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# Drug–drug interaction between levetiracetam and non-vitamin K antagonist anticoagulants

**François-Xavier Mathy[1], Elisabeth Dohin[2], François Bonfitto[1], and Barbara Pelgrims[2]***

[1]UCB Pharma, Chemin du Foriest, 1420 Braine l'Alleud, Belgium; and [2]UCB Pharma, 60, Allee de la Recherche, 1070 Brussels, Belgium

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**This commentary refers to 'The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation', by Steffel *et al.*, 2018, pages 1330–1393.**

In the updated guide on NOAC use in patients with non-valvular atrial fibrillation, the European Heart Rhythm Association recommends against the use of the antiepileptic drug, levetiracetam, due to potential P-glycoprotein-mediated drug–drug interaction (DDI).[1] While the summary of product characteristics of apixaban, and edoxaban list phenytoin, carbamazepine, and phenobarbital, and dabigatran's lists phenytoin and carbamazepine, none lists levetiracetam as a P-gp inducer.

In a Phase I trial, healthy volunteers received concomitant levetiracetam and digoxin, a P-gp substrate.[2] Administration of a P-gp inducer with digoxin would be expected to decrease digoxin plasma concentrations; however, repeated levetiracetam exposure had no effect on digoxin steady-state pharmacokinetics.[2] Absence of effect on digoxin pharmacodynamics, as measured by ECG parameters, supports this lack of interaction.[2] P-gp and CYP450 enzyme expression induction by xenobiotics is primarily mediated by the pregnane X receptor (PXR). Since levetiracetam does not induce CYP450 enzyme expression, as supported by clinical data,[3] it is unlikely to activate PXR, and therefore, induce P-gp expression. Finally, levetiracetam has no effect on the expression, or function of the products of the ABC transporter genes, ABCB1 (coding for P-gp), ABCC1, ABCC2, and ABCG2, in human cell lines.[4] Importantly, P-gp function is species-specific; levetiracetam is a substrate of mouse, but not of rat or human P-gp.[5] Data obtained in non-human models may not be relevant to humans.

The recommendation appears to be solely based on results from *in vivo* animal models. However, clinical data, which supersede animal model data, demonstrate that levetiracetam is not a P-gp inducer. Evidence presented here support the absence of any clinically relevant DDI between levetiracetam and NOACs. The recommendation could potentially constitute a serious safety risk for patients treated concomitantly with levetiracetam and a NOAC, if levetiracetam is substituted.

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* Corresponding author. Tel: +32 2 559 9720, Fax: +32 2 559 9673, Email: Barbara.Pelgrims@ucb.com