

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202439Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

202,439

NAME OF APPLICANT/NDA HOLDER

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

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Xarelto ®

ACTIVE INGREDIENT(S)

rivaroxaban

STRENGTH(S)

15 mg and 20 mg

DOSAGE FORM

oral tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

a. United States Patent Number

7,157,456

b. Issue Date of Patent

1/2/2007

c. Expiration Date of Patent

2/8/2021

d. Name of Patent Owner

Bayer Schering Pharma Aktiengesellschaft
Attention: Chief Patent Counsel of Bayer HealthCare
AG

Address (of Patent Owner)

City/State

Leverkusen

ZIP Code

51368, Germany

FAX Number (if available)

Telephone Number

011-49-214-30-1

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Philip S. Johnson, Esq.
Chief Intellectual Property Counsel
Johnson & Johnson

Address (of agent or representative named in 1.e.)

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933-7003

FAX Number (if available)

(732) 524 -2138

Telephone Number

(732) 524 - 2368

E-Mail Address (if available)

pjohnso4@its.jnj.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

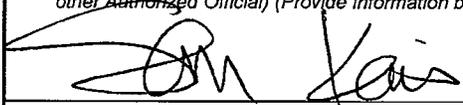
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? (See Addendum)		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).		<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.			
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?			
		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		<input type="checkbox"/> Yes	<input type="checkbox"/> No
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:			
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
	<input type="checkbox"/> Yes <input type="checkbox"/> No		
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes	

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



12/20/2010

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Samuel M. Kais

Address

Office of the General Counsel, Johnson & Johnson
One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933-7003

Telephone Number

(510) 248-2356

FAX Number (if available)

(732) 524 - 2138

E-Mail Address (if available)

skais1@its.jnj.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Addendum to FORM FDA 3542a

NDA Number: 202,439

Dated: December 20, 2010

Supplemental Response to Question 2.2:

Applicant understands the term "claim" as used in this question to mean a claim limited to one or more different polymorphs of the active ingredient described in the NDA, and with this understanding, the answer to this Question 2.2 is No. Accordingly, submission of additional test data is not necessary.

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

202,439

NAME OF APPLICANT/NDA HOLDER

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

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Xarelto ®

ACTIVE INGREDIENT(S)

rivaroxaban

STRENGTH(S)

15 mg and 20 mg

DOSAGE FORM

oral tablet

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

a. United States Patent Number

7,585,860

b. Issue Date of Patent

09/08/2009

c. Expiration Date of Patent

12/11/2020

d. Name of Patent Owner

Bayer Schering Pharma Aktiengesellschaft
Attention: Chief Patent Counsel of Bayer HealthCare
AG

Address (of Patent Owner)

City/State

Leverkusen

ZIP Code

51368, Germany

FAX Number (if available)

Telephone Number

011-49-214-30-1

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Philip S. Johnson, Esq.
Chief Intellectual Property Counsel
Johnson & Johnson

Address (of agent or representative named in 1.e.)

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933-7003

FAX Number (if available)

(732) 524-2138

Telephone Number

(732) 524-2368

E-Mail Address (if available)

pjohnso4@its.jnj.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? (See Addendum) Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

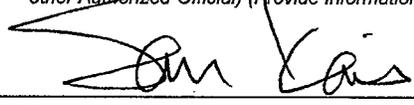
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/20/2010

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Samuel M. Kais

Address

Office of General Counsel
Johnson & Johnson, One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933-7003

Telephone Number

(510) 248-2356

FAX Number (if available)

(732) 524-2138

E-Mail Address (if available)

skais1@its.jnj.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
 - 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.
- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Addendum to FORM FDA 3542a

NDA Number: 202,439

Dated: December 20, 2010

Supplemental Response to Question 2.2:

Applicant understands the term "claim" as used in this question to mean a claim limited to one or more different polymorphs of the active ingredient described in the NDA, and with this understanding, the answer to this Question 2.2 is No. Accordingly, submission of additional test data is not necessary.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE FILING
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*For Each Patent That Claims a Drug Substance
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and/or Method of Use*

NDA NUMBER

202,439

NAME OF APPLICANT/NDA HOLDER

Johnson & Johnson Pharmaceutical Research
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ACTIVE INGREDIENT(S)

rivaroxaban

STRENGTH(S)

15 mg and 20 mg

DOSAGE FORM

oral tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

a. United States Patent Number

7,592,339

b. Issue Date of Patent

09/22/2009

c. Expiration Date of Patent

12/11/2020

d. Name of Patent Owner

Bayer Schering Pharma Aktiengesellschaft
Attention: Chief Patent Counsel of Bayer HealthCare
AG

Address (of Patent Owner)

City/State

Leverkusen

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51368, Germany

FAX Number (if available)

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011-49-214-30-1

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Philip S. Johnson, Esq.
Chief Intellectual Property Counsel
Johnson & Johnson

Address (of agent or representative named in 1.e.)

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933-7003

FAX Number (if available)

(732) 524-2138

Telephone Number

(732) 524-2368

E-Mail Address (if available)

pjohnso4@its.jnj.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

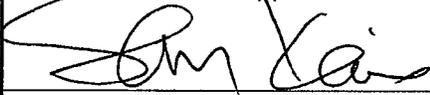
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).		<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.			
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		<input type="checkbox"/> Yes	<input type="checkbox"/> No
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:			
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) Claim Numbers: 1, 6, 10, and 11.	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) XARELTO® is a direct Factor Xa inhibitor indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in accordance with proposed labeling, including for example, (Section I) Indications and Usage, (Section 12.1) Clinical Pharmacology, Mechanism of Action, (Section 14) Clinical Studies, (Table 4) Strokes and Systemic Embolism in ROCKET-AF Study, and the Medication Guide.		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.			<input type="checkbox"/> Yes

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



12/20/2010

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Samuel M. Kais

Address

Office of General Counsel
Johnson & Johnson, One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933-7003

Telephone Number

(510) 248-2356

FAX Number (if available)

(732) 524-2138

E-Mail Address (if available)

skais1@its.jnj.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 202439

SUPPL # n/a

HFD # 110

Trade Name XARELTO

Generic Name rivaroxaban

Applicant Name Janssen Pharmaceuticals

Approval Date, If Known 4 November 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22406

Xarelto Tablets for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing: hip replacement

surgery or knee replacement surgery

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

ROCKET-AF: ROCKET-AF was a randomized, double-blind, double-dummy, noninferiority study evaluating the efficacy and safety of administering rivaroxaban 20 mg once daily (15 mg for renal impaired) compared to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

ROCKET-AF: ROCKET-AF was a randomized, double-blind, double-dummy, noninferiority study evaluating the efficacy and safety of administering rivaroxaban 20 mg once daily (15 mg for renal impaired) compared to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 75238 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Alison Blaus
Title: Regulatory Health Project Manager
Date: 2 November 2011

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

ALISON L BLAUS
11/03/2011

NORMAN L STOCKBRIDGE
11/03/2011

Blaus, Alison

From: Greeley, George
ent: Thursday, October 06, 2011 9:29 AM
fo: Blaus, Alison
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Stockbridge, Norman L.
Subject: NDA 202-439 Xarelto

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Alison,

This email serves as confirmation of the review for Xarelto (Rivaroxaban) conducted by the PeRC PREA Subcommittee on September 28, 2011.

The Division presented a full waiver in pediatric patients for the indication of prevention of stroke and systemic embolism in subjects with atrial fibrillation because there are too few patients with disease/condition to study.

The PeRC agreed with the Division to grant a full waiver for this product.

(b) (4)

The pediatric record is attached for Xarelto.



1_Pediatric_Record
.pdf (66 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

 Please consider the environment before printing this e-mail.

Organization: **DCRP**
 Appl Type No: **NDA 202439**
 Submission Type #: **ORIG - 1**

Product Name: **RIVAROXABAN**
 Applicant: **JANSSEN PHARMACEUTICALS INC**
 Submission Status: **PENDING**

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level	Submission Indication
1/5/2011	TABLET	N	1/5/2011	11/5/2011	TYPE 1/4	XARELTO (TM) (RIVAROXABAN) IS INDICATED FOR PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN SUBJECTS WITH ATRIAL FIBRILLATION.

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
1,477	WAIVED	FULL	0	16	TOO FEW CHILDREN WITH DISEASE/CONDITION TO STUDY	NON-VALVULAR ATRIAL FIBRILLATION (AF) IS RARE IN THE PEDIATRIC POPULATION.	

Orga	Product	Appl Typ	Subm Ty	Applic	Subm	FDA Rec	Dosage	Orph	Subm	Goal Du	Subm	Su	Pe	PREA S	Pediat	Min Va	Max V	Waive	Waive	Study
DC	RIVAR	NDA	ORIG -	JAN	PEN	1/6/201	TABL	N	1/5/2	11/5/2	TYP	X	1	WAIV	FUL	0	18	TOO	NON	



Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

DEBARMENT CERTIFICATION
XARELTO[®] (rivaroxaban) tablets NDA 202,439

Johnson & Johnson Pharmaceutical Research and Development, L.L.C. certifies that we did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food and Drug and Cosmetic Act in connection with this application.

Sanjay Jalota, MRPharmS
Senior Director, Global Regulatory Affairs
Cardiovascular / Metabolism Therapeutic Area

17 Dec 2010

Date

920 Route 202 South
Raritan, NJ 08869

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202439 BLA # n/a	NDA Supplement # n/a BLA STN # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: XARELTO Established/Proper Name: rivaroxaban Dosage Form: tablet		Applicant: Janssen Pharmaceuticals Agent for Applicant (if applicable): Johnson & Johnson PRD
RPM: Alison Blaus		Division: Cardiovascular & Renal Products
<p><u>NDA's:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is : <u>5 November 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None Hematology CR on 27 May 2009; Hematology AP on 1 July 2011

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input checked="" type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AFIB Approval 4 Nov 2011; DVT Approval 1 Jul 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Done
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Done
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Included with Action Letter
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	Yes 12 May 2011
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 10Nov11 <input checked="" type="checkbox"/> DMEPA 21Oct11 <input checked="" type="checkbox"/> DRISK 4Nov11 <input checked="" type="checkbox"/> DDMAC 19Oct11; 21Oct11 <input checked="" type="checkbox"/> SEALD 4 Nov11 (two) <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	17 Feb 11
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>28 September 2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Done
❖ Internal memoranda, telecons, etc.	Done
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 27 Oct 2009
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 12 Sep 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Top-line Meeting 8 Nov 2010
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	8 September 2011
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4 Nov 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6 Oct 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	n/a
• Clinical review(s) (<i>indicate date for each review</i>)	4 Feb 2011 (two) & 10 Aug 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Please see 10Aug11 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	3 November 2011
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	31 October 2011
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 4 November 2011
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 2Aug11 (two); 16Aug11 (two); 31Aug11; 2Sep11; 23Sep11

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None 3Feb11; 28Jul11
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None 3Feb11; 10Aug11; 21Oct11
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 4Feb11; 17Feb11; 13Jun11; 1Aug11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc 11May11
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 18Apr11 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 31Jan11
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None 27Jun11; 5Oct11
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input type="checkbox"/> None 5Oct11 (Biopharm review)

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	granted; See 27Jun11 CMC review
<input checked="" type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	granted; See 27Jun11 CMC review
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 12Jan11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

ALISON L BLAUS
11/08/2011

Blaus, Alison

From: Blaus, Alison
Sent: Tuesday, October 25, 2011 10:54 AM
To: Rhoge, Alla [JRDUS]
Cc: 'Jalota, Sanjay [JRDUS]'
Subject: NDA 202439 - Carton/Container Labeling

Importance: High

Hello!

Please find below the review comments from DMEPA regarding the carton and container labeling for XARELTO. As you know, we need to have agreement on the labeling prior to the PDUFA date. Please amend the labeling to incorporate the below and submit formally to the NDA. One submitted, DMEPA will review again and let me know the outcome. Please do not send via email.

*** Container Labels and Carton Labeling – 15 mg and 20 mg**

1. Add a space between the number and mg unit of measure to improve the readability of the statement of strength. For example, "15mg" should be revised to read "15 mg".
2. We remind the Applicant of their requirement to comply with 21 CFR 208.24:

A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or if it is enclosed in the carton (for example, for unit of use packaging configurations):

"Dispense the enclosed Medication Guide to each patient." or
"Dispense the accompanying Medication Guide to each patient."

Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

A minimum of four Medication Guides would be provided with a bottle of 100 or a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

A minimum of one Medication Guide would be provided with a unit of use container where it is expected that all tablets/capsules would be supplied to the patient.

3. Increase the prominence of the three middle numbers in the NDC number as this information is how the pharmacist identifies the correct strength for drug products. For example, NDC 50458-578-30 becomes 50458-**578**-30 for the 15 mg strength of Xarelto.
4. Add an image of the tablet to the container label.

*** 4.2.2 Container Label and Carton Labeling – 15 mg only**

1. Revise the color block for the 15 mg strength such that it is not the same color as the proprietary name (purple) and it does not overlap in color with the other strengths. The use of the same colors for both areas of the label diminishes the prominence of the strength.

*** 4.2.3 Container Labels**

1. Decrease the prominence of the graphic that appears just after the manufacturer's name, 'Janssen' at the bottom of the label.

*** 4.2.4 Blister Labels – 15 mg and 20 mg**

1. Revise the proposed blister labels such that the strengths for this drug product are well differentiated. As proposed, the same information is presented in the same sized, black font on a white background and looks similar to the approved 10 mg strength.

Please do not hesitate to contact me should you have any questions!

Thank you!

Alison

Alison Blaus

Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Food and Drug Administration
alison.blaus@fda.hhs.gov
p:(301) 796 1138
f:(301) 796 9838

Address for desk and courtesy copies:

Food and Drug Administration
10903 New Hampshire Avenue
White Oak, Building 22, Room 4158
Silver Spring, MD 20993

Address for official submissions to your administrative file:

Division of Cardiovascular and Renal Products
FDA, CDER, HFD 110
5901 B Ammendale Rd.
Beltsville, MD 20705 1266

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

/s/

ALISON L BLAUS
10/25/2011



NDA 202439

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Janssen Pharmaceuticals, Inc.
Attention: Alla Rhoge, Pharm.D.
Associate Director, Global Regulatory Affairs
1000 U.S. Highway 202
P.O. Box 300
Raritan, NJ 00869-0602

Dear Dr. Rhoge:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto (rivaroxaban) Tablets, 15 & 20 mg.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)¹. The pervasiveness and egregious nature of the violative practices by (b) (4)¹ has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from (b) (4), as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

(b) (4)

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] ^{(b) (4)} during the time period of concern [REDACTED] ^{(b) (4)}. Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM

10/05/2011

E.Fromm for N.Stockbridge



NDA 202439

Janssen Pharmaceuticals, Inc.
Attention: Alla Rhoge, Pharm.D.
Associate Director, Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Rhoge:

We acknowledge your July 14, 2011 correspondence notifying the Food and Drug Administration that the corporate name has been changed from

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

to

Janssen Pharmaceuticals, Inc.

for NDA 202439 for Xarelto (rivaroxaban) Tablets, 15 and 20 mg.

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have Drug Master Files (DMFs) referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their DMF(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
07/21/2011



NDA 202439

INFORMATION REQUEST

Ortho McNeil Janssen
Attention: Alla Rhoge PharmD.
Manager, Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Rhoge:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto (rivaroxaban) Tablets.

We also refer to your January 4, 2011 and May 17, 2011 submissions, containing Chemistry, Manufacturing, and Control data in support of your NDA.

We are reviewing the Chemistry, Manufacturing, and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The use of (b) (4) for identity test is not included in the drug product specification. Clarify the reasons for inclusion of (b) (4) method validation data in this NDA.
2. Provide information on analytical procedures used to accept the rivaroxiban drug substance from Bayer. If the procedures are not the same as those described in DMF 021581, appropriate validation data should also be provided.
3. According to USP<467>, all drug substances and drug products are subject to relevant control of solvents likely to be present in a drug substance or drug product. Include residual solvent testing in the drug product specification or provide justification for omission of this test from the drug product specification.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Ramesh K. Sood, Ph.D.
Chief, Branch I
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
06/10/2011



NDA 202439

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Ortho McNeil Janssen
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

ATTENTION: Alla Rhoge, PharmD
Manager, Global Regulatory Affairs

Dear Dr. Rhoge:

Please refer to your New Drug Application (NDA) dated January 4, 2011, received January 5, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rivaroxaban Tablets, 15 mg and 20 mg.

We also refer to your February 18, 2011, correspondence, received February 18, 2011, requesting review of your proposed proprietary name, Xarelto. We have completed our review of the proposed proprietary name, Xarelto and have concluded that it is acceptable.

The proposed proprietary name, Xarelto, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your February 18, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Alison Blaus, at 301-796-1138.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/12/2011



NDA 202439

DISCIPLINE REVIEW LETTER

Ortho McNeil Janssen
Attention: Alla Rhoge PharmD., Manager
Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Rhoge:

Please refer to your New Drug Application (NDA) dated January 4, 2011, received January 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for XARELTO (rivaroxaban) Tablets.

We also refer to your submissions dated January 18 (two), 21, 28, and 31, February 2, 4 (two), 8, 9, 11, 15 (two), 16, 18 (four), 25, and 28, and March 1, 4, 8, 16, 18 (two), 28, 29, 30, and 31, April 1, 6, 8, 15 (two), 18, 22, 25, 26, 28, and 29 (two), and May 2, 2011.

We are nearing completion of our review of the non-clinical section of your application and have identified the following issues.

1. A dose-related increase in the incidence of valvular fibrosis was observed in the hearts of male and female rats in the two-year carcinogenicity study. Based on our experience with similar drugs, valvular fibrosis is not an expected finding in such a study and additional information is needed to address this safety concern.
 - a. Please provide recent historical control data for this finding (e.g., data from the last five years) from the laboratory that conducted the study (Bayer Schering Pharma AG).
 - b. Provide any available additional description of the finding, such as the specific valves and the specific valvular structures involved.
 - c. Drug-induced valvular heart disease has been linked to effects on 5-HT_{2B} receptors, circulating serotonin levels, and the serotonin transporter, among other factors.
 - i. The study report R-8463 (Effects of Rivaroxaban in radioligand binding assays) you submitted did not clearly describe the methods or the species (i.e., animal or human) or isoforms of the receptors used. Please provide this information, and in particular for the serotonin receptors and transporters.
 - ii. Please evaluate the binding of rivaroxaban and its major metabolites to the human and rat 5-HT_{2B} receptor relative to the binding of appropriate agonist and antagonist positive controls for these receptors.

- d. Please provide any additional information that may help us assess this finding, such as the effect of rivaroxaban on serotonin plasma levels, serotonin transporter activity and expression, or the release of stored serotonin from platelets.
 - e. Please submit a comprehensive analysis of the clinical experience with rivaroxaban (clinical trial and post-marketing data) that addresses the clinical relevance of this finding. Specifically,
 - i. Analyze rivaroxaban’s controlled clinical trial safety data for adverse events suggestive of the onset or worsening of valvular heart disease involving any of the four cardiac valves. Because the clinical manifestations of this potential drug toxicity may overlap with the manifestations of other conditions frequently seen in your study populations (e.g., heart failure), we encourage you to devise a plan to help address this issue and submit it for review prior to conducting your analyses. Your response to this request should include information on the incidence and prevalence of new and/or worsening valvular disease in rivaroxaban-treated patients and in patients randomized to the comparator arms of these studies, adjusted as appropriate for the number of patients exposed, dose, and duration of treatment. Analyses may be presented for individual studies, and, where appropriate, using data pooled across studies.
 - ii. Analyze the rivaroxaban post-marketing experience for reports meeting the criteria described above.
 - iii. Provide any additional information/analyses that you think would help address whether or not there is a clinically important human counterpart to the pathology noted in the rat carcinogenicity study.
2. We acknowledge the responses from the manufacturer of the rivaroxaban drug product on April 8, 2011 and the DMF holder for the rivaroxaban drug substance on April 4, 2011 concerning the bis-oxamine-urea impurity. We note that the DMF holder acknowledges that the (b) (4) impurity was present in the rivaroxaban lots used for genotoxicity testing at concentrations below (b) (4).
- You concluded that the (b) (4) impurity lacks structural alerts for Ames mutagenicity based on an analysis using Derek for Windows and MultiCASE (MC4PC). The FDA QSAR analysis also predicted the (b) (4) impurity to be negative in the Ames test with MC4PC and found no structural alerts with Derek for Windows. However the FDA QSAR analysis using MC4PC gave a positive prediction for the in vivo micronucleus test for the (b) (4) impurity. The latter prediction was the basis for the overall positive genotoxicity conclusion for the (b) (4) impurity.
- Despite this positive genotoxicity conclusion, we acknowledge that the (b) (4) impurity was present in the rivaroxaban lots used for carcinogenicity testing at concentrations up to (b) (4). In the carcinogenicity tests, the rat exposure to the (b) (4) impurity was at least (b) (4) higher than the expected human exposure to the impurity if it were present in the 20-mg dose at the maximum of (b) (4). Given the presence of the (b) (4) impurity in the lots used for carcinogenicity testing and the lack of a positive finding in the QSAR analysis for the Ames test, we agree that the (b) (4) impurity in the rivaroxaban drug substance can be consider non-genotoxic and subject to the guidelines outlined in ICH-Q3A(R2).
3. The submitted rat carcinogenicity study report (PH-36242) provided p-value tables for the conventional Peto Test for neoplastic lesions and Armitage Test for non-neoplastic lesions. It did not

include tables for the Fisher Exact Test for neoplastic and non-neoplastic lesions or the Exact Peto Trend Test for neoplastic lesions. Please provide the following tables for the rat carcinogenicity study report (PH-36242):

- a. Fisher Exact Test (one-sided) on Neoplastic Lesions
- b. Fisher Exact Test (one-sided) on Non-Neoplastic Lesions
- c. Trend Test Statistics on Neoplastic Lesions ("Exact Peto test")

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
05/04/2011



NDA 202439

FILING COMMUNICATION

Ortho McNeil Janssen
Attention: Alla Rhoge PharmD., Manager
Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Rhoge:

Please refer to your New Drug Application (NDA) dated January 4, 2011, received January 5, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for XARELTO (rivaroxaban) Tablets.

We also refer to your submissions dated January 18 (two), 21, 28, and 31, February 2, 4 (two), 8, 9, 11, 15 (two), 16, 18 (four), 25, and 28, and March 1, 4, 8, and 16, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 5, 2011.

Your NDA does not qualify for a priority review because it neither provides effective therapy where none exists nor does it provide a significant improvement to marketed products. Two other drugs, warfarin and dabigatran, are currently marketed in the USA for prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. The PI for dabigatran indicates it was shown in the RE-LY trial to be superior to warfarin for this indication. In the confirmatory trial for rivaroxaban, ROCKET-AF, the intent-to-treat analysis did not demonstrate superiority of rivaroxaban to warfarin.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 24, 2011.

During our filing review of your application, we identified the following potential review issues:

1. ROCKET utilized an active-comparator, warfarin, whose efficacy and safety are dependent on titration of the dose to a therapeutic INR of 2.0-3.0. You report that the mean time in therapeutic range in the warfarin arm of ROCKET was 55%, far lower than that reported in other recent warfarin controlled trials in atrial fibrillation. We are concerned that the administration of warfarin in ROCKET was inadequate to be a proper comparator for evaluating the efficacy of rivaroxaban.
2. In both ROCKET and J ROCKET, the rate of stroke and non-CNS systemic emboli increased markedly in rivaroxaban-treated subjects in the period immediately following discontinuation of rivaroxaban. We are concerned that this finding suggests that cessation of rivaroxaban results in a hypercoagulable state. If so, patients who miss doses of rivaroxaban may be at increased risk for thrombotic events, reducing or eliminating its effectiveness. Additionally, it does not appear that you have adequate data to instruct health care providers in a method for safely transitioning patients from rivaroxaban to other anticoagulant therapies (e.g., warfarin and dabigatran).
3. Rivaroxaban has a short half life (5-9 hours) and when administered once-daily, has a peak-to-trough drug concentration ratio of about 10. Consequently, we are concerned that the once daily dosing regimen you propose results in marked diurnal variation of pharmacodynamic effect. We plan to assess if the safety and effectiveness of rivaroxaban could be substantially improved by administering it more frequently than once a day.
4. In ROCKET, a single dose of rivaroxaban was studied (with dose adjustment for patients with renal impairment). This dose was derived from studies conducted in the VTE indication and may not be optimal for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. To help determine the appropriate dose, we plan to review the relationship between exposure and pharmacodynamic endpoints (e.g., prothrombin time, INR, FXa, PiCT, etc) and outcome (e.g., ischemic stroke, hemorrhagic stroke, major bleeds, critical organ bleeds, etc).
5. You do not recommend routine monitoring of coagulation parameters in your proposed package insert (PI). We plan to review whether the benefit/risk of rivaroxaban could be substantially improved by routine measurement of coagulation parameters.
6. We do not understand why the impurity (b)(4) is specified at (b)(4) when the maximum percentage in lots used for toxicology studies was (b)(4) and was either not detected or present at (b)(4) in the lots used for the genotoxicity assays. If you are unable to lower the specification limit for (b)(4) then we expect you to qualify the higher level.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. We do not expect a response to these review issues, and we may not review any such response during the current review cycle.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Please delete the registered trademark symbol, “®”, that appears after every “XARELTO” throughout the Highlights and Full Prescribing Information (FPI). The registered trademark symbol is acceptable only once in FPI.
2. The Agency recommends use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page. The half-page Table of Contents should also appear on the same page as the Highlights.
3. Please ensure text, both font style and size, is consistent throughout the label. For example if you use “Arial” for Headings and “Times New Roman” for all other information, make sure all sections of the FPI are consistent. Please also ensure that no headings or section numbers are in italics (e.g., Section 6, **ADVERSE REACTIONS**).
4. In section 6.1, **Commonly-Observed Adverse Drug Reactions in Double-Blind Controlled Clinical Studies**, the standard verbatim statement, “Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”, should precede the presentation of adverse reactions not follow them.
5. Please include a section 6.2, **Post Marketing Experience**, to detail the adverse reactions identified from foreign spontaneous reports. In 6.2, please also include the following verbatim statement or appropriate modification, “The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
6. Per 21 CFR 201.57, please amend Section 8.4, **Pediatric Use**, to read, “Safety and effectiveness have not been established in pediatric patients.”
7. Under Section 17, **PATIENT COUNSELING INFORMATION**, please change (b) (4) [REDACTED] to “*See FDA-approved patient labeling (Medication Guide)*”.
8. Upon review of the Medication Guide, we have the following comments:
 - a. Overall word simplification is needed. Technical terms should be removed if possible and replaced. For example, (b) (4) [REDACTED] should be updated to “doctor”.
 - b. Please refer to the approved Medication Guide for PRADAXA for appropriate terms and overall organization of a Medication Guide.
 - c. The possible side effects section of the Medication Guide needs to designate/separate which effects are “serious” and those that are “common”. This section should also not reiterate those events listed in the Warnings/Precautions sections of the Medication Guide.

We request that you resubmit labeling that addresses these issues by April 1, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Cardiovascular and Renal Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

STEPHEN M GRANT
03/17/2011

DSI CONSULT: Request for Clinical Inspections

Date: 25 February 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Susan Thompson
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Martin Rose, M.D., JD, Medical Officer
Preston Dunnmon, MD, Medical Officer
Aliza Thompson, M.D., Team Leader, Medical Officer
Norman Stockbridge, M.D., Ph.D., Division Director/ Division of
Cardiovascular & Renal Products

From: Alison Blaus, Regulatory Health Project Manager/ Division of
Cardiovascular & Renal Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: 202439

Applicant: Ortho-McNeill-Janssen Pharmaceuticals

Applicant contact information:

Alla Rhoge, PharmD

Global Regulatory Affairs, Cardiovascular & Metabolism

Johnson & Johnson Pharmaceutical R&D

e-mail: arhoge@its.jnj.com

Phone: 908 927-4758

Fax: 908 927-7114

Drug Proprietary Name: XARELTO

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): XARELTO® (rivaroxaban) tablets are indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

PDUFA: 5 November 2011

Action Goal Date: 5 November 2011

Inspection Summary Goal Date: 5 September 2011

DSI Consult

Reference ID: A08200258

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
001045 Sotolongo, Rodolfo, P, M.D. Southeast Texas Clinical Research Center 2693 North Street, Beaumont, TX, 77702 United States	39039039- AFL-3001	N 37	3rd Largest US site, time in therapeutic range for INR (TTR) 44%, with many low TTR pts. In the RE-LY study of dabigatran, the median site TTR was about 67%, so this site was quite poor, especially for a US site.
064001 Richards, Mark, A, Ph.D. Christchurch Hospital Riccarton Avenue, Private Bag 4710 Christchurch, Christchurch, 8011 New Zealand	39039039- AFL-3001	N 49	Large site with 4 Rivaroxaban post treatment primary events vs 0 during treatment. Post treatment events occurred at an unusually high rate in the rivaroxaban arm this site had more of these events than any other site. We are quite concerned about this phenomenon and want to learn more about it.
034039 Alvarez, Pere, , M.D. Hospital de Viladecans Avda. Gava 38, Servicio de Cardiologia Viladecans, Barcelona, 08840 Spain	39039039- AFL-3001	N 47	4/23 Warfarin pts had primary endpoints, vs 0/23 Rivaroxaban pts.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
001362 Zelenka, Jason, T, M.D. Clearwater Cardiovascular and Interventional Consultants - Countryside Office 1840 Mease Dr., Ste. 202 Safety Harbor, FL, 34695 United States	39039039- AFL-3001	N 42	2nd Largest US site, 2 warfarin events
063004 Tirador, Louie, S, M.D. Saint Paul's Hospital Rm. 206 Gen. Luna St., Iloilo City, Western Visayas, 5000 Philippines	39039039- AFL-3001	N 129	Largest site globally, had 2 rivaroxaban post treatment primary events
040012 Militaru, Constantin, -, M.D. Cardiomed SRL, str N Titulescu bloc E 3 ap 1, Craiova, Dolj, 200147 Romania	39039039- AFL-3001	N 66	Largest site with TTR < 40% (TTR 35.5). This represents very poor performance possibly it performed poorly in GCP areas.
042022 Jandik, Josef, , Ph.D. Oblastni Nemocnice Nachod Purkynova 446, Nachod, Nachod, 547 01 Czech Republic	39039039- AFL-3001	N 39	6 primary events, 6 major bleeds (a disproportionately large number for both given the number enrolled)

III. Site Selection/Rationale

The rationale for selecting individual sites is provided in the table above.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): low time in therapeutic range for Warfarin,

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify). Largest enrollment, low TTR, asymmetric occurrence of primary outcome events between study arms, high incidence of major bleeding (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include several foreign sites in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Audits are requested for 2 domestic sites and 5 international sites, with the rank order being the order that they appear on the table above. Though marketed in Europe, rivaroxaban, if approved, will be an NME in the United States that will be made available to a substantial number of the approximately 2.5 million Americans who have atrial fibrillation. This is a population that is at risk for embolic events as a complication of their disease state, and also at risk for bleeding complications of the anticoagulation therapy given to avoid the occurrence of embolic events.

The ROCKET study is effectively the single pivotal study based on which US approval is sought, with supportive data being provided by J-ROCKET (its smaller Japanese counterpart assessing a lower dose for the Japanese population). ROCKET is a very large trial with over 14,000 patients enrolled from 1187 sites in 45 countries, based on which the sponsor is claiming both rivaroxaban's non-inferiority and superiority to vitamin K antagonists (VKAs) which are the de facto standard of care for prophylaxing embolic events in high risk AFib patients. Due to the large global nature of the trial, it would be optimal that more sites be audited/sampled to provide a more representative view of the study conduct as a whole. Of the subjects enrolled (ITT), approximately 2682 of 14269

(81%) were enrolled from sites outside of the US and Canada. As a reflection of this fact, 2/7 sites proposed for auditing are North American (29%), while 5/7 (71%) are located in other geographies.

In addition to concerns raised by the sheer size and complexity of the ROCKET trial, additional sites are suggested for audit due to data integrity issues that were identified in this sponsor's submission of rivaroxaban for approval to prevent DVT/PE following hip or knee replacement surgery (NDA 22046). These data integrity issues were identified as an item in the complete response letter issued to the sponsor on May 27, 2009 that required correction and/or explanation by the sponsor as a condition of further approval consideration.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

- Verify that all potential efficacy endpoint events were reported to the sponsor; of particular interest is the reporting of transient ischemic attacks (TIAs), strokes (ischemic and/or hemorrhagic), non-CNS systemic embolic events, myocardial infarctions, and deaths
- Verify that all potential safety endpoint events and important adverse events were reported to the sponsor; the focus should be on the reporting of clinically significant bleeding events and liver function abnormalities; the reported follow-up of these patients (date beyond which follow-up information no longer available if patient withdrew from study) should also be confirmed
- Verify the integrity of the INR data submitted for patients assigned to warfarin; the data should be reviewed for its accuracy, the completeness of reporting (e.g. was additional monitoring done/were additional values obtained that were not reported), adherence to the protocol specified frequency of INR monitoring; the reported action taken with regard to warfarin dose adjustment/changes should also be verified
- Verify study medication (rivaroxaban and warfarin) start and stop dates (of note, patients could go on and off therapy during the course of the trial); verify the reasons given for temporary/permanent study medication discontinuation
- Special attention should be afforded to the accurate reporting of efficacy and safety endpoint events as defined above, as well as adverse events, that took place between the last dose of study drug and the day 30 follow up visit (dates inclusive).

Should you require any additional information, please contact Alison Blaus at 301-796-1138, Preston Dunnmon at 301-796-7640, or Martin Rose at 301-796-1957.

Concurrence: (as needed)

Medical Team Leader
Medical Reviewer
Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

ALISON L BLAUS
02/25/2011

PRESTON M DUNNMON
02/25/2011

MARTIN ROSE
02/25/2011

ALIZA M THOMPSON
02/25/2011

NORMAN L STOCKBRIDGE
02/25/2011

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Alison Blaus, ODE 1/DCaRP, (301)796-1138
------------------------------	---

REQUEST DATE 2 February 2011	IND NO. 75238	NDA/BLA NO. 202439	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
---------------------------------	------------------	-----------------------	---

NAME OF DRUG: XARELTO (rivaroxaban) Tablets	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: NME	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting): 5 October 2011 (or 2 weeks after substantially complete labeling provided).
--	-------------------------------------	--------------------------------	--

NAME OF FIRM: Ortho-McNeil-Janssen Pharmaceuticals	PDUFA Date: 5 November 2011
---	-----------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply)	TYPE OF APPLICATION/SUBMISSION	REASON FOR LABELING CONSULT
<input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION

EDR link to submission:

<\\CDSESUB1\EVSPROD\NDA202439\202439.ENX>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 2 June 2011 – DDMAC invited

Labeling Meetings: TBD – Will invite DDMAC to all meetings

Wrap-Up Meeting: TBD – Will invite DDMAC to all meetings

SIGNATURE OF REQUESTER: Alison Blaus

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/s/

ALISON L BLAUS
02/04/2011

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE

FROM:
Alison Blaus, ODE 1/DCaRP, (301)796-1138

DATE
4 February 2011

IND NO.
75238

NDA NO.
202439

TYPE OF DOCUMENT
NDA Submission

DATE OF DOCUMENT
5 January 2011

NAME OF DRUG
rivaroxaban

PRIORITY CONSIDERATION
Standard NDA Review

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
5 September 2011

NAME OF FIRM: Ortho-McNeill-Janssen Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | Carton/Container Labels |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review these carton/container labels for this NDA, rivaroxaban. Rivaroxaban is indicated for patients with atrial fibrillation This NDA was submitted on 5 January 2011 and the PDUFA goal is 5 November 2011.

EDR Location: : \\CDSesub1\evsprod\NDA202439\202439.ENX

PDUFA DATE: 5 November 2011

ATTACHMENTS: Draft Package Insert, Container and Carton Labels (please see these documents at the above EDR location.

CC: Archival IND/NDA 202439

HFD 110/Division File

HFD 110/RPM

HFD 110/Reviewers and Team Leaders

Reference ID: 2901259
NAME AND PHONE NUMBER OF REQUESTER

METHOD OF DELIVERY (Check one)

Alison Blaus	<input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

ALISON L BLAUS
02/04/2011



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/s/

ALISON L BLAUS
02/04/2011

REQUEST FOR CONSULTATION

TO (Office/Division): Karl Lin, Team Leader, Division of Biometrics 6 (Applications in Pharmacology / Toxicology)

FROM (Name, Office/Division, and Phone Number of Requestor): Alison Blaus, ODE 1/DCaRP, (301)796-1138

DATE 25 January 2011	IND NO. 75238	NDA NO. 202439	TYPE OF DOCUMENT NDA Submission	DATE OF DOCUMENT 5 January 2011
NAME OF DRUG rivaroxaban		PRIORITY CONSIDERATION Standard NDA	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE End of April 2011

NAME OF FIRM: Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI)

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE NDA MEETING
<input type="checkbox"/> END OF PHASE 2a MEETING
<input type="checkbox"/> END OF PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|---|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END OF PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS
<input type="checkbox"/> IN VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

COMMENTS / SPECIAL INSTRUCTIONS:

We are requesting your assistance in the review of the carcinogenicity data for rivaroxaban. This submission is located at the following link:

\\CDSESUB1\EVSPROD\NDA202439\202439.ENX

The data regarding carcinogenicity arrived in the submission dated 30December 2010 (date in Global Submit) and 5January2011 (date in DARRTS), module 4.2.3. The Pharmacology/ Toxicology reviewer for this IND/NDA is Patricia Harlow (301-796-1082). Once a statistician has been assigned, please let myself and Pat know that person. This data will need to be taken in front of the Exec CAC at the beginning of May, so we are hoping to have at least a draft review from your team prior to the Exec CAC since we will need it to finalize our reviews before then. If you have any questions, please do not hesitate to contact me or Pat. Thank you in advance! Alison

Reference ID: 2896055

SIGNATURE OF REQUESTOR Alison Blaus	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

ALISON L BLAUS
01/25/2011



NDA 202439

NDA ACKNOWLEDGMENT

Ortho-McNeil-Janssen Pharmaceuticals, Inc
c/o Johnson & Johnson Pharmaceutical Research
& Development, L.L.C.
Attention: Alla Rhoge, Pharm.D.
Manager, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Rhoge:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Xarelto (rivaroxaban)

Date of Application: January 4, 2011

Date of Receipt: January 5, 2011

Our Reference Number: NDA 202439

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 6, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinformo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 202439, submitted on January 4, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
01/13/2011