Model Based Exposure-Response Analysis of Rivaroxaban to Assess the Adequacy of Current Bioequivalence Limits in Generic New Oral Anticoagulant Drugs

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Objectives: To assess the performance of current recommended bioequivalence (BE) assessment criteria for rivaroxaban by exploring its exposure clinical response relationship for bleeding risk and prevention of venous thromboembolism (VTE).

Methods: The relationships between rivaroxaban exposure measurements (e.g. minimum concentration at steady state) and clinical outcomes (i.e. the probability of major bleeding and VTE) from 7145 patients under total hip arthroplasty (THA) and total knee arthroplasty (TKA) treated with rivaroxaban were modeled using NONMEM® 7.3. Model evaluation was performed using predictive checks and non-parametric bootstrap (NPB). Simulations were conducted to assess whether or not the current BE limits are appropriate for generics drugs of rivaroxaban.

Results: A shallow relationship was observed between explored exposure measurements and the probability of VTE after rivaroxaban administration. Trough concentrations were found to be a statistically significant predictor of the probability of major bleeding. This relationship was better described using a power function. Visual predictive check and NPB confirmed model adequacy. Based on the simulations results, the relative risk of major bleeding of a hypothetical test product (with 20% change in AUC) will not statistically differ from brand drug.

Conclusions: A generic drug of rivaroxaban passing currently recommended BE assessment is predicted to have similar safety and efficacy profiles to the brand drug in THA and TKA patients.