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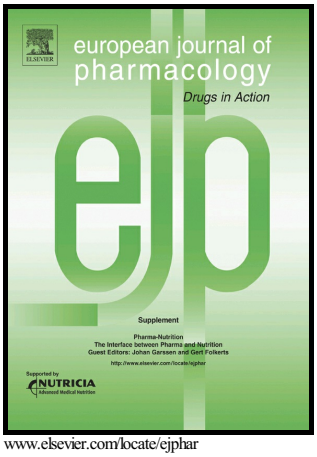

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PII: S0014-2999(18)30469-2
DOI: https://doi.org/10.1016/j.ejphar.2018.08.019
Reference: EJP71944

To appear in: *European Journal of Pharmacology*

Received date: 9 June 2018
Revised date: 13 August 2018
Accepted date: 15 August 2018

Cite this article as: Xiaomiao Qiu, Weiting Wang, Zhuanyou Zhao, Shuangyong Sun and Lida Tang, Pre-clinical pharmacodynamic study of a novel oral factor Xa inhibitor zifaxaban, *European Journal of Pharmacology,* https://doi.org/10.1016/j.ejphar.2018.08.019

Pre-clinical pharmacodynamic study of a novel oral factor Xa inhibitor zifaxaban

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Abstract

Zifaxaban is an orally active, direct Factor Xa (FXa) inhibitor that is in development for the prevention and treatment of arterial and venous thrombosis. This study was conducted to investigate the biochemical and pharmacological activity of zifaxaban. *In vitro* activity was evaluated by enzyme, platelet aggregation, and clotting assays. *In vivo* effects were examined in venous thrombosis, arteriovenous-shunt thrombosis, carotid thrombosis, and bleeding models in rats. Zifaxaban competitively inhibits human FXa (IC_{50} = 11.1 nM) with > 10,000-fold greater selectivity than other serine proteases. It did not impair platelet aggregation induced by collagen, adenosine diphosphate (ADP) or arachidonic acid. It significantly prolonged clotting time, prothrombin time (PT), and activated partial thromboplastin time (APTT) in the plasma of humans, rabbits, and rats, with a relatively weak effect on thrombin time (TT). In venous thrombosis models in rats, zifaxaban strongly suppressed thrombus formation with ED_{50} values of 3.09 mg/kg, and its best efficacy time occurred at 2 h after administration. In arteriovenous-shunt