

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202439Orig1s000**

**CHEMISTRY REVIEW(S)**

## **NDA 202,439**

**XARELTO® (rivaroxaban) 15mg and 20mg Film Coated  
Tablets  
Johnson & Johnson Pharmaceutical  
Research and Development, L.L.C. (J&JPRD)**

**Pei-I Chu, Ph.D.  
Office of New Drug Quality Assessment DPA1  
For Division of Psychiatry Drug Products**

**Review of Chemistry, Manufacturing, and Controls**

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# Chemistry Review Data Sheet

1. NDA 202,439
2. REVIEW # 2
3. REVIEW DATE: September 2, 2011
4. REVIEWER: Pei-I Chu, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 202439 Review #1 by Pei-I Chu	June 23, 2011.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	03-January-2011

7. NAME & ADDRESS OF APPLICANT:

Name: JJPRD LLC  
Address: 920 US Highway 202, PO Box 300  
Raritan, NJ 00869-0602  
Representative: Alla Rhoge  
Telephone: 908-927-4758

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Xarelto
- b) Non-Proprietary Name (USAN): Rivaroxaban
- c) Code Name/# (ONDC only):N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

## Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Factor Xa inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 15mg, 20mg

13. ROUTE OF ADMINISTRATION: Oral

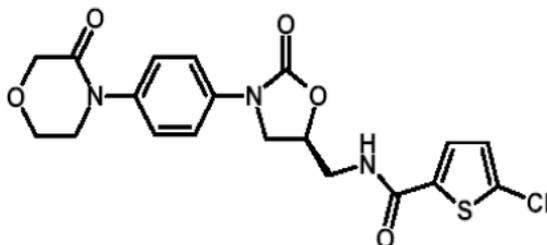
14. Rx/OTC DISPENSED:  X  Rx   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product Form Completed  
 X  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide  
5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl) methyl)thiophene-2-carboxamide



Molecular Formula : C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>5</sub>S  
Molecular Weight : 435.89

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
21581	II	Bayer	Drug substance	1	Adequate	5/27/2011	
21580	II	Bayer	10mg tablet	1	Adequate	6/01/2011	
21592	II	Johnson and Johnson	10mg tablet	1	Adequate	6/01/2011	
(b) (4)				4			Sufficient information in application
				4			Sufficient information in application
				4			Sufficient information in application
				4			Sufficient information in application
				4			Sufficient information in application
				4			Sufficient information in application
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				4			Sufficient information in application

<sup>1</sup> Action

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under “Comments”)

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75238	Commercial
IND	(b) (4)	Commercial
IND	64892	Commercial

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	---	---
EES	acceptable	1/26/2011	Office of compliance
Pharm/Tox	acceptable	4/30/2011	Patricia Harlow
Biopharm	acceptable	7/01/2011	T. Ghosh
LNC	NA	---	---
Methods Validation	NA	---	---
OPDRA	NA	---	---
DMEPA			
EA	NA	---	---
Microbiology	NA	---	---

## The Chemistry Review for NDA 202439

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

NDA 202439 has been reviewed for the chemistry, manufacturing, and controls section. An information request letter was sent to the sponsor on June 12, 2011. The sponsor has provided adequate responses to the IR questions on June 30, 2011. Office of compliance has determined the drug substance, drug product and packaging facilities are adequate. Pre-approval inspections for the drug substance, drug product and packaging sites are not needed based on profile. This NDA is recommended for **approval** from the perspective of chemistry, manufacturing and controls.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

See NDA 202439 Review #1 by Pei-I Chu, June 23, 2011.

##### Drug Product

The sponsor has provided 12 month stability data at 25°C/60% RH and 30°C/65% RH for the blister package in an amendment on July 11, 2011. The results suggest that the drug in the blister package remains stable at this storage condition. In the original submission, the sponsor has provided 36 months of stability data for the pivotal batches packaged in bottle at 25°C/60% RH and 30°C/75% RH as well as 6 months of stability data at 40°C/75% RH. Based on the fact the drug product is also stable in an open dish storage condition at either 25°C/60%RH, 25°C/80% RH, 30°C/75% RH, or 40°C/75%RH for 24 months, a 36 months expiration dating is granted for both the bottle and the blister package.

##### Drug Substance

See Review #1 by Pei-I Chu, June 23, 2011

## Chemistry Review Section

**B. Description of How the Drug Product is Intended to be Used**

For patients with creatinine clearance  $\geq 50$  mL/min: 20 mg orally, once daily with food. For patients with creatinine clearance 30 to  $< 50$  mL/min: 15 mg orally, once daily with food.

**C. Basis for Approvability or Not-Approval Recommendation**

This NDA is recommended for approval from the perspective of chemistry, manufacturing and controls.

**II. Administrative****A. Reviewer's Signature**

Pei-I Chu, Ph.D.

**Endorsement Block**

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Kasturi Srinivasachar, Ph.D.
Chemistry Branch Chief :	Ramesh Sood, Ph.D.
Chemistry Project Manager :	Tu-Van Lambert

**C. CC Block**

Orig. NDA-202439

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/s/  
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PEI-I CHU  
09/27/2011

RAMESH K SOOD  
09/27/2011

## **NDA 202,439**

**XARELTO® (rivaroxaban) 15mg and 20mg Film Coated  
Tablets**

**Johnson & Johnson Pharmaceutical  
Research and Development, L.L.C. (J&JPRD)**

**Pei-I Chu, Ph.D.**

**Office of New Drug Quality Assessment DPA1  
For Division of Psychiatry Drug Products**

**Review of Chemistry, Manufacturing, and Controls**

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B. Environmental Assessment Or Claim Of Categorical Exclusion .....	126

# Chemistry Review Data Sheet

1. NDA 202,439
2. REVIEW # 1
3. REVIEW DATE: June 23, 2011
4. REVIEWER: Pei-I Chu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed  
Original

Document Date  
03-January-2011

7. NAME & ADDRESS OF APPLICANT:

Name: JJPRD LLC  
Address: 920 US Highway 202, PO Box 300  
Raritan, NJ 00869-0602  
Representative: Alla Rhoge  
Telephone: 908-927-4758

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Xarelto
- b) Non-Proprietary Name (USAN): Rivaroxaban
- c) Code Name/# (ONDC only):N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

## Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Factor Xa inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 15mg, 20mg

13. ROUTE OF ADMINISTRATION: Oral

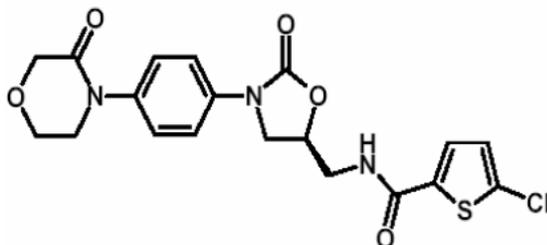
14. Rx/OTC DISPENSED:  X  Rx   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide  
5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl) methyl)thiophene-2-carboxamide



Molecular Formula : C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>5</sub>S  
Molecular Weight : 435.89

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
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21580	II	Bayer	10mg tablet	1	Adequate	6/01/2011	
21592	II	Johnson and Johnson	10mg tablet	1	Adequate	6/01/2011	
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<sup>1</sup>

codes for DMF Table:

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Action

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	---	---
EES	acceptable	1/26/2011	Office of compliance
Pharm/Tox	acceptable	4/30/2011	Patricia Harlow
Biopharm	acceptable		T. Ghosh
LNC	NA	---	---
Methods Validation	NA	---	---
OPDRA	NA	---	---
DMEPA			
EA	NA	---	---
Microbiology	NA	---	---

## The Chemistry Review for NDA 202439

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

NDA 202439 has been reviewed for the chemistry, manufacturing, and controls section. An information request letter was sent to the sponsor on June 12, 2011. The approval of this NDA will be determined when the agency receives the IR response from the sponsor. Office of compliance has determined the drug substance, drug product and packaging facilities are adequate. Pre-approval inspections for the drug substance, drug product and packaging sites are not needed based on profile.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

NDA 202439 is filed for Xarelto™ (rivaroxaban) 15mg and 20mg immediate release tablets for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Rivaroxaban is claimed to be a potent and highly selective Factor Xa inhibitor. FXa directly converts prothrombin to thrombin through the prothrombinase complex and ultimately leads to fibrin clot formation and activation of platelets by thrombin. Selective inhibition of FXa can terminate the amplified burst of thrombin generation. NDA 22406 was filed to Division of Hematology (DHP) in 2008 for rivaroxaban 10mg tablet for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. The drug substance information is referenced in DMF 21581. NDA 202439 also referenced DMF 21581 for details of the characterization, manufacturing and testing of rivaroxaban drug substance.

##### Drug Product

The drug product for NDA 202439 is film coated immediate release tablets available in two strengths, 15 mg and 20 mg. The recommended dose for patients with creatinine clearance  $\geq 50$  mL/min is 20 mg orally, once daily with food. For patients with creatinine clearance between 30 to 50 mL/min, the recommended dose is 15 mg orally, once daily with food. The

## Chemistry Review Section

15 and 20 mg strengths are distinguished by shape, color and markings. Each tablet has the same core weight of (b) (4). The composition of the rivaroxaban tablet include micronized rivaroxaban drug substance, microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and opadry red/or opadry dark red film coat. All the excipients used in the core tablet formulation are standard compendial excipients. The commercial film coating powders are non-compendial but they are composed of compendial ingredients. Formulation development of the rivaroxaban 15 and 20 mg tablets was performed by Bayer Schering Pharma AG, based on the development done for the 10 mg tablet at pilot scale for NDA 22406. The basic steps in the manufacturing process consist of (b) (4).

The manufacturing process was optimized using DOE to establish the range of manufacturing process parameters. Standard specifications for solid oral dosage forms have been proposed. No new degradation products have been observed in the drug product. The product will be commercialized in 30 mL, 75 mL and 160 mL HDPE bottles with child resistant closures and induction seals as well as 10-mil (b) (4) blisters. Primary stability studies have been performed on pilot scale batches packaged in bottles and on commercial scale batches packaged in blisters. The primary stability studies in bottles were conducted on 3 batches of each strength using a bracketing approach for bottle configurations. The 3 batches of each strength were packaged in each of 2 extreme bottle configurations 45 mL bottle with 340 tablets and 150 mL bottles with 6 tablets. 36 months of stability data are available for these batches stored at 25°C/60% RH and 30°C/75% RH and 6 months of data are available at 40°C/75% RH. For blisters, 9 months of data at 25°C/60% RH and 30°C/65% RH are available and 6 months of data at 40°C/75% RH have been submitted. An expiration dating period of 36 months is granted for the bottle. An expiration dating for the blister configurations will be determined in the second review.

### Drug Substance

Rivaroxaban is a synthetic small molecule of molecular weight 435.89. It is a non-hygroscopic, white to yellowish white powder which is practically insoluble in water, 0.1N hydrochloric acid, and aqueous buffer solutions. It is slightly soluble in methanol, acetonitrile, acetone, and dichloromethane. According to BCS classification system, it is considered a class 2 compound with low solubility and high permeability. It has one stereogenic center and is synthesized as a single enantiomer. In order to improve bioavailability, the drug substance is micronized.

(b) (4)  
The firm selected the (b) (4) most stable form (Mod. I) for development and this form is controlled in batch release testing using Raman spectroscopy. Details of the characterization, manufacturing and testing including stability testing are provided in DMF 21581. This DMF has been originally reviewed by Josephine Jee on 4/09/2009 and found to be inadequate to support NDA 22406. The DMF holder has responded to the deficiencies identified in the review and the responses have been evaluated by Joyce Critch in Branch II. DMF 21581 is found to be adequate in the second review cycle.

## Chemistry Review Section

**B. Description of How the Drug Product is Intended to be Used**

For patients with creatinine clearance  $\geq 50$  mL/min: 20 mg orally, once daily with food. For patients with creatinine clearance 30 to  $< 50$  mL/min: 15 mg orally, once daily with food.

**C. Basis for Approvability or Not-Approval Recommendation**

The approval of this NDA will be determined when the agency receives the IR response from the sponsor.

**II. Administrative****A. Reviewer's Signature**

Pei-I Chu, Ph.D.

**Endorsement Block**

Chemist Name:	Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Kasturi Srinivasachar, Ph.D.
Chemistry Branch Chief :	Ramesh Sood, Ph.D.
Chemistry Project Manager :	Tu-Van Lambert

**C. CC Block**

Orig. NDA-202439

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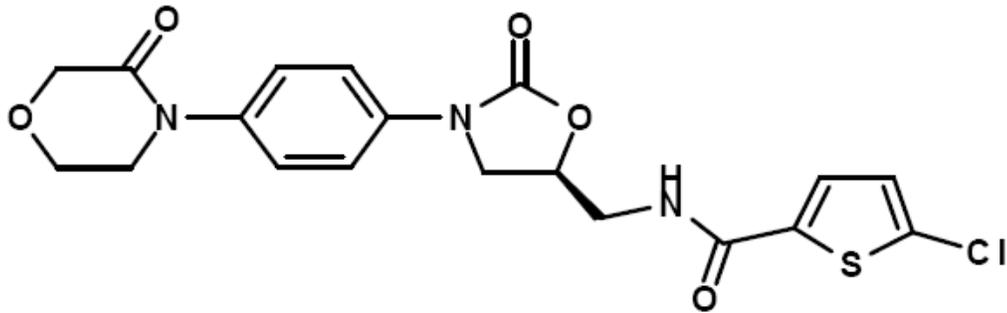
/s/  
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PEI-I CHU  
06/27/2011

RAMESH K SOOD  
06/27/2011

Initial Quality Assessment  
Branch I

**OND Division:** Division of Cardiovascular and Renal Products  
**NDA:** 202439  
**Applicant:** Johnson & Johnson Pharm. Research & Development  
**Letter Date:** Jan 05, 2011  
**Stamp Date:** Jan 05, 2011  
**PDUFA Date:** Nov 05, 2011  
**Tradename:** Xarelto  
**Established Name:** Rivaroxaban  
**Dosage Form:** Tablets, 15 and 20 mg  
**Route of Administration:** Oral  
**Indication:** Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation  
**Assessed by:** Kasturi Srinivasachar  
**ONDQA Fileability:** Yes



## Summary

This is an e-CTD 505(b)(1) NDA application for a NME, rivaroxaban. Rivaroxaban is claimed to be a potent and highly selective Factor Xa inhibitor. An NDA (22406) for rivaroxaban for a different indication (DVT and PE) was submitted to DHP in 2008 and received a CR letter which included CMC deficiencies. This NDA has been resubmitted to DHP on Dec. 30, 2010 with responses to these deficiencies. The drug substance information for both NDAs is the same and cross-referenced to DMF 21581. The drug product for NDA 22406 is a 10 mg tablet whereas for NDA 202439 two strengths, 15 and 20 mg tablets, are proposed. The majority of the drug product information for NDA 22406 was submitted in two DMFs 21580 and 21592. In contrast, drug product information for NDA 202439 has been submitted in the application and the above DMFs are referenced only for the development work.

Clinical development of rivaroxaban was carried out under IND 75,238; however, there is another IND [REDACTED] (b) (4). Only one CMC specific meeting has been held with the sponsor of IND 75,238 in the form of a Pre-NDA teleconference on April 21, 2010. The attendees included the review team from DHP in view of their prior experience with rivaroxaban. Most of the discussion revolved around the stability plans for the drug product the bracketing design, the submission of updates to the stability data for the blister package configuration during the review cycle and the leveraging of some stability data from bottles to blisters for the purpose of assigning an expiration date. J& J were told that it is expected that at least 12 months' data will be available at the time of NDA submission for blisters in order to support a commercially viable expiry date. Regarding Biopharmaceutics, the sponsor enquired if an in-vitro demonstration of pilot versus commercial scale product equivalence would obviate the need for a bioequivalency study for the 15 and 20 mg strengths. The Agency responded that this approach seemed feasible but would depend on the acceptability of the proposed dissolution methodology during NDA review. The sponsor was asked to formally request a biowaiver in the NDA submission.

## Drug Substance

Rivaroxaban is a synthetic small molecule of molecular weight 435.89. It is a non-hygroscopic, white to yellowish white powder which is practically insoluble in water. It has one stereogenic center and is synthesized as a single enantiomer. [REDACTED] (b) (4)

[REDACTED] The manufacturing process gives the [REDACTED] (b) (4) most stable form (Mod. I) and this is also routinely controlled in batch release testing using Raman Spectroscopy. Details of the characterization, manufacturing and testing including stability testing are provided in DMF 21581. This has been reviewed and found to be inadequate to support NDA 22406. The DMF holder has responded to the deficiencies identified in the review and these will be evaluated by the reviewer assigned by Branch II to the resubmission of NDA 22406.

## Drug Product

The drug product for this NDA is film coated immediate release tablets available in two strengths, 15 mg and 20 mg. This is in contrast to NDA 22406 in DHP for the DVT and PE indications where only one strength of 10 mg was developed. The 15 and 20 mg strengths are distinguished by shape, color and markings. Standard compendial excipients are used in the

core tablet formulation. The amounts of the excipients for the two strengths are the same (b) (4)

The commercial film coating premix powders are non-compendial but are composed of compendial ingredients. Formulation development of the rivaroxaban 15 and 20 mg tablets was performed by Bayer Schering Pharma AG, based on the development done for the 10 mg tablet at pilot scale. All 3 strengths are similar in formulation with differences only in the ratio of drug substance to excipients. Information on the 10 mg film coated tablet formulation development is provided in the pharmaceutical development section of Bayer Schering's and J & J's drug product DMFs 21580 and 21592 respectively. Both these DMFs were considered inadequate to support NDA 22406. As part of the resubmission of the NDA, the responses to the deficiencies identified in these DMFs will be reviewed by the Branch II CMC reviewer. The manufacturing process development for rivaroxaban 15 and 20 mg tablets relies on the work done for the 10 mg tablets at both pilot and commercial scale as detailed in the two DMFs referenced above. The basic steps in the manufacturing process consist of (b) (4)

The Applicant has provided a detailed discussion of the unit operations of the commercial manufacturing process in section 3.2.P.2.3. (b) (4)

The manufacturing process was optimized using DoE to establish a robust manufacturing process for the 15 and 20 mg strengths. A set of proven acceptable range of operation parameters has been identified. A comparison of dissolution profiles of the 15 and 20 mg tablets manufactured at pilot and commercial scale in 5 different media show that f2 factors under all conditions are between 50 and 100 showing equivalence. The Applicant states that in-vivo bioequivalence studies are unnecessary.

Standard specifications for solid oral dosage forms have been proposed. No degradation products have been specified. Batch analysis results have been submitted for pilot scale and commercial scale batches. The product will be commercialized in 30 mL, 75 mL and 160 mL HDPE bottles with child resistant closures and induction seals as well as 10-mil blisters. (b) (4)

Primary stability studies have been performed on pilot scale batches packaged in bottles and on commercial scale batches packaged in blisters. In addition, confirmatory site-specific stability studies are being carried out on commercial scale batches packaged in bottles. The primary stability studies in bottles were conducted on 3 pilot scale batches of each strength using a bracketing approach for bottle configurations. The 3 batches of each strength were packaged in each of 2 extreme bottle configurations 45 mL bottle with 340 tablets and 150 mL bottles with 6 tablets. 36 months of data are available for these batches stored at 25°C/60% RH and 30°C/75% RH and 6 months of data are available at 40°C/75% RH. For blisters, 9 months of data are available at 25°C/60% RH and 30°C/65% RH and 6 months of data have been submitted for storage at 40°C/75% RH. The confirmatory site-specific stability studies in bottles have been initiated. An expiration dating period of 36 months is proposed for both bottle and blister configurations.

## Critical Review Issues

### Drug Substance

- Review #1 of DMF 21581 concluded that it was inadequate to support NDA 22406. The DMF holder has amended the DMF with responses to the deficiencies identified. Since the same DMF is referenced for NDA 202439, it should be confirmed whether it is now adequate.
- (b) (4) starting materials have structural alerts for genotoxicity, however, there is no discussion of this issue in Review #1. Although it is unlikely that the drug substance would contain residual amounts of these compounds above the TTC given the number of intervening synthetic steps, the DMF holder's justification for not including these impurities in the drug substance specification needs to be critically evaluated and discussed with the reviewer of NDA 22406.

### Drug Product

- DMFs 21580 and 21592 have an inadequate status. The DMF holders have amended these DMFs with responses to the deficiencies identified. Since these DMFs are also referenced for NDA 202439, it should be confirmed whether they are now adequate with no pending issues.
- ONDQA Biopharmaceutics: The in-vitro dissolution profiles used to demonstrate equivalence of 15 and 20 mg tablets manufactured at pilot and commercial scale should be reviewed and the Applicant's claim that an in-vivo bioequivalence study is unnecessary evaluated. It should be noted that the proposed dissolution method for the 15 and 20 mg strengths uses a medium of pH 4.5 acetate buffer with 0.4% SDS whereas for the 10 mg strength only 0.2% SDS was used. Is this increase in surfactant level justified? Is the acceptance criterion of Q (b) (4) justified?
- The detailed manufacturing process development for the 15 and 20 mg strengths of rivaroxaban in Sec 3.2.P.2.3 should be critically evaluated including the multivariate DoEs for various unit operations and the proven acceptable ranges established for operating parameters.
- (b) (4)
- The postapproval stability commitment for the first three commercial batches of drug product is for long term storage conditions and does not include accelerated conditions. Is this acceptable? Note that primary commercial scale stability studies in blisters and site-specific commercial scale studies in bottles have been performed at accelerated conditions.
- Can a 36 month shelf-life be granted for the blister configuration based on 9 months' primary data, statistical analysis and other supportive data from batches stored in open containers at thermal and hydrolytic stress conditions?

**Comments and Recommendations**

The application is fileable. Facilities have been entered into EES and an overall recommendation of “Acceptable” has already been issued by the Office of Compliance. A single reviewer is recommended since the review will involve only the drug product.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead

Jan 28, 2011  
Date

Ramesh Sood, Ph.D.  
Branch Chief

Jan 28, 2011  
Date

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

**NDA Number: 202439**

**Applicant: J & J Pharmaceutical Stamp Date: 05-Jan. 2011**  
**Research and Development,**  
**L.L.C.**

**Established/Proper Name:**  
**Rivaroxaban/XARELTO**

**NDA Type: 1 (NME)**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		Looks to be in standard eCTD format.
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		Overall "Acceptable" recommendation by Office of Compliance on Jan 12, 2011
6	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion is requested.
7	Does the section contain controls for the drug substance?	X		Full details in DMF 21581
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		DP expiration dating proposed 36 mos. for all strength/pkg configurations
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		

13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		Section 3.2.R.
15	Is a separate microbiological section included?		X	Solid oral dosage form. See section 3.2.P.2.5
16	Have all DMF references been identified?	X		DMF 21581 for Drug Substance DMFs 21580 and 21592 for Drug Product Packaging DMFs see Sec. 1.4.2

**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?     Yes**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter:  
**None identified so far.**

Kasturi Srinivasachar  
Product Quality Reviewer

28-Jan 2011  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KASTURI SRINIVASACHAR  
01/31/2011

RAMESH K SOOD  
01/31/2011