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 22408/003
Org. Code: 161
Priority: 1S
Stamp Date: 29-JUL-2008
PDUFA Date: 03-JUL-2011
Action Goal: 04-MAY-2011
District Goal: 04-MAY-2011

Sponsor: JOHNSON AND JOHNSON
Brand Name: XARELTO (RIVAROXABAN) ORAL 10 MG
Generic Name: RIVAROXABAN
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 301-796-3592
J. BROWN Team Leader 301-796-1652

Overall Recommendation: ACCEPTABLE by A. INYARD (6) (6)
ACCEPTABLE by JOHNSONE (6) (6)

Establishment: CFN: 3003294966
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

QA 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.
### Establishment Evaluation 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)

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 12-JAN-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

**Profile:** TABLETS, PROMPT RELEASE

**OAI Status:** NONE

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**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:** 19-JAN-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:**
- **CFN:** 2242843
- **FEI:** 2242843
- **ORTHOMCNEILL-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:** 06-APR-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION
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/s/

JANICE T BROWN
06/14/2011

HARIPADA SARKER
06/14/2011
EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 22406/000
Sponsor: JOHNSON AND JOHNSON

Org: 161
920 US HWY 202 SOUTH

mp Date: 28-JUL-2008
RARITAN, NJ 088690602

JFA Date: 03-JUL-2011

Estab. Name: XARELTO (RIVAROXABAN) ORAL 10 MG

trict Goal: 04-MAY-2011

Generic Name: RIVAROXABAN

Product Number; Dosage Form; Ingredient; Strengths
001; TABLET, FILM COATED; RIVAROXABAN; 10MG

\ Contacts:
T. LAMBERT
Project Manager
301-796-4246

J. CRICH
Review Chemist
301-796-3882

J. BROWN
Team Leader
301-796-1652

rail Recommendation: ACCEPTABLE

ACCEPTABLE on () by A. INYARD ( )

ACCEPTABLE on () by JOHNSONE

abishment:

CFN: 3003229486

FEI: 217-233 FRIEDRICH-EBERT STRASSE

BAYER HEALTHCARE AG
WUPPERTAL, GERMANY 42117

AADA:

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F NO:

DUG SUBSTANCE MANUFACTURER

DUG SUBSTANCE PACKAGER

DUG SUBSTANCE STABILITY TESTER

file:

NON-STERILE API BY CHEMICAL SYNTHESIS

QAI Status: NONE

\ Milestone:

OC RECOMMENDATION

12-JAN-2011

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ACCEPTABLE

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BASED ON FILEReview
BASED ON PROFILE

une 9, 2011 4:12 PM
FDA Confidential - Internal Distribution Only Page 1 of 2
Establishment: BAYER SCHERING PHARMA AG CHEMPARK LEVERKUSEN, , GERMANY

F No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER FINISHED DOSAGE MANUFACTURER

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

Milestone: OC RECOMMENDATION

Date: 12-JAN-2011

Status: ACCEPTABLE

Type: BASED ON PROFILE

File: TABLETS, PROMPT RELEASE OAI Status: NONE

Milestone: OC RECOMMENDATION

Date: 19-JAN-2011

Status: ACCEPTABLE

Type: DISTRICT RECOMMENDATION

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

F No: GURABO, PR 00778

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

File: TABLETS, PROMPT RELEASE OAI Status: NONE

Milestone: OC RECOMMENDATION

Date: 08-APR-2011

Status: ACCEPTABLE

Type: DISTRICT RECOMMENDATION

Establishment: ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS INC.

F No: 1125 TRENTON HARBOURTON RD

AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

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

Milestone: OC RECOMMENDATION

Date: 08-JUN-2011

Status: ACCEPTABLE

Type: 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

Administrative: 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_{3}O_{5}S 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 inadequate 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
MEMORANDUM
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 Crieh, 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 $Q = \text{in 15 minutes for both Bayer and Johnson & Johnson-manufactured rivaroxaban 10 mg drug product, using the dissolution methodology described in the dossier.}$

**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 $20^\circ\text{C-25^\circC (68^\circF- 77^\circF)}$ or room temperature; excursions permitted to $15^\circC - 30^\circC (59^\circF - 86^\circF)$ [see USP Controlled Room Temperature] is granted.”
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/s/

JANICE T BROWN
06/15/2011

RICHARD T LOSSTRITTO
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**

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| FDA Contacts:    |                |                |                     |
| T. LAMBERT       | Project Manager | 301-798-4246   |
| J. CRICH         | Review Chemist  | 301-798-3882   |
| J. BROWN         | Team Leader     | 301-798-1652   |

**Overall Recommendation:**
- ACCEPTABLE on 06-JUN-2011 by A. INYARD
- ACCEPTABLE on 26-MAY-2009 by JOHNSON

**Establishment:**
- CFN: 3003229486
- FEI: 3003229486
- BAYER HEALTHCARE AG
- 217-203 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
- GAI 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.
## CHEMISTRY REVIEW TEMPLATE

### Chemistry Assessment Section

Attachment 1: Acceptable Facility Inspection – Continued

**FDA CDER EES**  
**ESTABLISHMENT EVALUATION REQUEST**  
**SUMMARY REPORT**

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/s/

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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
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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:

<table>
<thead>
<tr>
<th>Previous Documents</th>
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<tr>
<td>CMC Review # 1</td>
<td>12-MAY-2009</td>
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6. SUBMISSION(S) BEING REVIEWED:

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<td>51</td>
<td>21-MAY-2009</td>
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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:
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-morpholinyl)phenyl]-1,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide

![Chemical Structure]

Molecular Formula: C_{19}H_{18}ClN_{3}O_{5}S  
M.W.: 435.89
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<td>27-MAY-2011</td>
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<td>Reviewed by Joyce Crich</td>
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</table>

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:

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<td>BAY 59-7939 Tablets Bayer Corporation</td>
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<td>Microbiology</td>
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*DMEPA: Division of Medication Error Prevention and Analysis*
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 and aqueous buffer solutions, slightly soluble in acetone, macrogol 400 (polyethylene glycol) It is a class 2 compound with low solubility and high permeability.
based on BCS classification system. In order to improve bioavailability, the drug
substance is micronized.

The 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, 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 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.
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 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. 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 (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 blister packs.

Janssen Ortho Pharmaceuticals submitted batch analyses for three (3) commercial-scaled batches 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 and 1 batch 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 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 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°C - 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)
Executive Summary Section

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
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  Sponsor: JOHNSON AND JOHNSON
Org Code     : 160                  920 US HWY 202
Priority     : 1S                  RARITAN, NJ 088690602

Stamp Date   : 28-JUL-2008  Brand Name : XARELTO (RIVAROXABAN MG
PDUFA Date   : 28-MAY-2009
Action Goal  : Estab. Name:
District Goal: 29-MAR-2009  Generic Name: RIVAROXABAN
                      Dosage Form: (TABLET)
                      Strength   : 10 MG

FDA Contacts: D. LEAMAN   Project Manager
1-796-1424
J. JEE       Review Chemist
1-796-1375
S. POPE      Team Leader
1-796-1436

Overall Recommendation: ACCEPTABLE on 26-MAY-2009 by E. JOHNSON (HFD-32 0) 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:  TCM  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
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

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
Stamp: 28-JUL-2008
Regulatory Due: 28-MAY-2009
OXABAN

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

Priority: 1S
Org Code: 160

Action Goal: District Goal: 29-MAR-2009
Brand Name: XARELTO (RIVAROXABAN)
Estab. Name: ORAL 10 MG
Generic Name: RIVAROXABAN
Dosage Form: (TABLET)
Strength: 10 MG

Application Comment:
BAYER AG AT MANUFACTURER OF DS (on 26-MAR-2009 by J. JEE () 301-796-1375)

FDA Contacts:
ct Manager D. LEAMAN 301-796-1424 , Proj
w Chemist J. JEE 301-796-1375 , Revie
Leader S. POPE 301-796-1436 , Team

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

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

DMF No: 

Responsibilities:  
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER

Profile:  
CTX

OAI Status:  
NONE

Estab. Comment:  
SITE ALSO PERFORMS EYES WILL NOT ALLOW DATA ENTRY--C CRUZ IS AWARE VIA PHONE CONVERSATION
WITH M FOLKENDT AND D MESMER

SITE ALSO PERFORMS RELEASE TESTING AND STABILITY TESTING DS

CTX) (on by S. GOLDBE () 301-796-2055)

Milestone Name Creator

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BASED ON FILE REVIEW

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SUBMITTED TO OC JEE

OC RECOMMENDATION ADAMSS

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Profile:  
TCM

OAI Status:  
NONE

Milestone Name Creator

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SUBMITTED TO DO STOCKM

DO RECOMMENDATION JOHNSONE

OC RECOMMENDATION STOCKM

ACCEPTABLE

BASED ON FILE REVIEW

ACCEPTABLE

DISTRICT RECOMMENDATI
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 . ALSO PERFORMS QUALITY CO

NTROL TESTING, STABILITY STORAGE AND TESTING, RELEASE TESTING, AN

FOR DRUG SUBSTANCE. (on (8)(4) by D. MESMER (HFD-800)

301-796-

4023)
SUBMITTED TO OC MESMERD

SUBMITTED TO DO STOCKM

ASSIGNED INSPECTION T (0)(4) PS

JOHNSONE

INSPECTION PERFORMED (0)(4)

JOHNSONE

DO RECOMMENDATION (0)(4)

JOHNSONE ACCEPTABLE

INSPECTION

OC RECOMMENDATION (0)(4)

JOHNSONE ACCEPTABLE

DISTRICT RECOMMENDATI

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Establishment: CFN 2650104 FEI 3002942061

JANSSEN ORTHO L.L.C.

CARR # 933 KM 0.1

GURABO, PR 007789626

DMF No:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

EMilestone Name Creator

Date Type Insp. Date Decision & Reason

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SUBMITTED TO OC JEE (0)(4)
SUBMITTED TO DO
FERGUSONS

DO RECOMMENDATION
RHERNAND

ACCEPTABLE

BASED ON FILE REVIEW

ACCEPTABLE RECOMMENDATION BASED ON FIRM PREVIOUS INSPECTION RESULTS

OC RECOMMENDATION
FERGUSONS

ACCEPTABLE

DISTRICT RECOMMENDATION
ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Establishment: CFN 2211100 FEI 2211100
ORTHOMCNEIL 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-
OF THE DS.
(on by J. JEE () 301-796-1375)

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<th>Date</th>
<th>Type</th>
<th>Insp. Date</th>
<th>Decision &amp; Reason</th>
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</table>

SUBMITTED TO OC
JEE

OC RECOMMENDATION
FERGUSONS

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

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<th>Date</th>
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<th>Decision &amp; Reason</th>
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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.

Administrative

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 (C₁₉H₁₈ClN₃O₅S, 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 acetone, 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. 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
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CHEMISTRY REVIEW

Executive Summary Section
NDA 22-406
XARELTO (rivaroxaban) Tablets
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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:

<table>
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<tr>
<td>Pre-NDA</td>
<td>13-DEC-2007 (Priority Review Designation)</td>
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<td>Pre-NDA CMC Mtg.</td>
<td>05-DEC-2005 EOP2</td>
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<td>07-NOV-2007 (Preliminary Responses)</td>
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<td>NDA 22-406, Original</td>
<td>14-FEB-2008</td>
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<td></td>
<td>29-JUL-2008</td>
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6. SUBMISSION(S) BEING REVIEWED:

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<tr>
<td>NDA 22-406</td>
<td>29-JUL-2008</td>
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<tr>
<td>NDA 22-406 – CMC Info. on DP</td>
<td>24-NOV-2008</td>
</tr>
<tr>
<td>NDA 22-406 - Response to IR Letter - CMC</td>
<td>19-DEC-2008</td>
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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/TYPEx:

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
f) Laboratory Codes: None provided.
g) Chemical Name (IUPAC):  None provided


g) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type:  1
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: ___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]-1,3-oxazolidin-5-yl) methyl)-2-thiophenecarboxamide

![Chemical Structure]

Molecular Formula: C19H18ClN3O5S

M.W.: 435.89

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<td>13-MAR-2009</td>
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<td>23-MAR-2009</td>
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<td>26-MAR-2009</td>
<td>Review by J.Jee</td>
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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
Other Documents:

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<td>IND</td>
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<td>BAY 59-7939 Tablets Bayer Corporation</td>
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<td>DMF</td>
<td>21592</td>
<td>Rivaroxaban Tablets Janssen Ortho, L.L.C</td>
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<td>DMF</td>
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<td>Rivaroxaban Drug Substance Bayer Healthcare</td>
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<td>DMF</td>
<td>21580</td>
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18. CONSULTS/CMC-RELATED REVIEWS:

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<td>EES</td>
<td>Site inspections</td>
<td>29-AUG-2008</td>
<td>S.Adams</td>
<td>Pending as of the date of this review.</td>
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<td>Pharm/Tox</td>
<td>General PT review</td>
<td>Pending</td>
<td>Y. Chopra, Ph.D.</td>
<td>Pending</td>
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<td>Biopharm</td>
<td>Dissolution and Bioavail/Bioequiv.</td>
<td>31-MAR-2009</td>
<td>T. Ghosh, Ph.D.</td>
<td>Recommended acceptance criterion for dissolution testing to Q= at 15 minutes using the currently proposed dissolution methodology</td>
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<td>DMEPA</td>
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<td>Methods Validation</td>
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<td>EA</td>
<td>Categorical Exclusion</td>
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<td>J.Jee</td>
<td>Categorical exclusion granted (see attached review).</td>
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<td>Microbiology</td>
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<td>Solid dosage form – N/A.</td>
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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:

  **Regarding rivaroxaban drug substance:**
  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).

  **Regarding rivaroxaban drug product:**
  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 at 15 minutes.
  6. The container and closure system is not adequately described in the NDA.
CHEMISTRY REVIEW

Executive Summary Section
XARELTO (rivaroxaban) Tablets
Page 7 of 34 Pages

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 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 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, 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.
CHEMISTRY REVIEW

Executive Summary Section
NDA 22-406
XARELTO (rivaroxaban) Tablets

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 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. 3 batches of drug product in blister packs, and 1 batch in . 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 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 and 1 batch 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 provided, 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 and aqueous buffer solutions, slightly soluble in acetone, , macrogol 400 (polyethylene glycol), . 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_{3}O_{5}S (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 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 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. 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 35 days; however, 35 days 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

24 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
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 oxazolidin 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 rivaroxaban 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 or 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.
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.

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

<table>
<thead>
<tr>
<th>DMF Number</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>LOA Included</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-580</td>
<td>Bayer Healthcare</td>
<td>Rivaroxaban Tablets, 10 mg</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>21-581</td>
<td>Bayer Healthcare</td>
<td>Rivaroxaban micronized drug substance</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>21-592</td>
<td>Janssen Ortho</td>
<td>Rivaroxaban Tablets, 10 mg</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

All three DMF’s are assessable through EDR.
<table>
<thead>
<tr>
<th>Facility</th>
<th>Address</th>
<th>Responsibility</th>
<th>CGMP Inspection Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen Ortho, LLC (DMF 21-592)</td>
<td>State Road 933 KM 0.1 Mamey Ward Gurabo, Peurto Rico 00778 Contact : Nancy Micalizzi, Associate Director, Cross Pharma Regulatory Affairs, Johnson &amp; Johnson Pharmaceutical Research &amp; Development, LLC 920 Route 202 South Raritan, NJ 08869 908-92702703 FAX : 908-231-0056 (wmail : <a href="mailto:nmicaliz@prdus.jnj.com">nmicaliz@prdus.jnj.com</a>)</td>
<td>Manufacturer of Rivaroxaban Tablets, 10 mg (film coated tablets)</td>
<td>X</td>
</tr>
<tr>
<td>Bayer Healthcare (DMF 21-581)</td>
<td>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 : <a href="mailto:robert.kelly@bayer.com">robert.kelly@bayer.com</a>)</td>
<td>Synthesis of rivaroxaban</td>
<td>X</td>
</tr>
<tr>
<td>Bayer Healthcare (DMF 21-580)</td>
<td>51368 Leverkusen, Germany Contact : Robert Kelly (US Agent), Director, Regulatory Affairs P.O. Box 1000, Montville, NJ 07045-1000 973-487-2161 (email : <a href="mailto:robert.kelly@bayer.com">robert.kelly@bayer.com</a>)</td>
<td>Manufacture of bulk product</td>
<td>X</td>
</tr>
</tbody>
</table>

(1) packaging is done at Janssen Ortho, site indicated in above table. It also appears that some packaging is done at Ortho-McNeil-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.

<table>
<thead>
<tr>
<th>Item</th>
<th>Consult To</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Microbiology (may need for assessment of microbial purity ?)</td>
<td>Should determine whether these limits need microbiology consult</td>
</tr>
</tbody>
</table>

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

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