Clinical Pharmacokinetics (2019) 58:979–980
https://doi.org/10.1007/s40262-019-00787-9

LETTER TO THE EDITOR

Author's Reply to Trechot: "Comment on Levothyrox® New and Old Formulations: Are they Switchable for Millions of Patients?"

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Published online: 12 June 2019

We thank Dr. Trechot for his valuable comments [1] on our recent article in *Clinical Pharmacokinetics* [2]. These provide us with the opportunity to clarify what we have said, and indicate what we have not said. First, we did not conclude the absence of individual bioequivalence (IBE) for the levothyroxine formulations. Second, we did not conclude a lack of average bioequivalence (ABE) for the new and old formulations of Levothyrox®. Third, we did not propose that a lack of either switchability or prescribability would explain the thousands of adverse drug reactions (ADR) that have been reported to the French pharmacovigilance network. To be clear, a BE study is an observational study; it does not provide explanations of underlying mechanisms accounting for ADRs. It can however generate hypotheses and thereby stimulate further investigations. It is in this context that the hypothesis of Dr. Trechot is welcome, because (as explained by others), knowledge of, and evidence for, mechanisms play a central role in assessing and ensuring the stability of drug formulations [3], as well as in vivo consequences, as hypothesized by Dr. Trechot.

In our article [2], we questioned the impact of the use of mannitol as a vehicle for levothyroxine, a drug allocated to class 3 of the Biopharmaceutical Classification System (BCS) [4]. Our concern was based on reports that sugar alcohols, such as mannitol, have been shown to influence the absorption of poorly permeable drugs through their osmotic loads [5]. This postulated, yet plausible, interaction between levothyroxine and mannitol is systematically ignored by those who argue that a direct effect attributable to mannitol is unlikely to solely explain ADRs. It is also of interest, from a mechanistic perspective, to report that changes in the crystal structure of levothyroxine can lead to enhanced degradation of the molecule from loss of water molecules in lattice channels, which allows access to molecular oxygen; the waters of hydration play a vital role in the in vitro stability of crystal structure. These considerations have led to a proposal to update current guidelines, to identify different types of instability associated with crystal hydrates during product development, and thereby to facilitate establishing pharmaceutically equivalent drug products [6].

Compliance with Ethical Standards

Funding No sources of funding were used in the preparation of this reply.

Conflict of interest Didier Concordet, Peggy Gandia, Jean-Louis Montastruc, Alain Bousquet-Mélou, Peter Lees, Aude A. Ferran, and Pierre-Louis Toutain declare no relevant potential conflicts of interest.

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This reply refers to the article available at https://doi.org/10.1007/s40262-019-00784-y.

A comment refers to the article available at https://doi.org/10.1007/s40262-019-00747-3.

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