CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215859Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215859
Assessment #01

Drug Product Name	XARELTO (rivaroxaban) for oral suspension
Dosage Form	Granule, For Suspension
Strength	1 mg/mL rivaroxaban oral suspension.
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Janssen Pharmaceuticals Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original CMC submission	06/22/2021	All
Amendment	08/26/2021	Drug Substance, Drug Product, Micro
Amendment	09/30/2021	Micro
Amendment	10/04/2021	Manufacturing
Amendment	10/22/2021	Biopharm
Amendment	10/22/2021	Drug Product
Amendment	11/04/2021	Drug Product
Amendment	11/16/2021	Biopharm

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Ben Zhang	Suong Tran
Drug Product	Dan Berger	Ee-Sunn (Joanne) Chia
Manufacturing	Nancy Waites, Caryn McNab (ORA)	Daniel Obrzut
Microbiology	Marijke Koppenol-Raab	Yan Zheng
Biopharmaceutics	Rebecca Moody	Om Anand
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead	Dan Berger	
Laboratory (OTR)	NA	NA
Environmental	NA	NA

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends approval of NDA 215859 for marketing of XARELTO (rivaroxaban) for oral suspension 1 mg/mL. The applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed product. All facilities are in good standing.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Janssen seeks a priority review of NDA 215859 XARELTO® (rivaroxaban) oral suspension under 505(b)(1) to support inclusion of the proposed new indications in pediatric patients for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and additional cardiovascular disorders. This June 22, 2021 submission is a response to a Written Request for pediatric studies of rivaroxaban (Xarelto), with a PDUFA goal date of December 22, 2021.The proposed maximum dose is 20 mg per day, to be taken with food. The Applicant contends that the proposed treatment provides substantial improvement over available anticoagulant therapies for the serious and life- threatening conditions of venous thromboembolism (VTE) and thromboprophylaxis in children with congenital heart disease after the Fontan procedure.

XARELTO® (rivaroxaban) granules, (b) (4) for oral suspension contains 155 (b) (4) mg of (b) (4) rivaroxaban, suspension excipients (b) (4) (b) (4) The product is supplied in a 200-mL amber colored type (b) (4) glass bottle closed with a white opaque (b) (4) screw cap. The product is co-packaged with two 5 mL syringes for oral dosing and a press-in bottle adaptor. Prior to use, 150 mL of purified water is added to the granules at a pharmacy to provide a 1 mg/mL rivaroxaban oral suspension. The current commercial formulation was used throughout clinical studies, with smaller quantities filled into the bottles ((b) (4) g and (b) (4) g versus the current (b) (4) g per bottle). The stability data submitted provides adequate support for the proposed expiry dating period of 30 months at 25°C, based on extension of shelf-life as per ICH Q1E. The drug product suspension can be stored for up to 60 days at room temperature, which is dosed multiple times using the co-packaged oral syringes. Data was provided demonstrating adequate stability of the suspension in the bottle for 60 days, and compatibility with the co-packaged syringe and nasogastric tubes was demonstrated. Key quality issues assessed during the review included homogeneity of the suspension, redispersibility, uniformity of dosing and microbial content, which were confirmed to be acceptable for the drug product. Based on the review of NDA 215859, XARELTO® (rivaroxaban) oral suspension is determined to be of acceptable quality,

with minimal risks to patients identified from a CMC perspective when used as directed.

Proposed Indication(s) including Intended Patient Population	Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), reduce risk of stroke and embolism, and additional cardiovascular disorders.
Duration of Treatment	Once a day for at least 3 months in children >2 years old with thrombosis, up to 12 months when clinically necessary. For children <2 years old, treatment for 1 month, or up to 3 months when clinically necessary.
Maximum Daily Dose	20 mg/day
Alternative Methods of Administration	Oral tablets.

B. Quality Assessment Overview

Drug Substance: Adequate

Rivaroxaban is a synthetic small molecule. The drug substance is the S enantiomer. The [redacted] (b) (4) has been used throughout the whole development. Particle size distribution [redacted] (b) (4) The applicant referenced all CMC information on the drug substance to DMF [redacted] (b) (4). The DMF has been reviewed and found adequate to support other applications. Recent updates have been reviewed and found adequate to support this NDA.

A new manufacturing site at [redacted] (b) (4) has been added in addition to the original manufacturing site registered for the synthesis of Rivaroxaban drug substance, [redacted] (b) (4) The [redacted] (b) (4) [redacted], quality control procedures and specifications of the active substance Rivaroxaban manufactured in [redacted] (b) (4) are the same as those already approved. Batch analyses data for the drug substance batches manufactured at the new [redacted] (b) (4) site is consistent with those from current sites.

The specification from the drug product manufacturer is consistent with the specification from DMF [redacted] (b) (4), and the NDA includes batch analyses data for 3 drug substance batches used in the three primary drug product stability batches. All 3 drug substance batches meet the specified acceptance criteria, confirming suitability for use in the drug product. An updated risk assessment on the elemental impurities shows that the elemental impurity levels are consistently observed below the LOD, and the risk from such impurities are low.

The drug substance is packed in [redacted]. Stability data for drug substance batches manufactured at [redacted] show no trend of degradation or increase of impurities through [redacted] months at [redacted] RH and [redacted] RH. Stability studies are ongoing for the [redacted] batches, with [redacted] months data available at long-term, intermediate and accelerated conditions. No changes or degradants have been observed.

Drug Product: Adequate

Rivaroxaban granules for oral suspension contains 155 [redacted] mg of rivaroxaban per bottle, for multiple dosing by an oral syringe. The product is diluted with 150 mL of purified water by a pharmacist to a final concentration of 1 mg/mL rivaroxaban. All excipients are compendial, not of human or animal origin, and present at acceptable levels for the maximum daily dose of 20 mg based on the FDA Inactive Ingredients database. The drug product specifications are adequate to ensure quality and all drug product batches meet specified acceptance criteria. Resuspendability and homogeneity of the diluted mixture was established to be acceptable during pharmaceutical development studies, with consistent doses dispensed over a 28-day period. Minimal risks were identified regarding potential [redacted] impurities, and ICP-MS results confirmed that elemental impurities are adequately controlled. The key analytical methods are the HPLC method used to assess identification, assay, and related compounds. Primary packaging for the commercial product consists of a 200 mL Type [redacted] glass bottle with a [redacted] co-packaged with two oral dosing syringes, and one press-in bottle adapter (PIBA). The container closure components meet USP requirements and 21 CFR compendial criteria. Syringe device components meet the requirements of physicochemical and extractables test as per USP as well as in-vitro biological reactivity tests. The co-packaged syringes are washed with water after each dose and discarded after a bottle is finished, or within 60 days. Registration drug product batches meet all acceptance criteria during long-term and accelerated stability studies for 18 months and six months respectively, with no significant changes or increases in degradants. Rivaroxaban granules for oral suspension are not photosensitive and meet purity specifications following exposure to light, heat and high humidity in stress test studies. In-use stability was confirmed for a 2-month period, supporting the labeling recommendation of 60 days storage after dilution. The overall stability data submitted provides adequate support for the proposed expiry dating period of 30 months from the date of manufacture at 25°C, based on extension of shelf-life as per ICH Q1E. In summary, rivaroxaban granules for oral suspension are of acceptable quality, with minimal risks to patients identified when used as directed.

Labeling: Adequate

All labeling deficiencies have been addressed. Edits to the carton and container labels are addressed by DMEPA, for consistency with the PI. The Prescribing Information, Medication Guide and labels comply with all regulatory requirements from a CMC perspective.

Manufacturing: Adequate

The manufacturing process of the drug product consists of (b) (4) This is a new pediatric indication for an already approved drug, NDA 22406 (Xarelto (Rivaroxaban) tablet, film coated). This NDA is for granules for oral suspension. This NDA (NDA 215859) serves as the Sponsor's response to a Written Request for pediatric studies of rivaroxaban (Xarelto) for the purpose of pediatric exclusivity determination, and to fulfill the PREA PMRs under NDA 022406.

In a formulation study, it was determined that the particle size distribution (PSD) of the drug substance that had been established for the Rivaroxaban coated tablets was also appropriate for Rivaroxaban granules (b) (4) for oral suspension.

(b) (4)

(b) (4)

No PAIs were conducted, all facilities are deemed adequate with ORA concurrence. OPMA recommends approval.

Biopharmaceutics: Adequate

This submission serves as the Applicant's response to a Written Request for pediatric studies of rivaroxaban (Xarelto) for the purpose of pediatric exclusivity determination, and to fulfill the PREA post-marketing requirements under NDA 022406 (Rivaroxaban IR Tablets).

The proposed pediatric drug product is formulated as granules filled in a bottle, that can be administered as a suspension after addition of (b) (4) water, with a concentration of 1 mg/mL. The formulation offers dose flexibility, high convenience, and compliance for patients with dysphagia. The recommended dose is based on the body weight of the patient and all doses are to be taken with feeding or with food to optimize absorption.

The proposed indications for Rivaroxaban Oral Granules are: (1) treatment of venous thromboembolism (VTE) and the reduction in risk of recurrent VTE in pediatric patients from birth to less than 18 years (after at least 5 days of initial parenteral anticoagulant treatment), and (2) thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease (CHD) who have undergone the Fontan procedure.

In support of this submission, the Applicant provided efficacy and safety data from two pivotal in pediatric patients (EINSTEIN Jr Phase 3, and UNIVERSE Phase 3) as well as two studies that demonstrated bioequivalence between the granules-for-oral-suspension formulation and the standard IR Tablet (Study Nos. 19365 and 19366).

This Biopharmaceutics assessment is focused on the assessment of the proposed dissolution method and acceptance criterion for quality control (QC) testing of rivaroxaban granules for oral suspension at release and on stability.

The FDA approved quality control dissolution method and acceptance criterion (finished drug product batch release and stability testing) are as follows:

Medium	0.022 M Acetate Buffer pH 4.5
Volume/Temp	900 mL; 37°C
USP Apparatus	2 (paddle)
Rotational Speed	50 rpm
Acceptance Criterion	NLT (b) (4)% (Q) of the labeled amount of rivaroxaban is dissolved in 30 minutes

From the Biopharmaceutics perspective, NDA 215859 for the proposed Xarelto® (Rivaroxaban) Granules for Oral Suspension; 1 mg/mL, is Adequate and recommended for **Approval**.

Microbiology: Adequate

The proposed drug product is a non-sterile granule formulation of rivaroxaban intended for oral administration following suspension in water. The drug product is manufactured using (b) (4)

(b) (4)

The potential for BCC contamination was demonstrated to be low for the solid drug product as well as the the constituted solution. Antimicrobial effectiveness testing (AET) per USP<51> was performed on two primary stability batches at the initial timepoint and after 12 months of storage of the granules. Additionally, the Applicant commited (b) (4)

The tests and acceptance criteria are adequate to assure the microbiological quality of the subject drug product.

A post-approval proposal (b) (4)

(b) (4)

Stability studies for the granules are adequate to support the proposed shelf life. The reconstituted suspension is to be stored at room temperature between 20-25°C (with excursion permitted to 15°C to 30°C)

and used within 60 days. In-use stability studies performed at the beginning of shelf-life and after 12 months of storage confirmed that all samples met the specifications for (b) (4) and microbiological Tests. In response to an Information Request, the Applicant agreed to revise the pharmacy preparation instructions to use purified water for drug product constitution.

The Applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Suspendability & homogeneity of reconstituted drug product.	Medium	(b) (4)	Acceptable	-
Physical Stability of diluted product	Insoluble drug substance, storage time	Low		Acceptable	-
Content Uniformity	Suspendability & homogeneity of reconstituted drug product.	Medium		Acceptable	-
Microbial Content	Formulation, container closure	Low		Acceptable	-
Dissolution	Drug substance solubility, polymorphism	Medium		Acceptable	-

Particle Size	Manufacturing process, drug substance solubility	Medium	(b) (4)	Acceptable	-

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date:

Dan Berger November 18, 2021

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	N/A	
	II			Adequate	09/02/21	
	III			Active	N/A	Sufficient information in NDA
	III			Active	N/A	
	III			Active	N/A	
	IV			Active	N/A	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	022406, 202439	Tablets for treatment of deep vein thrombosis, treatment of pulmonary embolism, stroke and cardiovascular events.

2. CONSULTS

None.

Dan Berger

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Ee-Sunn (Joanne) Chia

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	XARELTO	Adequate
Established name(s)	Rivaroxaban	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	1 mg/mL (once reconstituted)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Pharmacy: Tap the bottle until all granules flow freely. Add 150 mL of purified water for reconstitution. Shake for 60 seconds. Check that all granules are wetted and the suspension is uniform. Push the adaptor into bottleneck and recap bottle. (b) (4) [redacted] The suspension must be used within 60 days. Read instructions For Use.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	For oral solution.	Adequate
Strength(s) in metric system	1 mg/mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White to off-white granules; once reconstituted, provide flavored white to off-white opaque liquid	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Xarelto, rivaroxaban	Adequate
Dosage form(s) and route(s) of administration	XARELTO granules for oral suspension	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Anhydrous citric acid, hypromellose, mannitol, microcrystalline cellulose & carboxymethylcellulose sodium, sodium benzoate, sucralose, sweet and creamy flavor and xanthan gum.	Adequate
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	Factor Xa (FXa) inhibitor	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, $C_{19}H_{18}ClN_3O_5S$, 435.89.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Practically insoluble in water and aqueous media.	Adequate

* 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral suspension	Adequate
Strength(s) in metric system	1 mg/mL (once reconstituted)	Adequate
Available units (e.g., bottles of 100 tablets)	Amber glass bottle containing 155 mg rivaroxaban	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white granules, NDC 50458-575-01	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	NA	NA
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature between 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Storage conditions and inactive ingredient list is provided in the Medication Guide. This information complies with all regulatory requirements from a CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Bottle and carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Xarelto (rivaroxaban)	Adequate
Dosage strength	1 mg/mL	Adequate
Route of administration	oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	155 mg of rivaroxaban	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	50458-575-01	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 68°F to 77°F (20°C to 25°C); excursions permitted between 59°F to 86°F (15°C to 30°C)	°F and °C Reversed from usual. Adequate following requested edits sent to DMEPA for the Applicant.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Finished Product Manufactured by: (b) (4)	Adequate
Medication Guide (if applicable)	Storage and active/inactive ingredients listed.	Adequate
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Adequate*

DMEPA has agreed to address the required edits to the storage information. With the required edits, the labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Edits to the carton and container labels are addressed by DMEPA, for consistency with the PI. The Prescribing Information, Medication Guide and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger November 8, 2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Ee-Sunn Chia November 8, 2021

Dan Berger

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Ee-Sunn (Joanne) Chia

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	505 (b)(1) Xarelto® (Rivaroxaban) Granules for Oral Suspension
NDA Number	215859
Assessment Cycle Number	1
Drug Product Name/ Strength	Rivaroxaban granules for oral suspension; 1 mg/mL
Route of Administration	Oral
Applicant Name	Janssen Research & Development, LLC
Therapeutic Classification/ OND Division	Anti-thrombocytosis; Division of Non-Malignant Hematology (DNH)
LD	NDA 022406 and NDA 202439 (Xarelto® IR Tablets)
Proposed Indication	Treatment of (1) Venous Thromboembolism (VTE) and the reduction in the risk of recurrent VTE in pediatric patients, and (2) thromboprophylaxis in pediatric patients with Congenital Heart Disease (CHD) after the Fontan Procedure.

Assessment Recommendation: **Adequate**

Assessment Summary:

On 06/22/2021, the Applicant, Janssen Research & Development, LLC[1], submitted an NDA under 505(b)(1) seeking marketing approval for Xarelto® (Rivaroxaban) Granules for Oral Suspension (1 mg/mL). This submission serves as the Applicant's response to a Written Request for pediatric studies of rivaroxaban (Xarelto) for the purpose of pediatric exclusivity determination, and to fulfill the PREA post-marketing requirements under NDA 022406 (Rivaroxaban IR Tablets).

The proposed pediatric drug product is formulated as granules filled in a bottle, that can be administered as a suspension after addition of (b) (4) water, with a concentration of 1 mg/mL. The formulation offers dose flexibility, high convenience, and compliance for patients with dysphagia. The recommended dose is based on the body weight of the patient and all doses are to be taken with feeding or with food to optimize absorption.

The proposed indications for Rivaroxaban Oral Granules are: (1) treatment of venous thromboembolism (VTE) and the reduction in risk of recurrent VTE in pediatric patients from birth to less than 18 years (after at least 5 days of initial parenteral anticoagulant

[1] Rivaroxaban (JNJ-39039039, BAY 59-7939) was co-developed under a collaboration license agreement between Bayer AG and Janssen Pharmaceuticals, Inc. Marketing applications in the US are submitted by Janssen Research & Development, LLC on behalf of Janssen Pharmaceuticals, Inc. Module 2.5 (Page 9).

treatment), and (2) thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease (CHD) who have undergone the Fontan procedure.

In support of this submission, the Applicant provided efficacy and safety data from two pivotal in pediatric patients (EINSTEIN Jr Phase 3, and UNIVERSE Phase 3) as well as two studies that demonstrated bioequivalence between the granules-for-oral-suspension formulation and the standard IR Tablet (Study Nos. 19365 and 19366).

This Biopharmaceutics assessment is focused on the assessment of the proposed dissolution method and acceptance criterion for quality control (QC) testing of rivaroxaban granules for oral suspension at release and on stability.

The FDA approved quality control dissolution method and acceptance criterion (finished drug product batch release and stability testing) are as follows:

Medium	0.022 M Acetate Buffer pH 4.5
Volume/Temp	900 mL; 37°C
USP Apparatus	2 (paddle)
Rotational Speed	(b) (4) 50 rpm
Acceptance Criterion	NLT (b) (4) % (Q) of the labeled amount of rivaroxaban is dissolved in 30 minutes

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
API Particle Size	Medium	As rivaroxaban is a low solubility drug substance, particle size may impact dissolution.	Low	(b) (4) Applicant has implemented (b) (4) It is noted that the dissolution method and acceptance criterion can discriminate against changes to the API particle size.

Overall Recommendation: From the Biopharmaceutics perspective, NDA 215859 for the proposed Xarelto® (Rivaroxaban) Granules for Oral Suspension; 1 mg/mL, is **Adequate** and recommended for **Approval.**

[2] The API particle size specification is the same as that listed for the approved Rivaroxaban Tablets (adult formulation).

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0001 (1) Original Submission	June 22, 2021
0025 (25) IR Response	October 22, 2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: N/A

B.1 BCS DESIGNATION

Assessment: No BCS Designation request was made; however, based on the submitted data, rivaroxaban appears to be BCS Class II.

Solubility: According to the Applicant, rivaroxaban is practically insoluble in water and aqueous media pH 1-9. Rivaroxaban has a solubility of 5-7 mg/L at 25°C, independent of pH. See Table 1 below for solubility at 37°C in various pH media.

Table 1. Solubility of rivaroxaban in aqueous media of different pH at 37°C

Medium	Solubility (mg/mL)
0.1 M HCl pH 1	0.0111
0.01 M HCl pH 2	0.0111
Acetate buffer pH 4.5	0.0133
Phosphate buffer pH 6.8	0.0100

Permeability: The Applicant investigated the permeability of rivaroxaban using a validated Caco-2 assay and found rivaroxaban to be highly permeable[3].

Dissolution: See below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: Adequate

Dissolution Method:

Method Conditions/ Acceptance Criterion	Rivaroxaban Granules (b) (4) for Oral Suspension
Medium	0.022 M Acetate Buffer pH 4.5
Volume/Temp	900 mL; 37°C
USP Apparatus	2 (paddle)
Rotational Speed	50 rpm
Acceptance Criterion	NLT (b) (4) % (Q) of the labeled amount of rivaroxaban is dissolved in 30 min

[3] NDA 215859 Module 2.5 Clinical Overview (Page 26)

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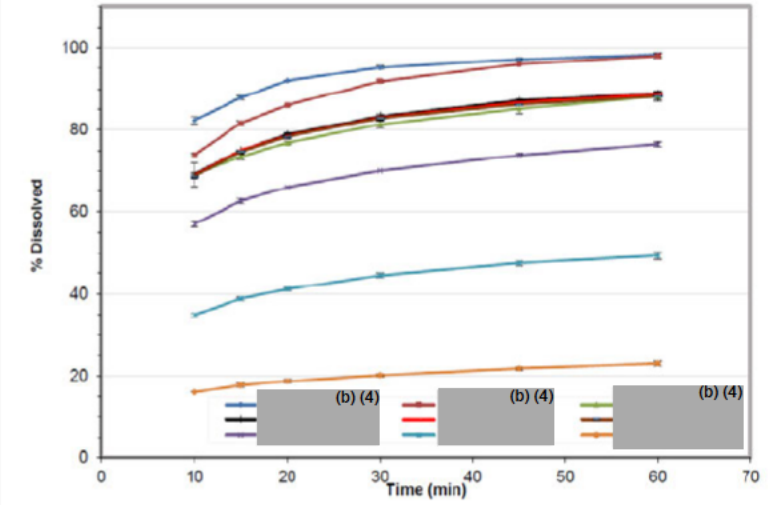
(b) (4)

- ***Discriminating ability of the dissolution method:*** The Applicant confirmed the discriminating nature of the selected dissolution method by producing different drug product batches using (1) drug substance of different particle sizes, (2) a change in drug product composition, or (3) different process parameters.

  The average dissolution profiles of drug product batches with different particle size using the proposed dissolution method are represented in Figure 3 below.

Figure 3. Dissolution profiles of batches manufactured with different API particle sizes.



The dissolution rate of rivaroxaban, as a BCS Class II drug substance, is affected by particle size. As the particle size of rivaroxaban increases, the dissolution profiles become slower and incomplete. The proposed dissolution method was able to distinguish batches with aberrant PSDs. Nevertheless, the Applicant implemented (b) (4) to further mitigate risk. It is noted that the PS

specification for the (b) (4) drug substance used for manufacturing Rivaroxaban Granules is the same specification listed for the approved Rivaroxaban Tablets.

While the dissolution method was able to discriminate against changes to the drug substance particle size, it was not sensitive (b) (4) (b) (4) or changes in the pH of the suspension after reconstitution. The Applicant showed that when the drug product was stressed at 60°C for 2 weeks, similar dissolution profiles as compared with the non-stressed sample were observed. Therefore. suggesting that the drug product is stable, and the dissolution method was not demonstrated to be able to detect changes on stability.[4]

- ***Dissolution Acceptance Criterion:*** In response to the IR dated 10/12/2021, the Applicant provided full profile dissolution data for exhibit batches and all batches used in pivotal clinical trials and the BE study. The average dissolution profiles for the aforementioned batches are presented below in Figure 4. It is noted that all batches meet the proposed acceptance criterion of "NLT (b) (4)% (Q) of the labeled amount of rivaroxaban dissolved in 30 minutes."

Figure 4. Dissolution profiles of batches used for BE Study, Registration, and Clinical Trials (Phase 3 Universe and Einstein Junior Clinical Trials).

(b) (4)

Table 2. Description of Batches Used for Setting the Dissolution Specification

DP Batch	Manufacturer's Batch	Batch Size (kg)	Batch Use
[a]CDHKV	KM6024J	(b) (4) kg	Primary Stability and Development
[a]CDHKW	KM6024K		Primary Stability and Development
[a]CDHKX	KM60274	kg	Primary Stability and Development
[b]KM6020B	KM6020B	kg	Phase 3 Clinical
[b]KM6023D	KM6023D	kg	Development
[b]KM601KX	KM601KX	kg	Phase 3 Clinical and Development
[b]KM601H6	KM601H6	kg	Phase 3 Clinical
[b]KM601N2	KM601N2	kg	Phase 3 Clinical
[b]KM600S5	KM600S5	kg	Development
[b]KM600SE	KM600SE	kg	Phase 3 Clinical
[b]KM6010S	KM6010S	kg	Phase 3 Clinical and Development
[b]KM600R8	KM600R8	kg	Phase 3 Clinical and Development
[b]KM600PT	KM600PT	kg	Phase 3 Clinical
[b]KM60026	KM60026	kg	Phase 3 Clinical
[b]KM600N4	KM600N4	kg	Phase 3 Clinical
[b]KM600PC	KM600PC	kg	Phase 3 Clinical and Development
[b]KM600PF	KM600PF	kg	Phase 3 Clinical
[b]KM50141	KM50141	kg	Phase 3 Clinical

[a] Granules Manufactured at (b) (4) and Packaged at (b) (4)

[b] Granules Manufactured and Packaged at (b) (4)

[4] NDA 215859 Module 3.2.P.2 Dissolution Method Development

Reviewer's Comment:
The dissolution method has been optimized for dissolution medium, volume, and paddle rotation speed. Further, based on the provided information, the Applicant's use of (b) (4) mL suspension volume for dissolution testing is adequately justified. Specifically, as the formulation is intended (mostly) for children (birth to less than 18 years), the dose volume typically ranges from 0.8 mL to 3 mL three times a day (patients weighing between 2.6 kg and 12 kg). A dose volume of 5 mL (5 mg) twice a day is recommended for patients weighing between 12 kg to <30 kg. A suspension sample volume of (b) (4) mL is therefore acceptable (b) (4) (b) (4)

With regards to the dissolution acceptance criterion, all batches could meet an acceptance criterion of "NLT (b) (4)% (Q) in (b) (4) minutes;" however, it is noted the proposed specification time of 30 minutes can discriminate against batches with particle sizes (b) (4) outside the specified distribution (b) (4) Drug products made with drug substances with a (b) (4) or greater are unable to meet the acceptance criterion of "NLT (b) (4)% (Q) at 30 minutes." In addition, the Applicant evaluated the risk of overall batch rejection based on clinical phase 3, primary stability, and development batches and found an acceptance criterion of Q= (b) (4)% at (b) (4) minutes to be over discriminatory (estimated batch rejection rate of 15%).[5] Therefore, the Applicant's proposed acceptance criterion and dissolution method are acceptable for the quality control (QC) dissolution testing of the proposed drug product.

The recommended QC dissolution method and acceptance criterion are as follows:

Method Conditions/ Acceptance Criterion	Rivaroxaban Granules (b) (4) for Oral Suspension
Medium	0.022 M Acetate Buffer pH 4.5
Volume/Temp	900 mL; 37°C
Apparatus	II
Speed	50 rpm
Acceptance Criterion	NLT (b) (4)% in 30 minutes

In addition to the dissolution test for quality control of the drug product, it is noted that the Applicant has a suspendability specification of (b) (4) to ensure a homogenous suspension and adequate dosing.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: N/A

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Adequate

[5] NDA 215859 Module 3.2.P.5.6 Justification of Specifications (Page 13)

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(b) (4)

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: N/A

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: N/A

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: N/A

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: N/A

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: N/A

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: N/A

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: N/A

B.12 BRIDGING OF FORMULATIONS

Assessment: N/A

No bridging is necessary. Drug product batches used in phase 3 clinical trials and registration batches are representative of the to-be-marketed product.

B. 13 BIOWAIVER REQUEST

Assessment: N/A

A biowaiver request is not needed.

[7] NDA 215859 Module 3.2.P.2 Formulation Development (Page 12).

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: N/A

Lifecycle Management Considerations

N/A

BIOPHARMACEUTICS LIST OF DEFICIENCIES

(b) (4)

[redacted]

[8] NDA 215859 Seq 0025 CMC Response to FDA Communication of 12 October 2021.

(b) (4)

Overall, the Applicant's response is adequate.

[9] NDA 215859 Seq 0031 CMC Response to FDA Communication of 12 November 2021.
[10] NDA 215859 Seq 0018 CMC Response to FDA Communication of 27 September 2021. Content Uniformity Analysis of Exhibit Batches.

Om Anand

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Rebecca Moody

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215859
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Rivaroxaban granules, (b) (4) for oral suspension
Route of Administration	Oral
Applicant Name	Janssen Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	OND/OCHEN/DNH
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile granules

Assessment Recommendation: **Adequate**

Assessment Summary: The proposed drug product is a non-sterile granule formulation of rivaroxaban intended for oral administration following suspension in water. The drug product is manufactured using (b) (4) .

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 Original Submission	6/22/2021
0011 Quality IR Response	8/26/2021
0017 Quality IR Response	9/30/2021

Highlight Key Issues from Last Cycle and Their Resolution:

Remarks: The formulation of rivaroxaban granules for oral suspension is a new market presentation. The formulation (b) (4) for use in children was initially described in IND 64892, which was submitted for a (b) (4) rivaroxaban oral suspension. Following further development, clinical studies were initiated with a granule formulation under IND 64892.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug product is non-sterile. The drug substance will not be reviewed here.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product – White to off-white granules in an amber glass bottle containing 155g rivaroxaban (total fill weight (b) (4)g per bottle). Prior to administration, 150mL of water is added to the granules in the bottle by the pharmacy, resulting in a 1mg/mL rivaroxaban oral suspension. The product is co-packaged with two 5mL syringes used for oral dosing and a press-in bottle adaptor (PIBA), which are supplied by (b) (4). Following suspension of the granules, the PIBA is inserted in the bottle neck, and the bottle is capped.

Drug product composition –

Ingredient	Function	Content per bottle (mg)
Rivaroxaban (b) (4)	Active Ingredient	(b) (4)
Citric Acid Anhydrous, USP/NF	(b) (4)	
Flavor Sweet and Creamy		
Hypromellose 5 cP, USP/NF		
Mannitol, USP/NF		
Microcrystalline Cellulose and Carmellose Sodium, USP/NF		
Sodium Benzoate, USP/NF		
Sucralose, USP/NF		
Xantham Gum, USP/NF		
(b) (4)		

Description of container closure system –

Component	Description	Manufacturer
Bottle	Type (b) (4) amber glass bottle, 200mL	(b) (4)
Cap	White opaque (b) (4) screw cap with seal liner	

Assessment: *Adequate*

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbial control of the product.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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