claimed that “Xonvea® gastro-resistant tablets do not show any release of drug substances after this period (pH 1.2 or pH 4.5), protecting them from any degradation due to acidic pH”. This lack of release in pH 1.2 or 4.5 can be explained by the polymer used in the formulation, which presents gastro-resistant properties as widely described in the public domain.

Regarding the drug release, as can be seen in the dissolution profiles presented in our article and the dissolution profiles submitted by Urso et al¹ in their comments to our article, Cariban® does not reach complete dissolution within a 3 hours’ time frame while Xonvea® does. Therefore, Xonvea® does release 100% of both drugs within the first hour after the pH change, while Cariban® does not release the entire amount of the drug after the same time, according to the experimental comparison performed. We thank the authors (Urso et al¹) for the additional data concerning the extended dissolution time profiles for Cariban® (7 hours).

The point about translation of *in vitro* data to *in vivo* results is well taken. In fact, this concern was already mentioned in our article². We claimed that “*in vitro* data cannot automatically correspond to *in vivo* data as it is an experimental approach regarding pharmacological aspects”². Great care has been taken to express the presented hypotheses in our article² as speculations. To ensure this is clear to the reader, conditional tenses have been used in the results and conclusions. Further clinical investigation is needed to prove the presented hypotheses.

Finally, in table III comments, it should be noticed that Xonvea® doxylamine values are reported as a whole. In contrast, Cariban® doxylamine values are reported separately as its two enantiomers to be consistent with how this data is available in its original publications.

Indeed, little information is available regarding the pharmacokinetics of Cariban® formulation. Only one study can be found in the public domain, published in the product Summary of Product Characteristics (SmPC). The study examined the pharmacokinetic effects of doxylamine in 12 healthy women volunteers receiving an oral dose of 2 capsules (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) in fasted and fed state³. The mean pharmacokinetics parameters (±SD) for R-doxylamine, S-doxylamine, pyridoxine, pyridoxal, and pyridoxal 5-phosphate under fasting conditions are reported in the SmPC. The published results do not clarify if the presented pyridoxal 5-phosphate values are baseline corrected. Therefore, we preferred not to include them

Table I. Xonvea® study 160286. Pyridoxal 5'-phosphate baseline corrected and uncorrected pharmacokinetic parameters.

Pivotal study 160286	Baseline corrected Pyridoxal 5'-phosphate	Baseline uncorrected Pyridoxal 5'-phosphate
AUC _{0-72h} (ng·h/mL)	864.9 ± 304.61	1439.71 ± 433.04
C _{max} (ng/mL)	24.76 ± 8.56	32.72 ± 10.19
T _{max} (h)	7.50 (3.000-16.033)	7.500 (3.000-16.033)

in table III. As evaluated in Xonvea® pivotal pharmacokinetic study 160286^{4,5} differences can be observed between pyridoxal 5-phosphate plasma baseline corrected and uncorrected values.

We want to point out that clinical studies evaluating the doxylamine and pyridoxine combination efficacy and safety were also reviewed to investigate Cariban® and Xonvea® differences further. While it is true that clinical experience with doxylamine and pyridoxine has been extensively reported in the literature, it should be noticed that no clinical efficacy studies administering specifically Cariban® formulation were found in the public domain. It should be noticed that both products, Cariban® and Xonvea®, share the same indications and same posology^{3,6}.

Instead, Xonvea® has been approved in Europe, first in the UK in 2018, considering the Koren et al⁷ study together with another randomized placebo-controlled trial in 14 US centers undertaken in 1975⁷. In addition, complementary data on the study by Koren et al⁷ is reported in several publications⁹⁻¹¹.

In summary, we believe that our results support the hypothesis that Cariban® and Xonvea® have different dissolution results even when both products share the same functional polymer.

Conflict of Interest

Cristina Alcocer and Eugenia Rom are employees of Chemo Group. Pedro-Antonio Regidor is an employee of Exeltis Healthcare.

References

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