CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

CHEMISTRY REVIEW(S)

Attachment 1: Acceptable Facility Inspection

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22406/000	**Sponsor:**	JOHNSON AND JOHNSON
Org. Code:	161		920 US HWY 202 SOUTH
Priority:	1S		RARITAN, NJ 088690602
Stamp Date:	28-JUL-2008	**Brand Name:**	XARELTO (RIVAROXABAN) ORAL 10 MG
PDUFA Date:	03-JUL-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	RIVAROXABAN
District Goal:	04-MAY-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET, FILM COATED; RIVAROXABAN; 10MG

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	J. CRICH	Review Chemist	301-796-3882
	J. BROWN	Team Leader	301-796-1652

Overall Recommendation:	ACCEPTABLE	(b) (4)	by A. INYARD	()
	ACCEPTABLE	(b) (4)	by JOHNSONE	

Establishment:	**CFN:**	**FEI:** 3003229486	
	BAYER HEALTHCARE AG 217-233 FRIEDRICH-EBERT STRASSE WUPPERTAL, , GERMANY 42117		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE PACKAGER DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-JAN-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON FILE REVIEW BASED ON PROFILE		

Continued on next page.

Attachment 1: Acceptable Facility Inspection – Continued

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9610135 **FEI:** 3002806462		
	BAYER SCHERING PHARMA AG CHEMPARK LEVERKUSEN, , GERMANY		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER FINISHED DOSAGE MANUFACTURER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-JAN-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-JAN-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 2650104 **FEI:** 3002942061		
	JANSSEN ORTHO L.L.C. CARR # 933 KM 0.1 GURABO, PR 00778		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-APR-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 2242843 **FEI:** 2242843		
	ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS INC. 1125 TRENTON HARBOURTON RD TITUSVILLE, NJ 085601504		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	08-JUN-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Reference ID: 2959908

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/s/

JANICE T BROWN
06/14/2011

HARIPADA SARKER
06/14/2011

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

plication:	NDA 22406/000	**Sponsor:**	JOHNSON AND JOHNSON
l. Code:	161		920 US HWY 202 SOUTH
or:	1S		RARITAN, NJ 088690602
mp Date:	28-JUL-2008	**Brand Name:**	XARELTO (RIVAROXABAN) ORAL 10 MG
JFA Date:	03-JUL-2011	**Estab. Name:**	
ion Goal:		**Generic Name:**	RIVAROXABAN
trict Goal:	04-MAY-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET, FILM COATED; RIVAROXABAN; 10MG

A Contacts:	T. LAMBERT	Project Manager	301-796-4246
	J. CRICH	Review Chemist	301-796-3882
	J. BROWN	Team Leader	301-796-1652

erall Recommendation: ACCEPTABLE on (b) (4) by A. INYARD ()

ACCEPTABLE on (b) (4) by JOHNSONE

ablishment: **CFN:** **FEI:** 3003229486

BAYER HEALTHCARE AG
217-233 FRIEDRICH-EBERT STRASSE

WUPPERTAL, , GERMANY 42117

F No: **AADA:**

sponsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE STABILITY TESTER

file: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

t Milestone: OC RECOMMENDATION

estone Date: 12-JAN-2011

ision: ACCEPTABLE

ison: BASED ON FILE REVIEW
BASED ON PROFILE

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

ablishment: CFN: 9610135 FEI: 3002806462

BAYER SCHERING PHARMA AG
CHEMPARK

LEVERKUSEN, , GERMANY

F No: AADA:

sponsibilities: DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE MANUFACTURER

file: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE

t Milestone: OC RECOMMENDATION

estone Date: 12-JAN-2011

sion: ACCEPTABLE

son: BASED ON PROFILE

file: TABLETS, PROMPT RELEASE OAI Status: NONE

t Milestone: OC RECOMMENDATION

estone Date: 19-JAN-2011

sion: ACCEPTABLE

son: DISTRICT RECOMMENDATION

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ablishment: CFN: 2650104 FEI: 3002942061

JANSSEN ORTHO L.L.C.
CARR # 933 KM 0.1

GURABO, PR 00778

F No: AADA:

sponsibilities: FINISHED DOSAGE MANUFACTURER

file: TABLETS, PROMPT RELEASE OAI Status: NONE

t Milestone: OC RECOMMENDATION

estone Date: 06-APR-2011

sion: ACCEPTABLE

son: DISTRICT RECOMMENDATION

---

ablishment: CFN: 2242843 FEI: 2242843

ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS INC.
1125 TRENTON HARBOURTON RD

TITUSVILLE, NJ 085601504

F No: AADA:

sponsibilities: FINISHED DOSAGE STABILITY TESTER

file: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE

t Milestone: OC RECOMMENDATION

estone Date: 08-JUN-2011

sion: ACCEPTABLE

son: DISTRICT RECOMMENDATION

ONDQA Division Director's Memo

NDA 22-406, XARELTO™ (rivaroxaban) Tablets
10 mg, *immediate release, film-coated, tablets*
Date: 16-JUN-2010

Introduction

XARELTO™ (rivaroxaban) film coated immediate release tablets (10 mg) are indicated for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. Dose is once daily beginning after surgery once homeostasis has been established; not to exceed 35 days

Adminstrative: This is the second review cycle

On 27-MAY-2010, OND issued a Complete Response letter to the sponsor citing unresolved clinical, chemistry, manufacturing and controls (CMC), clinical pharmacology and labeling deficiencies that remained to be resolved before the application can be approved.

The sponsor submitted a complete response to the CR letter which was received 03-JAN-2011. Four additional CMC amendments and one labeling amendment to this response were also reviewed as received between 28-APR-2011 and 21-MAY-2011. Also, three DMFs were reviewed and found adequate as; one for the drug substance (Bayer Healthcare) and two for the drug product (Bayer Healthcare and Janssen-Ortho).

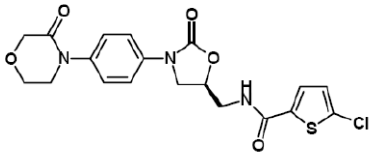
An overall acceptable recommendation was received from the Office of Compliance on 08-JUN-2011. The ONDQA Biopharm consult was acceptable on 02-MAY-2011 **(dissolution criterion of Q (b) (4) in 15 minutes approved)..**

No recommendations for any Phase 4 commitments are being made by ONDQA.

ONDQA recommends approval .

Drug Substance: Rivaroxaban

5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-moholinyl)phenyl]-l,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide



Molecular Formula: $C_{19}H_{18}ClN_3O_5S$ M.W.: 435.89

The drug substance is manufactured, tested and packaged by Bayer Schering Pharma.

The CMC information for Rivaroxaban drug substance is found in DMF 21581. This DMF was previously found to be **in**adequate to support NDA 22406. Refer to Chemistry Review #1 dated 12-MAY-2009. The DMF holder has adequately addressed all outstanding deficiencies

Drug Product: XARELTO, Film Coated, Immediate Release Tablets, 10 mg

The uncoated tablet core contains 10 mg of Rivaroxaban as the active pharmaceutical ingredient. The drug product is an immediate release formulation containing pharmaceutical excipients that are conventional in nature and consists of microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink (b) (4), a proprietary film-coating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

XARELTO™ Tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side and are supplied in 75 ml HDPE bottles of 30 tablets (NDC 50458-580-30) and in unit dose (10 mil (b) (4)) blister packs of 10 tablets/strip, 10 strips per carton container (NDC 50458-580-10). XARELTO™ Tablets (Rivaroxaban Film-Coated Tablets) are manufactured by Schering Pharma under DMF 21581 and Janssen Ortho Pharmaceutical under DMF 21592.

The approved expiry is 30 months in the HDPE bottles and 18 months in the (b) (4) blisters when stored at USP controlled room temperature.

ONDQA recommends approval.

Richard (Rik) Lostritto, Ph.D., Director
ONDQA Division I.

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/s/

RICHARD T LOSTRITTO
06/16/2011

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: NDA 22-406

DATE: 14-Jun-2011

FROM: Janice Brown, CMC Lead, DNDQA1/ONDQA

THROUGH: Richard Lostritto, Ph.D. Director, DNDQA1/ONDQA

SUBJECT: Final CMC recommendation for NDA 22-406

BACKGROUND

This New Drug Application (NDA 22-406, new molecular entity) is for an immediate release 10-mg oral tablet of Rivaroxaban (XARELTO) for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery filed July 29th, 2008, by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. on behalf of Ortho- McNeil-Janssen-Pharmaceuticals, Inc. This is the second review cycle for this application.

On May 27, 2010 the Division issued a Complete Response letter to the sponsor citing unresolved clinical, chemistry, manufacturing and controls (CMC), clinical pharmacology and labeling deficiencies that remained to be resolved before the product can be approved. Please see the May 12, 2009 Product Quality Review by Josephine Jee, Ph.D. for a complete summary of the CMC deficiencies. The sponsor submitted a complete response to the CR letter on December 30, 2010 (received on January 03, 2011).

CHEMISTRY, MANUFACTURING AND CONTROL (CMC)

1. Product Quality Review - Product Quality Review of the resubmission was completed by Joyce Crich, Ph.D. (May 12, 2011). The resubmission included responses to deficiencies for three DMF's; Bayer DMF 21580 for rivaroxaban 10 mg drug product, Bayer DMF 21581 for rivaroxaban drug substance, and J&J DMF 21592 for rivaroxaban 10 mg drug product. The NDA also included updated drug substance and drug product information in module 3. The CMC review of information in the resubmission concluded that all deficiencies were resolved and recommended approval of the NDA, pending an acceptable facility recommendation.

   The Office of Compliance has given an overall acceptable recommendation for the facilities on 08-Jun-2011 (see CMC review #3).

No recommendations on Phase 4 commitments were made.

2. Microbiology - The amendment dated May 1, 2009 to DMF 21581 was acceptable from a product quality microbiology standpoint (see comment dated February 14, 2011).

3. ONDQA Biopharmaceutics - Review of the resubmission was completed by Tapash K. Ghosh, Ph.D. (May 02, 2011). The applicant agreed to the dissolution specification of Q = (b) (4) in 15 minutes for both Bayer and Johnson & Johnson-manufactured rivaroxaban 10 mg drug product, using the dissolution methodology described in the dossier.

FINAL CMC RECOMMENDATION

From a CMC perspective, approval of NDA 22-406 is recommended. The action letter should include the following statement: "A 30 month shelf life for the drug product in HDPE bottles and a 18 month shelf life for the drug product in blisters, when stored at 20°-25°C (68°F - 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature] is granted."

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/s/

JANICE T BROWN
06/15/2011

RICHARD T LOSTRITTO
06/16/2011

NDA 22-406

CMC Review # 3

XARELTO (rivaroxaban) Tablets

Johnson & Johnson Pharmaceutical Research & Development. L.L.C.

Janice Brown, CMC Lead
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

The Chemistry Review for NDA 22-406

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Compliance has given an overall acceptable recommendation for the facilities on 08-Jun-2011 (see attachment 1). CMC agrees with the DMEPA labeling recommendations.

From a CMC standpoint, this NDA is recommended for approval.

As noted in CMC review #2, the shelf life for the HDPE bottles and blisters should be included in the action letter.

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

None

Attachment 1: Acceptable Facility Inspection

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22406/000	**Sponsor:**	JOHNSON AND JOHNSON
Org. Code:	161		920 US HWY 202 SOUTH
Priority:	1S		RARITAN, NJ 088690602
Stamp Date:	28-JUL-2008	**Brand Name:**	XARELTO (RIVAROXABAN) ORAL 10 MG
PDUFA Date:	03-JUL-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	RIVAROXABAN
District Goal:	04-MAY-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET, FILM COATED; RIVAROXABAN; 10MG

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	J. CRICH	Review Chemist	301-796-3882
	J. BROWN	Team Leader	301-796-1652

Overall Recommendation:	ACCEPTABLE	on 08-JUN-2011	by A. INYARD	()
	ACCEPTABLE	on 26-MAY-2009	by JOHNSONE	

Establishment:	**CFN:**	**FEI:** 3003229486	
	BAYER HEALTHCARE AG 217-233 FRIEDRICH-EBERT STRASSE WUPPERTAL, , GERMANY 42117		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE PACKAGER DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-JAN-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON FILE REVIEW BASED ON PROFILE		

Continued on next page.

Attachment 1: Acceptable Facility Inspection – Continued

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9610135 **FEI:** 3002806462

BAYER SCHERING PHARMA AG
CHEMPARK

LEVERKUSEN, , GERMANY

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE MANUFACTURER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-JAN-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JAN-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 2650104 **FEI:** 3002942061

JANSSEN ORTHO L.L.C.
CARR # 933 KM 0.1

GURABO, PR 00778

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-APR-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 2242843 **FEI:** 2242843

ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS INC.
1125 TRENTON HARBOURTON RD

TITUSVILLE, NJ 085601504

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-JUN-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 2959908

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/s/

JANICE T BROWN
06/14/2011

HARIPADA SARKER
06/14/2011

NDA 22-406

CMC Review # 2

XARELTO ™ (rivaroxaban) Tablets

Johnson & Johnson Pharmaceutical
Research & Development. L.L.C.

Joyce Z Crich, Ph.D

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

CMC REVIEW OF NDA 22-406
For the Division of Hematology Products, OODP/CDER

Table of Contents

CMC Review Data Sheet **5**

The Executive Summary **9**

I. Recommendations 9

A. Recommendation and Conclusion on Approvability 9

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 9

II. Summary of CMC Assessments 9

A. Description of the Drug Product(s) and Drug Substance(s) 9

B. Description of How the Drug Product is Intended to be Used 12

C. Basis for Approvability or Not-Approval Recommendation 12

III. Administrative 12

CMC Assessment **14**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 14

S. DRUG SUBSTANCE 14

S.1 General Information ..... **Error! Bookmark not defined.**

S.1.1 Nomenclature 14

S.1.2 Structure 15

S 1.3 General Properties 15

S.2 Manufacture 17

S.2.1 Manufacturers ..... **Error! Bookmark not defined.**

S.2.2 Description of Manufacturing Process and Process Controls ..... **Error! Bookmark not defined.**

S.2.3 Control of Materials ..... **Error! Bookmark not defined.**

S.2.4 Controls of Critical Steps and Intermediates ..... **Error! Bookmark not defined.**

S.2.5 Process Validation and/or Evaluation ..... **Error! Bookmark not defined.**

S.2.6 Manufacturing Process Development ..... **Error! Bookmark not defined.**

S.3 Characterization 17

S.3.1 Elucidation of Structure and other Characteristics ..... **Error! Bookmark not defined.**

S.3.2 Impurities ..... **Error! Bookmark not defined.**

S.4 Control of Drug Substance 17

S.4.1 Specification ..... **Error! Bookmark not defined.**

S.4.2 Analytical Procedures ..... **Error! Bookmark not defined.**

S.4.3 Validation of Analytical Procedures ..... **Error! Bookmark not defined.**

S.4.4 Batch Analyses ..... **Error! Bookmark not defined.**

S.4.5 Justification of Specification ..... **Error! Bookmark not defined.**

S.5 Reference Standards or Materials 17

S.6 Container Closure System 17

S.7 Stability 17

S.7.1 Stability Summary and Conclusions ..... **Error! Bookmark not defined.**

S.7.2 Postapproval Stability Protocol and Stability Commitment ..... **Error! Bookmark not defined.**

S 7.3 Stability Data ..... **Error! Bookmark not defined.**

P. DRUG PRODUCT 18

Reference ID: 2954863

P.1 Description and Composition of the Drug Product 18
P.2 Pharmaceutical Development 18
P.2.1 Components of the Drug Product 18
P.2.1.1 Drug Substance 18
P.2.1.2 Excipients 18
P.2.2 Drug Product 19
P.2.2.1 Formulation Development 19
P.2.2.2 Overages 19
P.2.2.3 Physicochemical and Biological Properties 19
P.2.3 Manufacturing Process Development 20
P.2.4 Container Closure System 20
P.2.5 Microbiological Attributes 20
P.2.6 Compatibility 20
P.3 Manufacture 21
P.3.1 Manufacturers Pending 21
P.3.2 Batch Formula 22
P.3.3 Description of Manufacturing Process and Process Controls 22
P.3.4 Controls of Critical Steps and Intermediates 22
P.3.5 Process Validation and/or Evaluation 22
P.4 Control of Excipients 23
P.4.1 Specifications 23
P.4.2 Analytical Procedures 23
P.4.3 Validation of Analytical Procedures 23
P.4.4 Justification of Specifications 24
P.4.5 Excipients of Human or Animal Origin 24
P.4.6 Novel Excipients 24
P.5 Control of Drug Product 24
P.5.1 Specification 24
P.5.2 Analytical Procedures 27
P.5.3 Validation of Analytical Procedures 27
P.5.4 Batch Analyses 27
P.5.5 Characterization of Impurities 27
P.5.6 Justification of Specification 27
P.6 Reference Standards or Materials 28
P.7 Container Closure System 28
P.7.1 System Description 28
P.7.2 Rationale to Selection of Package Components 29
P.7.3 Packaging System Suitability 29
P.7.3 Specifications and Methods 30
P.8 Stability 31
P.8.1 Stability Summary and Conclusion 32
P.8.2 Postapproval Stability Protocol and Stability Commitment 33
P.8.3 Stability Data 33

A. APPENDICES 37
A.1 Facilities and Equipment (biotech only) 37
A.2 Adventitious Agents Safety Evaluation 37
A.3 Novel Excipients 37

R. REGIONAL INFORMATION 37
R1 Executed Batch Records 37
R2 Comparability Protocols 37
R3 Methods Validation Package 37

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 38

A. Labeling & Package Insert 38

B. Environmental Assessment Or Claim Of Categorical Exclusion 42

C. Establishment Evaluation Report 42

Reference ID: 2954863

III. List Of Deficiencies Communicated and Resolved 42

Reference ID: 2954863

CMC Review Data Sheet

1. NDA # 22-406

2. REVIEW #: 2

3. REVIEW DATE: 29-MAY-2011

4. REVIEWER: Joyce Z Crich, Ph. D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review # 1	12-MAY-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Amendment (CMC information)	51	21-MAY-2009	21-MAY-2009
Resubmission/Cass 2	70	30-DEC-2010	03-JAN-2011
Amendment (Response to FDA 08-APR-2011 CMC IR-Biopharm/dissolution)	79	28-APR-2011	28-APR-2011
Amendment (Response to 13-APR-2011 EES IR, 21-APR-2011 LOA's IR)	80	04-May-2011	04-May-2011
Amendment (container and carton labeling)	82	10-MAY-2011	10-MAY-2011
Amendment (Response to 09-MAY-2011 telecon-Biopharm & update CMC info)	83	11-MAY-2011	11-MAY-2011
Amendment (Revised container and carton labeling)	N/A		

7. NAME & ADDRESS OF APPLICANT:

Name: Johnson & Johnson Pharmaceutical Research & Development. L.L.C.
Address: 920 U.S. Highway 202, P.O.Box 300, Raritan, NJ 00869-0602
Representative: Andrea F Kollath, DVM
Telephone: (9080 927-6522

8. DRUG PRODUCT NAME/CODE/TYPE:

Reference ID: 2954863

a) Proprietary Name: XARELTO™
b) Non-Proprietary Name: rivaroxaban
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

11. DOSAGE FORM: Tablet (Immediate Release Tablets)

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

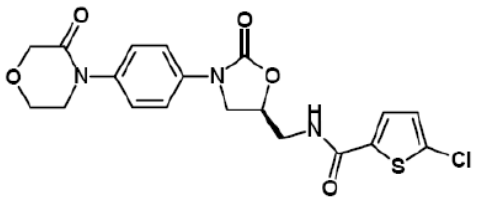
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-moholinyl)phenyl]-l,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide



Molecular Formula: $C_{19}H_{18}ClN_3O_5S$ M.W.: 435.89

Reference ID: 2954863

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF 21581	II	Bayer Healthcare	Rivaroxaban Drug Substance	1	Adequate	27-MAY-2011	Reviewed by Joyce Crich
DMF 21592	II	Janssen Ortho, L.L.C	Rivaroxaban Tablets	1	Adequate	01-JUN-2011	Reviewed by Joyce Crich
DMF 21580	II	Bayer Healthcare	Rivaroxaban Tablets	1	Adequate	01-JUN-2011	Reviewed by Joyce Crich

[1] Action codes for DMF Table:
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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,892	BAY 59-7939 Tablets Bayer Corporation
DMF	21592	Rivaroxaban Tablets Janssen Ortho, L.L.C
DMF	21581	Rivaroxaban Drug Substance Bayer Healthcare
DMF	21580	Rivaroxaban Tablets Bayer Healthcare

Reference ID: 2954863

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending as of the date of this review		Shawnte Adams
Pharm/Tox	Approval	12-MAY-2009	Yash Chopra, Ph. D
Biopharm	Acceptable for Dissolution and Bioavail/Bioequiv.	02-MAY-2011	Tapash Ghosh, Ph.D
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA*	Review of C/C labels pending (see 12-MAY-2011 review for proprietary name review)		
EA	Categorical exclusion granted	12-MAY-2009	Josephine Jee
Microbiology	N/A – solid dosage form		

*DMEPA: Division of Medication Error Prevention and Analysis

Reference ID: 2954863

The CMC Review for NDA 22-406

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this NDA is recommended for approval a 30 month shelf life for the drug product in HDPE bottles and a 18 month shelf life for the drug product in blisters, when stored at 20°-25°C (68°F - 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

The recommendation of Approval is pending an overall recommendation from Office of Compliance due to the pending inspection completion for Titusville site of J&J Ortho–McNeil-Janssen Pharmaceuticals, Inc.

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

None

II. Summary of CMC Assessments

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

This second-cycle CMC review addresses deficiencies in drug substance and drug product that were identified in the first-cycle review, as well as the labeling (PI/PPI and Container/Carton). All other information may be found in the Chemistry Review #1 dated 12-May-2009, by Josephine M Jee.

(1) Drug Substance

Rivaroxaban is a synthetic small molecule with one stereogenic center as pure (S) enantiomer. The chemical name for Rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1, 3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

Rivaroxaban has molecular weight 435.89 with a molecular formula as C19H18ClN3O5S. It is an odorless, non-hygroscopic, white to yellowish solid, practically insoluble in water. (b) (4) and aqueous buffer solutions, slightly soluble in (b) (4) acetone, (b) (4), macrogol 400 (polyethylene glycol) (b) (4) It is a class 2 compound with low solubility and high permeability

Reference ID: 2954863

based on BCS classification system. In order to improve bioavailability, the drug substance is micronized. [redacted] (b) (4) The [redacted] (b) (4) most stable form (Mod. I) was selected for development and is controlled in batch release testing using Raman spectroscopy.

The drug substance is manufactured, tested and packaged by Bayer Schering Pharma. The CMC information for Rivaroxaban is found in DMF 21581. An authorization from Bayer Schering Pharma dated 23-DEC-2010 is provided in NDA 22-406.

DMF 21581 was reviewed by Josephine Jee in the first-cycle review, and was found to be inadequate to support NDA 22406. Refer to Chemistry Review #1 dated 12-MAY-2009 (in DARRTS). The DMF holder has adequately addressed deficiencies identified in the first-cycle review and in the second-cycle review which was completed by Dr. Joyce Crich. This DMF is currently adequate to support NDA 22406. Refer to DMF 21581 Chemistry Review # 2 dated 27-MAY-2011 by Dr. Joyce Crich.

(2) Drug Product

XARELTO™ Tablets are film-coated tablets, which are indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

XARELTO™ Tablets are available as 10 mg film-coated tablets. The tablet core contains 10 mg of Rivaroxaban as the active pharmaceutical ingredient. The drug product is an immediate release formulation containing pharmaceutical excipients that are conventional in nature and consists of microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink [redacted] (b) (4), a proprietary film-coating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

XARELTO™ Tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a “10” on one side, and an “Xa” on the other side and are supplied in 75 ml HDPE bottles of 30 tablets (NDC 50458-580-30) and in unit dose (10 mil [redacted] (b) (4)) blister packs of 10 tablets/strip, 10 strips per carton container (NDC 50458-580-10). XARELTO™ Tablets (Rivaroxaban Film-Coated Tablets) are manufactured by Schering Pharma under DMF 21581 and Janssen Ortho Pharmaceutical under DMF 21592. Authorization letters from Bayer Schering Pharma dated 23-DEC-2010 and Janssen Pharmaceuticals dated 08-DEC-2010 are included in NDA 22-406.

Formulation development of Rivaroxaban 10 mg tablets was performed by Bayer Schering Pharma AG, the DMF 21580 holder. [redacted] (b) (4)

Reference ID: 2954863

Standard release and shelf life specifications for solid oral dosage forms have been proposed which are identical for both DMFs. Bayer-manufactured product would only be provided to J&J as bulk drug product, then be packaged and released for US market by J&J. The site of J&J Janssen Ortho at Gurabo, Puerto also manufactures drug product, besides the responsibility of packaging, labeling, and release testing.

Bayer Schering Pharma submitted batch analyses for seven (7) pilot-scaled batches [redacted] (b) (4) of Rivaroxaban film-coated tablets. Up to 24 months at 25°C/60% RH and 24 months at 30°C/75% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data were submitted for the 6 batches of drug product contained in different size of HDPE bottles [redacted] (b) (4) 3 batches of drug product in blister packs (12 months at 25°C/60% RH, 6 months at 40°C/75% RH) and 1 batch [redacted] (b) (4) (24 months at 25°C/60% RH and at 30°C/75% RH, 6 months at 40°C/75% RH). The stability data obtained from all batches tested by Bayer Schering Pharma conform to the Rivaroxaban Film-Coated Tablets specification at 25°C/60% RH for up to 24 months, at 30°C/70% RH for up to 24 months storage. The submitted stability data support the proposed 30 months shelf-life for the Bayer's product packaged in HDPE bottles, and 18 months shelf-life for the Bayer's product packaged in [redacted] (b) (4) blisters.

Janssen Ortho Pharmaceuticals submitted batch analyses for three (3) commercial-scaled batches [redacted] (b) (4) of Rivaroxaban film-coated tablets. Up to 18 months at 25°C/60% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data were submitted for the 2 batches of drug product contained in HDPE bottles [redacted] (b) (4) and 1batch of drug product in blister packs. The stability data obtained from all batches tested by Janssen Ortho Pharm. conform to the Rivaroxaban Film-Coated Tablets specification at 25°C/60% RH for up to 18 months storage. However, the provided site-specific stability data from J&J Janssen Ortho lacks of test data for any unspecified degradation product after 3 months time point (though test for sum of all degradation products are available and meet the acceptance criterion for all the data point up to 18 months), it is difficult to predict the trend of any unspecified degradation product and its impact to the quality of drug product in blister packs manufactured by J&J Janssen Ortho after 18 months.

In addition to the provided all stability data from the primary, supportive stress studies, and site specific study, taking consideration based on (1) the [redacted] (b) (4) different packaging configurations and different sites; (2) the recommendation stated in the Agency's Memorandum of 14-MAY-2009, it is concluded that a 30 month expiration dating period for drug product, Rivaroxaban 10 mg film-coated tablets, packaged in HDPE bottles, and a 18 month expiration dating period for the same drug product packaged in [redacted] (b) (4) blisters, can be granted, when stored at 20°-25°C (68°F - 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F). Note: J & J PRD proposes a 30 month expiry for Rivaroxaban 10 mg film-coated tablets, packaged in both bottles and blisters.

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

XARELTO™ (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

The recommended dose of XARELTO™ is 10 mg taken orally once daily. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established. The duration of treatment depends on the individual risk of the patient for venous thromboembolism, which is determined by the type of orthopedic surgery. For patients undergoing hip replacement surgery, the treatment duration of 35 days is recommended. For patients undergoing knee replacement surgery, the treatment duration of 14 days is recommended.

The safety and effectiveness of using XARELTO™ beyond the recommended dose or treatment duration have not been established. Therefore, any use of doses of more than 10 mg of XARELTO™ once daily or treatment beyond 35 days is not recommended.

XARELTO™ tablets are 10 mg, round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side. This drug product is supplied as follows: NDC 50458-580-10: blister packs of 10 (unit dose) NDC 50458-580-30: bottles of 30 tablets. The recommended storage condition is at 20°-25°C (68°F - 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

There are no outstanding Chemistry, Manufacturing and Controls issues for this NDA and for the supporting DMFs (DMF 21581 for drug substance; DMF 21580 for Bayer's drug product; and DMF 21591 for J&J Janssen Ortho's drug product).

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Joyce Crich, Ph.D, Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Janice Brown, Ph.D., CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Reference ID: 2954863

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DFS

31 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2954863

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE Z CRICH
06/01/2011

SARAH P MIKSINSKI
06/02/2011

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22406/000
Org Code : 160
Priority : 1S

Sponsor: JOHNSON AND JOHNSON
920 US HWY 202
RARITAN, NJ 088690602

Stamp Date : 28-JUL-2008
PDUFA Date : 28-MAY-2009
Action Goal :
District Goal: 29-MAR-2009

Brand Name : XARELTO (RIVAROXABAN) ORAL 10 MG
Estab. Name:
Generic Name: RIVAROXABAN
Dosage Form: (TABLET)
Strength : 10 MG

FDA Contacts:			
	D. LEAMAN	Project Manager	301-796-1424
	J. JEE	Review Chemist	301-796-1375
	S. POPE	Team Leader	301-796-1436

Overall Recommendation: ACCEPTABLE on 26-MAY-2009by E. JOHNSON(HFD-320) 301-796-3334

Establishment : CFN : 9610135 FEI : 3002806462
BAYER AG
D 51368
LEVERKUSEN, , GM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE MANUFACTURER

Profile : CTX OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-SEP-08

Decision : ACCEPTABLE

Reason : BASED ON FILE REVIEW

Profile : TGM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-MAR-09

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

BAYER HEALTHCARE AG

217-233 FRIEDRICH-EBERT STRASSE

WUPPERTAL, , GM 42117

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-MAY-09

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2650104 FEI : 3002942061

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

JANSSEN ORTHO L.L.C.

CARR # 933 KM 0.1

GURABO, PR 007789626

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-SEP-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2211100 FEI : 2211100

ORTHO-MCNEIL PHARMACEUTICAL, INC.

1000 US HIGHWAY 202

RARITAN, NJ 088691425

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-SEP-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 2242843 FEI : 2242843

ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS INC.

1125 TRENTON HARBOURTON RD

TITUSVILLE, NJ 085601504

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTX OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-SEP-08

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22406/000	Action Goal:	
Stamp:	28-JUL-2008	District Goal:	29-MAR-2009
Regulatory Due:	28-MAY-2009	Brand Name:	XARELTO (RIVAROXABAN)
Applicant:	JOHNSON AND JOHNSON	Estab. Name:	ORAL 10 MG
	920 US HWY 202	Generic Name:	RIVAROXABAN
	RARITAN, NJ 088690602		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	160	Strength:	10 MG

Application Comment: BAYER AG AT [redacted] (b)(4) AN -

MANUFACTURER OF DS (on 26-MAR-2009 by J. JEE () 301-796-1375)

FDA Contacts:	D. LEAMAN	301-796-1424	, Project Manager
	J. JEE	301-796-1375	, Review Chemist
	S. POPE	301-796-1436	, Team Leader

Overall Recommendation: ACCEPTABLE on 26-MAY-2009by E. JOHNSON(HFD-320) 301-796-3334

Establishment: CFN 9610135 FEI 3002806462

BAYER AG

D 51368

LEVERKUSEN, , GM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE MANUFACTURER

Profile: CTX OAI Status: NONE

Estab. Comment: SITE ALSO PERFORMS [redacted] (b)(4) (CSN
)

EES WILL NOT ALLOW DATA ENTRY--C CRUZ IS AWARE VIA PHONE CO
NVERSATION

WITH M FOLKENDT AND D MESMER

SITE ALSO PERFORMS RELEASE TESTING AND STABILITY TESTING DS
ROFILE

CTX) (on [redacted] (b)(4) by S. GOLDIE () 301-796-2055)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
SUBMITTED TO OC JEE	[redacted] (b)(4)			
OC RECOMMENDATION ADAMSS	[redacted] (b)(4)			ACCEPTABLE BASED ON FILE REVIEW

Profile: TCM OAI Status: NONE

EMilestone Name Creator	Date	Type	Insp. Date	Decision & Reason

---

SUBMITTED TO OC GOLDIES	(b) (4)			
SUBMITTED TO DO STOCKM	(b) (4)	PS		
DO RECOMMENDATION JOHNSONE	(b) (4)			ACCEPTABLE
				BASED ON FILE REVIEW
OC RECOMMENDATION STOCKM	(b) (4)			ACCEPTABLE
				DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN FEI

BAYER HEALTHCARE AG

217-233 FRIEDRICH-EBERT STRASSE

WUPPERTAL, , GM 42117

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: DMF 21581

BAYER HEALTHCARE AG IN [redacted] (b)(4)
ROXABAN

[redacted] . ALSO PERFORMS QUALITY CO
NTROL

TESTING ,STABILITY STORAGE AND TESTING, RELEASE TESTING, AN
D PACKAGING

FOR DRUG SUBSTANCE. (on [redacted] (b)(4) by D. MESMER (HFD-800)
301-796-

4023)

lestone Name	Date	Type	Insp. Date	Decision & Reason
Creator				

SUBMITTED TO OC [redacted] (b) (4)
MESMERD

SUBMITTED TO DO [redacted] (b) (4) PS
STOCKM

ASSIGNED INSPECTION T ([redacted] (b) (4)) PS
JOHNSONE

INSPECTION PERFORMED [redacted] (b) (4) [redacted] (b) (4)
JOHNSONE

DO RECOMMENDATION [redacted] (b) (4) ACCEPTABLE
JOHNSONE

INSPECTION

OC RECOMMENDATION [redacted] (b) (4) ACCEPTABLE
JOHNSONE

DISTRICT RECOMMENDATI
ON

Establishment: CFN 2650104 FEI 3002942061

JANSSEN ORTHO L.L.C.

CARR # 933 KM 0.1

GURABO, PR 007789626

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason
Creator				

SUBMITTED TO OC [redacted] (b) (4)
JEE

SUBMITTED TO DO [redacted] (b) (4) PS
FERGUSONS

DO RECOMMENDATION [redacted] (b) (4) ACCEPTABLE
RHERNAND

BASED ON FILE REVIEW

ACCEPTABLE RECOMMENDATION BASED ON FIRM PREVIOUS INSPECTION RESULTS ([redacted] (b) (4) VAI)

OC RECOMMENDATION [redacted] (b) (4) ACCEPTABLE
FERGUSONS

DISTRICT RECOMMENDATI
ON

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN 2211100 FEI 2211100

ORTHO-MCNEIL PHARMACEUTICAL, INC.

1000 US HIGHWAY 202

RARITAN, NJ 088691425

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

Estab. Comment: BAYER HEALTHCARE AG- [redacted] (b) (4)
OF THE DS.

(on [redacted] (b) (4) by J. JEE () 301-796-1375)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
SUBMITTED TO OC JEE	[redacted] (b) (4)			
OC RECOMMENDATION FERGUSONS	[redacted] (b) (4)			ACCEPTABLE BASED ON PROFILE

Establishment: CFN 2242843 FEI 2242843

ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS INC.

1125 TRENTON HARBOURTON RD

TITUSVILLE, NJ 085601504

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTX OAI Status: NONE

EMilestone Name Creator	Date	Type	Insp. Date	Decision & Reason
SUBMITTED TO OC JEE	(b) (4)			
OC RECOMMENDATION FERGUSONS	(b) (4)			ACCEPTABLE BASED ON PROFILE

ONDQA Division Director's Memo
NDA 22-406, XARELTO (rivaroxaban) Tablets
Date: 13-MAY-2009

Introduction

XARELTO (rivaroxaban) is a selective factor Xa inhibitor with antithrombotic activity and is indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. The drug product is proposed to be provided as 10 mg film coated tablets.

The drug substance and drug product portions of the application contain outstanding deficiencies. All three cross-referenced DMFs for drug substance and drug product are likewise deficient.

The pre approval inspection process (via EES) has not been completed as of this date. Therefore, **it is recommended that no action be taken until an overall recommendation has been entered into the EES electronic database**. Once that is entered, a CR letter may be sent.

Adminstrative

The original submission of this 505(b)(1) NDA was received 29-JUL-2008 from Johnson & Johnson Pharmaceutical Research & Development, LLC. Amendments dated 24-NOV-2008 and 19-DEC-2008 were reviewed.

This NDA is unusual in that virtually all of the drug substance and drug product information was provided by DMF (21581 for drug substance, plus 21580 and 21592 for the drug product tablets).

The corresponding IND is 64,892.

There are outstanding CMC deficiencies and the pre-approval inspection process is not yet completed. Therefore, **it is recommended that no action be taken until an overall recommendation has been entered into the EES electronic database**. Once that is entered, a CR letter may be sent.

Drug Substance

Rivaroxaban ($C_{19}H_{18}ClN_3O_5S$, MW=435.89) synthetic molecule that is a white to yellowish solid that is practically insoluble in water, 0.1M HCl, and aqueous buffer solutions. It is slightly soluble in some organic solvents including (b) (6), acetone, (b) (6) The molecule has one chiral center, and the drug substance is as the pure (S) enantiomer.

The DMF for the drug substance is deficient in that insufficient information is provided to establish adequate nomenclature, description, physicochemical properties, specifications, and stability.

There are outstanding CMC deficiencies and the pre-approval inspection process is not yet completed. Therefore, **it is recommended that no action be taken until an overall recommendation has been entered into the EES electronic database**. Once that is entered, a CR letter may be sent.

Drug Product

The 10 mg film-coated tablet is conventional immediate release in nature; containing usual excipients, microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and sodium lauryl sulfate. The film coating is Opadry Pink (b) (4). The proposed packaging includes HDPE bottles of thirty tablets and unit dose blister packs of ten tablets per strip with ten strips per carton.

The DMFs which support the 10 mg film-coated drug product tablets are deficient in that specifications are inadequate for dose content uniformity (do not meet USP criteria), the dissolution specifications are inappropriate and vary by manufacturing site; stability data are missing, and portions of the label remain inadequate (e.g., drug product established name, how supplied tablet description, and use of inappropriate graphics on container/carton labels).

Also note that the proposed proprietary name of XARELTO contains as the first two characters "**XA**". This may be associated with its proposed action on Factor **Xa**. If the drug is ever considered for another action, this would be an inappropriate association. Likewise, it is not clear if proprietary names should be connected to pharmacological actions in this manner. It is recommended that the proprietary name be reexamined with this possibility in mind when the application is amended post action.

There are outstanding CMC deficiencies and the pre-approval inspection process is not yet completed. Therefore, **it is recommended that no action be taken until an overall recommendation has been entered into the EES electronic database**. Once that is entered, a CR letter may be sent.

Rik Lostritto, Ph.D., Director, ONDQA Division III

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Lostritto
5/13/2009 04:42:54 PM
CHEMIST

CMC REVIEW OF NDA 22-406

REVIEW # 1

XARELTO ™ (rivaroxaban) Tablets

Johnson & Johnson Pharmaceutical Research & Development. L.L.C.

JOSEPHINE M. JEE
CMC REVIEWER

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE (BRANCH V)

FOR THE DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **3**

The Executive Summary **6**

I. Recommendations 6

A. Recommendation and Conclusion on Approvability 6

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 6

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment **11**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 11

S DRUG SUBSTANCE [Name, Manufacturer] 15

P DRUG PRODUCT [Name, Dosage form] 17

A APPENDICES 29

R REGIONAL INFORMATION 29

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 29

A. Labeling & Package Insert 29

B. Environmental Assessment Or Claim Of Categorical Exclusion 32

III. List Of Deficiencies To Be Communicated 34

Chemistry Review Data Sheet

1. NDA 22-406
2. REVIEW: No.1

3. REVIEW DATE: 29-MAR-2009

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA	13-DEC-2007 (Priority Review Designation)
Pre-NDA CMC Mtg.	05-DEC-2005 EOP2 07-NOV-2007 (Preliminary Responses) 14-FEB-2008
NDA 22-406, Original	29-JUL-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-406	29-JUL-2008
NDA 22-406 – CMC Info. on DP	24-NOV-2008
NDA 22-406 - Response to IR Letter - CMC	19-DEC-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Johnson & Johnson Pharmaceutical Research & Development. **L.L.C.**
Address: 920 U.S. Highway 202, P.O.Box 300
Raritan, NJ 00869-0602

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: XARELTO™
b) Non-Proprietary Name (USAN): rivaroxaban

International Nonproprietary Name (INN): None provided.
c) Code Name/# (ONDC only): None provided
Internal Codes:

d) CAS Registry Number: None provided
e) CAS Name: None provided
e) Laboratory Codes: None provided. None provided
f) Chemical Name (IUPAC): None provided

g) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1

- Submission Priority: **S**

9. LEGAL BASIS FOR SUBMISSION: 505(b)

10. PHARMACOL. CATEGORY: Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

11. DOSAGE FORM: Tablet (Immediate Release Tablets)
12. STRENGTH/POTENCY: 10 mg

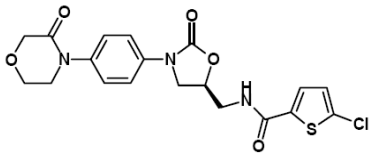
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product.

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

5-Chloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-moholinyl)phenyl]-l,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide



Molecular Formula: $C_{19}H_{18}ClN_3O_5S$ **M.W.**: 435.89

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF 21581	II	Bayer Healthcare	Rivaroxaban Drug Substance	1	Not Adequate	13-MAR-2009	Reviewed by J.Jee
DMF 21592	II	Janssen Ortho, L.L.C	Rivaroxaban Tablets	1	Not Adequate	23-MAR-2009	Reviewed by J.Jee
DMF 21580	II	Bayer Healthcare	Rivaroxaban Tablets	1	Not Adequate	26-MAR-2009	Review by J.Jee

[1] Action codes for DMF Table:
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")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,892	BAY 59-7939 Tablets Bayer Corporation
DMF	21592	Rivaroxaban Tablets Janssen Ortho, L.L.C
DMF	21581	Rivaroxaban Drug Substance Bayer Healthcare
DMF	21580	Rivaroxaban Tablets Bayer Healthcare

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	29-AUG-2008	S.Adams	Pending as of the date of this review.
Pharm/Tox	General PT review	Pending	Y. Chopra, Ph.D.	Pending
Biopharm	Dissolution and Bioavail/Bioequiv.	31-MAR-2009	T. Ghosh, Ph.D.	Recommended acceptance criterion for dissolution testing to Q= (b) (4) at 15 minutes using the currently proposed dissolution methodology
DMEPA	Labeling & Labels	29-JUL-2008	M. Safarik, PharmD	Pending
Methods Validation	N/A			
EA	Categorical Exclusion	N/A	J.Jee	Categorical exclusion granted (see attached review).
Microbiology	N/A			Solid dosage form – N/A.

The Chemistry Review for NDA 22-406

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application cannot be approved, until the following items are resolved:

- Submission of acceptable Package Insert labeling and container/carton labeling (see the four labeling deficiencies at end of section)
- Resolution of the deficiencies for DMF 21580 (Rivaroxaban Film-Coated Tablets, Bayer HealthCare Pharmaceuticals, Inc.)
- Resolution of the deficiencies for DMF 21581(Rivaroxaban Drug Substance, Bayer HealthCare Pharmaceuticals, Inc.)
- Resolution of the deficiencies for DMF 21592 (Rivaroxaban Film-Coated Tablets, Janssen Pharmaceuticals)
- An acceptable recommendation from the Office of Compliance (not received as of the date of this review)
- Resolution of the following deficiencies for NDA 22-406:

<u>Regarding rivaroxaban drug substance:</u>

1. The drug substance information is not adequate in that it does not meet 21 CFR 314.50 (d)(1)(ii). Insufficient information is provided to confirm nomenclature, description, physicochemical properties, specifications, the primary stability protocol, the post-approval stability commitment and primary stability data.

2. DMF 21-580 is currently inadequate to support this NDA (see above).

<u>Regarding rivaroxaban drug product:</u>

1. DMF 21-592 is currently inadequate to support this NDA (see above).

2. DMF 21-581 is currently inadequate to support this NDA (see above).

3. The drug product specification, as provided by Bayer HealthCare Pharmaceuticals, Inc. is inadequate because it does not propose analytical methods for test parameters Additionally, the proposed acceptance criteria for uniformity of dosage units do not meet the current USP requirements.

4. The proposed acceptance criteria for uniformity of dosage units and dissolution are different between Bayer HealthCare Pharmaceuticals and Janssen Ortho Pharmaceuticals. Justify this difference or alternatively, resolve the discrepancy.

5. The currently-proposed acceptance criterion for dissolution is not acceptable and is recommended to be Q (b) (4) at 15 minutes.

6. The container and closure system is not adequately described in the NDA.

7. The proposed stability study is inadequate in that no stability data are submitted for pilot or commercial batches. In addition, a postapproval stability protocol and stability commitment were not submitted for Bayer Pharmaceuticals, Inc.

The following comments are outstanding regarding the drug product labels:

1. Provide more specific description (e.g., color, shape, size, resin) for bottles used as containers (NDC 50458-580-30) in the How Supplied section. In addition, include the carton, as a container for (b) (4) dose blister packs, description in the How Supplied Section (section 16) of the package insert labeling.

2. Revise the established name to include the dosage form Xarelto™(rivaroxaban) Tablets" in the bottle label.

3. The size of the graphic on the principal display panel is more prominent than the size of the established name and proprietary name. The proprietary name, established name and strength should be the most prominent information on the bottle label.

4. Delete or relocate the statement (b) (4) as it crowds the bottle label.

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

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

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

Drug Product:

XARELTO™ Tablets are film-coated tablets, that are indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

XARELTO™ Tablets are available as 10 mg film-coated tablets. The tablet core contains 10 mg of rivaroxaban as the active pharmaceutical ingredient. XARELTO™ Tablets are packaged in HDPE bottles that contain 30 tablets and unit dose blister packs of 10 tablets/strip, 10 strips per carton container.

The drug product is an immediate release formulation containing pharmaceutical excipients that are conventional in nature and consists of microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and Opadry® Pink (b) (4), a proprietary film-coating mixture containing polyethylene glycol 3350, hypromellose, titanium dioxide, and ferric oxide red.

XARELTO™ Tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side and are supplied in bottles of 30 tablets (NDC 50458-580-30) and in unit dose blister packs of 10 (NDC 50458-580-10). XARELTO™ Tablets (Rivaroxaban Film-Coated Tablets) are manufactured by Schering Pharma under DMF 21581 and Janssen Ortho Pharmaceutical under DMF 21592. Authorization letters from Bayer Schering Pharma dated 23-JUN-2008 and Janssen Pharmaceuticals are included in NDA 22-406.

There is no stability data provided in the NDA itself. The following summary applies to the two cross-referenced DMFs for the drug product.

Bayer Schering Pharma submitted batch analyses for seven (7) pilot-scaled batches (b) (4) of rivaroxaban film-coated tablets. Up to 24 months at 25°C/60% RH and 24 months at 30°C/75% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data were submitted for the 6 batches of drug product contained in different size of HDPE bottles (b) (4) 3 batches of drug product in blister packs, and 1 batch in (b) (4). The stability data obtained from all batches tested by Bayer Schering Pharma conform to the Rivaroxaban Film-Coated Tablets specification at 25°C/60% RH for up to 24 months, at 30°C/70% RH for up to 24 months storage. The proposed shelf-life for the tablets is 36 months at controlled room temperature. The stability data submitted do not support this proposed shelf-life. Based on 24 months at 25°C/60% RH and 24 months at 30°C/75% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data provided , a 30-month shelf-life can be granted,.

Janssen Ortho Pharmaceuticals submitted batch analyses for three (3) commercial-scaled batches (b) (4) of rivaroxaban film-coated tablets. Up to 9 months at 25°C/60% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data were submitted for the 2 batches of drug product contained in HDPE bottles (b) (4) and 1batch of drug product in blister packs. The stability data obtained from all batches tested by Janssen Ortho Pharm. conform to the Rivaroxaban Film-Coated Tablets specification at 25°C/60% RH for up to 9 months storage. The proposed shelf-life of the tablets is 36 months at controlled room temperature. Based on 9 months at 25°C/60% RH long-term stability data, and up to 6 months at 40°C/75% RH accelerated stability data, a 12 month shelf-life can be granted.

Johnson & Johnson did not provide any information on batch analysis or stability study for the drug product. It referred entirely to the Bayer and Janssen DMFs.

An overall acceptable recommendation from the Office of Compliance has not yet been received..

Drug Substance:

Rivaroxaban is a selective direct factor Xa inhibitor with high oral bioavailability being developed as an antithrombotic agent.

Rivaroxaban is an odorless, non-hygroscopic, white to yellowish solid, practically insoluble in water (b) (4) and aqueous buffer solutions, slightly soluble in (b) (4) acetone, (b) (4), macrogol 400 (polyethylene glycol), (b) (4). It is a pure (*S*) enantiomer. Refer to DMF 21581, Rivaroxaban Drug Substance, Bayer HealthCare Pharma, AG for further information.

The chemical name for rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ (MW 435.89).

The drug substance is manufactured, tested and packaged by Bayer Schering Pharma. The CMC information for rivaroxaban is found in DMF 21581. An authorization from Bayer Schering Pharma dated 23-JUN-2008 is provided in NDA 22-406.

Rivaroxaban was accepted as a United States Adopted Name (USAN).

Bayer Schering Pharma submitted batch analyses for three (6) commercial size (b) (4) batches of rivaroxaban drug substance. Up to 24 months of long-term at 25°C/60% RH and 6 months at 40°C/75% RH stability data were submitted for 3 pilot-scaled batches ranging from (b) (4) and up to 12 months of long-term at 25°C/60% RH and 6 months at 40°C/75% RH stability data were submitted for six commercial scale batches packaged (b) (4) The stability data obtained from all batches tested by Bayer Schering Pharma conform with the Rivaroxaban Drug Substance specification at 25 °C / 60 % RH for up to 24 months storage. The proposed re-test period is (b) (4); however, (b) (4) re-test period is granted. This was conveyed to the DMF holder as a deficiency (please see the DMF review #1, dated 08-APR-2009.

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

XARELTO™ (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

The recommended dose of XARELTO™ is 10 mg taken orally once daily. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.
The duration of treatment depends on the individual risk of the patient for venous thromboembolism, which is determined by the type of orthopedic surgery. For patients undergoing hip replacement surgery, the treatment duration of 35 days is recommended. For patients undergoing knee replacement surgery, the treatment duration of 14 days is recommended.

The safety and effectiveness of using XARELTO™ beyond the recommended dose or treatment duration have not been established. Therefore, any use of doses of more than 10 mg of XARELTO™ once daily or treatment beyond 35 days is not recommended.

XARELTO™ tablets are 10 mg, round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side.
This drug product is supplied as follows:
NDC 50458-580-10: blister packs of 10 (unit dose)
NDC 50458-580-30: bottles of 30 tablets.
The recommended storage condition is at 25° C (77° F) or room temperature; excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

This NDA has multiple DMF deficiencies, as well as outstanding NDA deficiencies and a pending recommendation from the Office of Compliance. This NDA cannot be recommended for approval from a Chemistry, Manufacturing and Controls standpoint until these numerous deficiencies are completely and adequately resolved. For a list of the specific deficiencies, please refer to Section I(A) above.

III. Administrative

This NDA was submitted electronically (e-CTD) as a 505 application. The original submission submitted on 22-JUL-2008 did not provide CMC information; therefore, there was no Module 3 submitted in this application. Reference to **DMF 21581** for rivaroxaban (micronized) drug substance manufactured by Bayer Healthcare, **DMF 21592** for rivaroxaban tablets, 10 mg manufactured by (J&J) Janssen Ortho, LLC and **DMF 21580** for rivaroxaban tablets, 10 mg manufactured by Bayer Healthcare were referenced in the cover letter dated 22-JUL-2008 and the letters of cross-reference to these three (3) DMFs are found in Module 1.

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

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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.

/s/

Josephine Jee
5/12/2009 01:23:46 PM
CHEMIST

Sarah Pope
5/12/2009 02:40:35 PM
CHEMIST

Initial Quality Assessment (IQA)
Branch V

Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division: DMIHP
NDA: 22-406
Applicant: Johnson & Johnson Pharmaceutical Research & Development, LLC
Stamp Date: July 28, 2008
PDUFA Date: May 28, 2009
Trademark: Xarelto
Established Name: Rivaroxaban
Dosage Form: tablets
Route of Administration: oral
Indication: for prophylaxis of DVT or PE in patients undergoing hip or knee replacement surgery

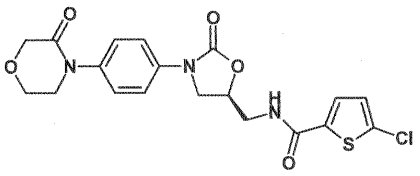
Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D.

	YES	NO
ONDQA Fileability:	_X	
Comments for 74-Day Letter		X (pending primary review)

Summary and Critical Issues:

A. Summary

The Drug Substance,"rivaroxaban" (BAY 59-7939), is 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide, and has the following chemical structure:



It is an odorless, non-hygroscopic, white to yellowish white powder, and is practically insoluble in water… It is a pure (S) enantiomer, and is highly selective inhibitor of Factor Xa with oral bioavailability. The asymmetric carbon atom (S configuration) is at the C5 of the oxaxolidin ring (the carbon to which is attached the thiophene carboxamide moiety). Rivaroxaban crystallizes in 3 modifications described in DMF 21-581. It

was invented by Bayer Healthcare AG, and is manufactured at Bayer Healthcare AG, Wuppertal, Germany. It is micronized at Bayer Healthcare AG at Leverkusen, Germany.

The proposed Drug Product is rivaraoxaban 10 mg film-coated oral tablets. Tablets are round, light red and are biconvex film-coated. They are marked with a triangle pointing down, above a "10" on one side and an "Xa" on the other side. Bulk drug product is manufactured by Bayer Healthcare AG, Leverkusen, Germany, and it is packaged by Jansen Ortho LLC (Puerto Rico). The packaging is described in DMF 21-592. The recommended dose is 10 mg taken orally daily. The indication is for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip of knee replacement surgery.

The entire CMC section for this NDA is contained in three DMF's, 21-581 (rivaroxaban, micronized drug substance – manufactured by Bayer Healthcare), 21-580 (rivaroxaban tablets, 10 mg drug product – also manufactured by Bayer) and 21-592 (rivaroxaban tablets, 10 mg drug product – manufactured J&J Jansen Ortho, LLC. Letters of reference for all three DMF's are contained within the NDA. I have briefly examined each of these DMF's, and the following is a preliminary assessment of the CMC content.

(b) (4)

(b) (4)

All of these issues that I have been discussing are preliminary in nature, and are only to alert the primary reviewer to what was seen in this initial assessment of the content of the DMF's to which reference to CMC was made by the applicant. The information

provided in the DMF's appeared to be complete and sufficient for substantive review to begin. There is a Memorandum dated November 7, 2007 that contains preliminary responses from the FDA to CMC questions from Bayer Healthcare in a Pre-meeting. The reviewer should be aware of this and consult it as background for the NDA.

C. Comments for 74-Day Letter

None at this point (initial assessment), and is pending primary review.

Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		
5.	Is a statement provided that all the facilities ate ready for cGMP / PAI inspection?	X		
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		Categorical exclusion, and provides the basis for the their claim of meeting the requirements. (Section 1.12.14)
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?		X	They have 24 months of long-term data. Based on this & other data maybe (b) (4)
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		
13.	Has the applicant provided a method validation package?	X		Not a separate package, but included in the NDA following analytical procedures
14.	Is a separate microbiological section included?		X	Microbial purity is provided in specs – may need microbiology consult

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
21-580	Bayer Healthcare	Rivaroxaban Tablets, 10 mg	X		
21-581	Bayer Healthcare	Rivaroxaban micronized drug substance	X		
21-592	Janssen Ortho	Rivaroxaban Tablets, 10 mg	X		

All three DMF's are assessable through EDR.

Production Facilities			
Facility	Address	Responsibility	CGMP Inspection Needed
Janssen Ortho, LLC (DMF 21-592)	State Road 933 KM 0.1 Mamey Ward Gurabo, Peurto Rico 00778 Contact : Nancy Micalizzi, Associate Director, Cross Pharma Regulatory Affairs, Johnson & Johnson Pharmaceutical Research & Deveolpment , LLC 920 Route 202 South Raritan, NJ 08869 908-92702703 FAX : 908-231-0056 (wmail : nmicaliz@prdus.jnj.com)	Manufacturer of Rivaroxaban Tablets, 10 mg (film coated tablets)	X
Bayer Healthcare (DMF 21-581)	Bayer Healthcare AG Friedrich-Ebert-Str 217-233 42117 Wuppertal, Germany 51368 Leverkusen, Germany Contact : Robert Kelly (US Agent), Director, Regulatory Affairs P.O. Box 1000, Montville, NJ 07045-1000 973-487-2161 (email : robert.kelly@bayer.com)	Synthesis of rivaroxaban Micronization of rivaroxaban bulk drug substance, packaging, QC, stability and testing, release (for manufacture of tablets)	X X
Bayer Healthcare (DMF 21-580)	51368 Leverkusen, Germany Contact : Robert Kelly (US Agent), Director, Regulatory Affairs P.O. Box 1000, Montville, NJ 07045-1000 973-487-2161 (email : robert.kelly@bayer.com)	Manufacture of bulk product[1]	X

(1) [redacted] (b) (4) packaging is done at Janssen Ortho, site indicated in above table. It also appears that some [redacted] (b) (4) packaging is done at Ortho-McNiel-Janssen Pharmaceuticals, Inc., Raritan, NJ. The reviewer needs to confirm the accuracy of this statement found in the DMF. QC is done at the above indicated Janssen Ortho facility,

as also stability storage and testing. As well, it appears that some stability storage and testing is done at the Raritan site; the reviewer needs to confirm this. Release testing is done at Janssen Ortho.

Consults To Be Initiated	
Item	Consult To
1. Microbiology (may need for assessment of microbial purity ?)	Should determine whether these limits need microbiology consult

Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D. Date: 09/02/2008

Branch Chief (Acting): Sarah Pope, Ph.D. Date:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eldon Leutzinger
9/2/2008 07:05:34 AM
CHEMIST

Sarah Pope
9/2/2008 09:22:22 AM
CHEMIST
Concur