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***APPLICATION NUMBER:***

# 215859Orig1s000

# NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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| Application number: | NDA 215859 |
| Supporting document/s: | 1 |
| Applicant's letter date: | June 22, 2021 |
| CDER stamp date: | June 22, 2021 |
| Product: | Xarelto (Rivaroxaban) Oral Suspension |
| Indication: | • Venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in children from birth to < 18 years of age,<br>• Thromboprophylaxis in pediatric patients 2 years of age and older with congenital heart disease (CHD) after the Fontan procedure |
| Applicant: | Janssen Pharmaceuticals Inc. |
| Review Division: | Division of Non-Malignant Hematology |
| Reviewer: | Bo Yeon Lee, Ph.D. |
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# 1 Executive Summary

## 1.1 Introduction

Rivaroxaban (JNJ-39039039, BAY 59-7939, Xarelto®) is a selective inhibitor of the serine protease coagulation Factor Xa (FXa) being developed for the prevention and treatment of thrombo-embolic events. (Reference NDAs 022406 and 202439)

Currently, Xarelto is approved in adult patients for the following indications; 1) to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation, 2) for treatment of deep vein thrombosis (DVT), 3) for treatment of pulmonary embolism (PE), 4) for reduction in the risk of recurrence of DVT or PE, 5) for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery, 6) for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients, 7) to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) (Xarelto USPI, revised 03/2020).

The Sponsor submitted this NDA 245859 for 2 indications in pediatric population: 1) venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in children from birth to < 18 years of age, and 2) thromboprophylaxis in pediatric patients 2 years of age and older with congenital heart disease (CHD) after the Fontan procedure

In support of the clinical development in pediatric population, the Sponsor conducted additional pharmacokinetics studies including protein binding using plasma from pediatric healthy volunteers and substrate characteristics towards fetal CYP3A7. There are no new pharmacology or toxicology studies submitted. There are no outstanding issues from a Pharmacology/Toxicology perspective that would prevent the approval of rivaroxaban for the proposed indications.

## 1.2 Brief Discussion of Nonclinical Findings

Xarelto® is an approved drug in adult populations and the Sponsor has submitted this NDA to support the clinical development and market authorization of rivaroxaban in pediatric populations.

The nonclinical program reviewed under reference NDAs 202439 and 022406 concluded that rivaroxaban was approvable for the indications listed above in adult patient population. The reference NDAs include nonclinical studies in juvenile, adolescent and adult rats, and the overall nonclinical assessment remains unchanged. In addition, the Sponsor submitted additional PK studies of pediatric protein binding and of substrate characteristics towards a fetal CYP isoform, which showed that the unbound fraction in pediatric plasma was higher than in adult plasma and that rivaroxaban is a poor substrate for the fetal isoform CYP3A7.

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