

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022406Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022406

SUPPL # N/A

HFD # 160

Trade Name Xarelto

Generic Name rivaroxaban

Applicant Name Johnson and Johnson

Approval Date, If Known July 3, 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?

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#

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:

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 ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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 ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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"):

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 #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! 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 <input type="checkbox"/>		! NO <input type="checkbox"/>
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: Tyree Newman
Title: Regulatory Project Manager, DHP, OODP
Date: June 10, 2011

Name of Office/Division Director signing form: Ann Farrell
Title: Acting Division Director, DHP, OODP

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/

TYREE L NEWMAN
06/15/2011

ANN T FARRELL
07/01/2011

EXCLUSIVITY SUMMARY

NDA # 022406

SUPPL # N/A

HFD # 160

Trade Name Xarelto

Generic Name rivaroxaban

Applicant Name Johnson and Johnson

Approval Date, If Known July 3, 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:

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

/s/

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

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

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22406 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A
Division Name: DHP PDUFA Goal Date: 7/3/2011 Stamp Date: 1/3/2011
Proprietary Name: Xarelto
Established/Generic Name: Rivaroxaban
Dosage Form: Tablet
Applicant/Sponsor: Johnson and Johnson Pharmaceutical Research & Development, LLC

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) N/A
(2) N/A
(3) N/A
(4) N/A

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- ☐ Yes. Please proceed to Section D.
☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
☐ No: Please check all that apply:
☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
☐ Completed for some or all pediatric subpopulations (Complete Sections D)
☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)☒ Necessary studies would be impossible or highly impracticable because:☐ Disease/condition does not exist in children☒ Too few children with disease/condition to study☐ Other (e.g., patients geographically dispersed): _____☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)☒ Justification attached.*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.***Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:☐ Disease/condition does not exist in children☐ Too few children with disease/condition to study☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification [†]
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmts@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
☒ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
☐ No: Please check all that apply:
☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
☐ Completed for some or all pediatric subpopulations (Complete Sections D)
☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- ☒ Necessary studies would be impossible or highly impracticable because:
☐ Disease/condition does not exist in children
☒ Too few children with disease/condition to study
☐ Other (e.g., patients geographically dispersed): _____
☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.

If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

1.9.1 Request for Waiver of Pediatric Studies

The sponsor is requesting a waiver for the conduct of a clinical program with rivaroxaban for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in pediatric patients (<18 years of age) undergoing total hip or knee replacement surgery. The rationale for the waiver for the conduct of such a clinical program in this indication is the rarity of joint replacement surgery in the pediatric population and the lower risk of DVT and PE (collectively referred to as venous thromboembolism [VTE]), which does not necessarily require routine prophylaxis.

Patients over 40 years old have a clearly increased risk for the development of VTE across multiple clinical settings compared with younger patients. The incidence of VTE in children is considered rare and usually happens only in the presence of a strong predisposing risk factor (Anderson 2003). However, even with a strong predisposing factor like major trauma, the incidence of clinically-detected VTE is lower in patients 17 years old or less compared with those over 17 years, based on a Level 1 trauma center registry (Azu 2005). VTE events were experienced in:

- 0 of 2320 (0.0%) trauma patients under the age of 13 years
- 2 of 1025 (0.2%) trauma patients between the ages of 13 to 17 years
- 57 of 10549 (0.5%) trauma patients older than 17 years

Based on these data, the authors concluded that VTE prophylaxis after trauma is unnecessary in children since the risk of clinically significant VTE is negligible. In adults, routine VTE prophylaxis after major trauma is a Grade 1A recommendation (Geerts 2008). Similarly, a review of all patients 17 years old or less hospitalized for at least 72 hours and having 2 or more risk factors for VTE, found only 1 case with symptomatic DVT (Rohrer 1996). Since this patient had at least 3 risk factors for VTE (i.e., head trauma, neurologic deficit, and multiple surgeries), the authors conclude that VTE prophylaxis is not required for patients with only 1 or 2 risk factors.

Total joint replacements are performed in the pediatric population primarily for the joint deformities and disabilities associated with juvenile rheumatoid arthritis (and similar conditions) (Kim 2008, Kitsoulis 2006). Since these procedures are technically challenging and will eventually lead to revision surgery due to the finite functional lifespan of the artificial joint, they are performed infrequently and only after medical therapy has failed. Joint replacement surgery is also occasionally performed in pediatric patients for malignant bone disease (e.g., with proximal femoral resection) (van Kampen 2008). Reflecting the low number of surgeries, the largest case series reported in the literature has been 47 patients from the Mayo Clinic (Klassen 1979). There does not appear to be any data in the literature on the occurrence of VTE following joint replacement surgery in pediatric patients, but based on the above data in other settings, the VTE risk would be expected to be substantially lower than for adults.

Since pediatric subjects were excluded from all rivaroxaban clinical studies and the risk of VTE is likely different from that in adults, the safety and effectiveness of rivaroxaban have not been established in children and adolescents <18 years of age and therefore, rivaroxaban is not recommended for use in this population in the proposed product labeling.

The conduct of a clinical program to establish the safety and effectiveness of rivaroxaban in the pediatric population after joint replacement surgery is not feasible due to the limited number of procedures performed and the low expected incidence of symptomatic VTE events in this population. Therefore, the sponsor requests a waiver for the conduct of such a clinical program.

References

- Anderson FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107;I-9-I-16. 5.4-1
- Azu MC, McCormack JE, Scriven RJ, Brebbia J, Shapiro MJ, Lee TK. Venous thromboembolic events in pediatric trauma patients: is prophylaxis necessary? *J Trauma Inj Infect Crit Care* 2005;59:1345-1349. 5.4-1
- Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:381S-453S. 5.4-1
- Kim HJ, Kahn B, Figgie MP. Total joint replacement in childhood arthritis. *Curr Rheumatol Rep* 2008;10(2):135-41. 5.4-1
- Kitsoulis PB, Stafilas KS, Siamopoulou A, Soucacos PN, Xenakis TA. Total hip arthroplasty in children with juvenile chronic arthritis: long-term results. *J Pediatr Orthop* 2006;26(1):8-12. 5.4-1
- Klassen RA, Parlasca RJ, Bainco AJ. Total joint arthroplasty. Applications in children and adolescents. *Mayo Clin Proc* 1979;54(9):579-82. 5.4-1
- Rohrer MJ, Cutler BS, MacDougall E, Herrmann JB, Anderson FA, Wheeler HB. A prospective study of the incidence of deep venous thrombosis in hospitalized children. *J Vascular Surg* 1996;24(1)46-9. 5.4-1
- van Kampen M, Grimer RJ, Carter SR, Tillman RM, Abudu A. Replacement of the hip in children with a tumor in the proximal part of the femur. *J Bone Joint Surg (American)* 2008;90(4):785-95. 5.4-1

Pediatric Research and Equity Act Waivers

NDA #:22-406 Supplement Type: N/A Supplement Number: N/A

Product name and active ingredient/dosage form: Xarelto (Rivaroxaban) Tablets

Sponsor: Johnson & Johnson

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to age 16 years.
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

3. Pediatric age group(s) to be waived. Birth to age 16 years.
4. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration

Alzheimer's disease

Amyotrophic lateral sclerosis

Atherosclerotic cardiovascular disease

Benign prostatic hypertrophy

Chronic Obstructive Pulmonary Disease

Erectile Dysfunction

Infertility

Menopausal and perimenopausal disorders

Organic amnesic syndrome

(not caused by alcohol or other psychoactive substances)

Osteoarthritis

Parkinson's disease

Postmenopausal Osteoporosis

Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:

Basal cell

Bladder

Breast

Cervical

Colorectal

Endometrial

Gastric

Hairy cell leukemia

Lung (small & non-small cell)

Multiple myeloma

Oropharynx (squamous cell)

Ovarian (non-germ cell)

Pancreatic

Prostate

Renal cell

Uterine

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

/s/

MARCUS A CATO
06/06/2011

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

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

DEBARMENT CERTIFICATION

XARELTO™ (rivaroxaban)

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.



Andrea Kollath, DVM,
Director, Global Regulatory Affairs
Cardiovascular Therapeutic Area

July 10-2008
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 22406 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: Tablets		Applicant: Johnson and Johnson Agent for Applicant (if applicable): N/A
RPM: Tyree Newman		Division: Hematology Products
<p>NDAs: 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: 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 checked="" 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>July 3, 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 CR May 27, 2009
❖ 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		<input type="checkbox"/> Received

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.

❖ Application Characteristics ²		
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan drug designation </div> <div> <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </div> </div> <div style="display: flex; justify-content: space-between;"> <div> <p>NDAs: Subpart H</p> <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <p>Subpart I</p> <input type="checkbox"/> Approval based on animal studies</div> <div> <p>BLAs: Subpart E</p> <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) <p>Subpart H</p> <input type="checkbox"/> Approval based on animal studies</div> </div> <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a FMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </div> <div> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required</p> </div> </div> <p>Comments:</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)	<input type="checkbox"/> Yes, dates	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No	
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
• 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 BLA: 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 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 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 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).

- (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?

☐ 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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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).

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.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist³

7/1/11

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (*approvals only*)

☒ Included

Documentation of consent/non-consent by officers/employees

☒ Included

Action Letters

❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) Cycle 2-7/1/11, Cycle 1-5/27/09

Labeling

❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

- Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

6/30/11

Cycle 2-12/30/10, Cycle 1-7/22/08

Lovenox

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

❖ 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 type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	6/30/11, 7/22/08
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	5/12/11
• Review(s) (<i>indicate date(s)</i>)	Cycle 2-5/12/11, Cycle 1-5/1/09
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 8/27/08 <input checked="" type="checkbox"/> DMEPA 6/15/11 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC Cycle 2-6/8/11, Cycle 1-12/19/08 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM 10/3/08, C/P 9/2/08, CMC 9/2/08
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
○ 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"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
• Date reviewed by PeRC <u>March 25, 2009</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
❖ 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>)	(Cycle 2)-C-6/30/11, ACK-6/28/11, C-6/21/11, C-6/15/11, C-6/15/11, C-6/15/11, C 6/7/11, IR 4/21/11, IR 4/21/11, IR 4/14/11, IR 4/8/11, ACK 2/22/10, IR 2/5/11, IR 2/5/11, MG 1/22/11, ACK 1/14/11, (Cycle 1)C 9/13/10, IR 8/2/10, IR 5/10/10, C 4/27/10, C 4.27.10, C 4/30/10, ACK 4/21/10, C 11/24/09, C 9/29/09, C 9/29/09, C 8/18/09, IR 8/14/09, TC 8/13/09, ACK 8/5/08, FC 10/1/08, IR 10/1/08, IR 10/9/08, IR 12/5/08, IR 12/12/08, DR 2/5/09, IR 2/11/09, IR 2/19/09, IR 1/12/09-4/6/09, IR 4/17/09, IR 4/30/09, IR 4/30/09, C 5/12/09, C 5/14/09
❖ Internal memoranda, telecons, etc.	M 11/2/09, M 12/01/08, M 12/15/08, M 12/17/08, M 1/28/09, M 2/3/09, M 2/10/09, M 3/26/09, M 4/17/09, M 5/11/09,
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 5/14/09
• 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 2/1/08, 1/11/08
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 9/5/06, 7/20/05
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	MM 10/15/10, MM 5/7/10, MM 12/10/09, MM 10/13/09, MM 7/14/09, MM 10/09/08, MM 11/25/08, MM 12/01/08, MM 1/23/09, MM 1/28/09, MM 1/28/09, MM 2/13/09, MM 3/6/09, MM 3/18/09, , MM 3/18/09, MM 4/1/09, MM 4/27/09, MM 4/30/09, MM 4/30/09
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	3/19/09
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	4/21/09
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/1/11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Cycle 2-7/1/11, Cycle 1-5/12/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3
Clinical Information⁵	

⁵ Filing reviews should be filed with the discipline reviews.

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	Cycle 2-6/14/11, 6/13/11, Cycle 1-5/27/09
• Clinical review(s) (indicate date for each review)	Cycle 2-6/3/11, Cycle 1-4/2/09
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<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 (indicate date of review/memo)	4/2/09
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input type="checkbox"/> None Biometrics Cycle 2-6/10/11, Cycle 1-2/26/09, Cycle 2- OSE 6/16/11, Cycle 1-2/13/09, MHT 6/10/11, QTC 3/5/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management • REMS Documents and Supporting Statement (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	<input checked="" type="checkbox"/> None Submission 7/28/08 DRISK 2/12/09
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested Cycle2-5/25/11, Cycle-1-9/17/10, 8/27/10, 4/27/10, 4/27/10, 4/27/10, 3/19/10, 12/8/09, 12/6/09, 12/3/09, 11/24/09, 10/8/09, 8/18/09, 6/4/09, 5/25/09, 3/17/09,
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 type="checkbox"/> None Cycle 2- 5/27/11, Cycle 1-5/8/09, 2/26/09
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Cycle 2- 5/27/11, Cycle 1-5/8/09, 2/26/09
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None Cycle 2-6/10/11, 5/27/11, Cycle 1-5/8/09, 2/26/09
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Cycle 2-6/3/11, Cycle 1- 10/6/10, 4/6/09
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Cycle 2-6/3/11, Cycle 1- 10/6/10, 4/6/09
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None Cycle 2-6/3/11, Cycle 1- 10/6/10, 4/6/09
❖ 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 type="checkbox"/> None Cycle 2 6/30/11, Cycle 1-5/12/09
• 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 5/12/09
❖ 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 checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 6/13/11, 4/18/11 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 type="checkbox"/> None Cycle 2-6/16/11, Cycle 1-5/13/09
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Cycle 2-6/16/11, Cycle 1-5/27/09
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None Cycle 2-6/2/11, 5/2/11, 3/23/11, Cycle 1-5/12/09, 4/1/09
❖ 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 checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	5/12/09
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁶)	Date completed: Cycle 2-6/14/11, Cycle 1-5/26/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

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.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- | | |
|-------------------------------------|-------------------------|
| <input type="checkbox"/> | Completed |
| <input type="checkbox"/> | Requested |
| <input type="checkbox"/> | Not yet requested |
| <input checked="" type="checkbox"/> | Not needed (per review) |

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/

TYREE L NEWMAN

07/05/2011

Newman, Tyree

From: Baugh, Denise
Sent: Thursday, June 30, 2011 5:42 PM
To: Newman, Tyree
Cc: Farrell, Ann T; Bridges, Todd
Subject: RE: NDA 22406 updated carton and containers (rivaroxaban)

Tyree, the revised label and labeling are acceptable.
Denise

-----Original Message-----

From: Newman, Tyree
Sent: Wednesday, June 29, 2011 9:29 PM
To: Baugh, Denise
Cc: Farrell, Ann T; Bridges, Todd
Subject: FW: NDA 22406 updated carton and containers (rivaroxaban)

Good evening Denise, please see the updated carton and container labels for your review.

Please inform me if the Sponsor addressed your requirements.

Kind regards,

Tyree

Mr. Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

-----Original Message-----

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Wednesday, June 29, 2011 6:52 PM
To: Newman, Tyree
Subject: RE: NDA 22406 updated carton and containers (rivaroxaban)

Hi Tyree
Attached are the updated labels for the bottle, the carton and the HUD blister.
Best regards
Andrea

-----Original Message-----

From: Kollath, Andrea [PRDUS]
Sent: Wednesday, June 29, 2011 9:57 AM
To: Newman, Tyree
Subject: RE: NDA 22406 updated carton and containers for NDA 022406

Hi Tyree
Thanks. We will send as soon as the revisions have been made.
Andrea

-----Original Message-----

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Wednesday, June 29, 2011 9:02 AM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 updated carton and containers for NDA 022406

Good morning Andrea, we have reviewed your updates to the carton and label containers and there are two issues which have not been satisfactorily addressed:

- 1) Increase the prominence of the established name by decreasing the font size/width of the proprietary name or increasing the font size/width of the established name such that they will be equally prominent.
- 2) Relocate the dosage form, 'tablets' to the left and relocate the strength, 10 mg to the right of it such that the dosage form and the strength appear on one line under the proprietary name.

Once you have made the updates, please send to my attention for review. If you have any additional questions, please let me know.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
07/01/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22406

**ACKNOWLEDGE CORPORATE
NAME CHANGE**

Johnson and Johnson Pharmaceutical Research and Development LLC
Attention: Andrea Kollath, D.V.M.
920 US Highway 202 South
PO Box 300
Raritan, NJ 08869-0602

Dear Dr. Kollath:

We acknowledge receipt on June 20, 2011, of your June 20, 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 the following new drug application:

NDA 22406 for Xarelto (Oral 10 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 Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Tyree Newman
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

TYREE L NEWMAN
06/28/2011

Newman, Tyree

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, June 24, 2011 2:10 PM
To: Newman, Tyree
Subject: RE: NDA 22406 teleconference minutes
Attachments: emfinfo.txt

[Thank you.](#)

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Friday, June 24, 2011 1:59 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 teleconference minutes

Good afternoon Andrea, per our teleconference yesterday regarding the Clinical Pharmacology section of the label for NDA 22406, I have summarized the meeting as follows:

The following attendees were present:

FDA Attendees (Agency):

- Joseph Grillo, Pharm.D.– Clinical Pharmacology Reviewer
- Julie Bullock, Pharm.D. – Clinical Pharmacology Team Leader
- Nitin Mehrotra – Pharmacometrics Reviewer
- Gabrielle Richterman, Pharm.D., student
- Tyree Newman – Regulatory Project Manager
- **Johnson and Johnson (Sponsor) attendees:**
- Gary Peters , MD, VP, Cardiovascular and Metabolism Clinical Development
- Paul Burton MD PhD FACC, VP Franchise Medical Leader
- Troy Sarich PhD, Compound Development Team Leader
- Kenneth Todd Moore, MS, Clinpharm Leader Rivaroxaban
- Judy Kinaszczuk, R.Ph. Director, Global Labeling
- Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead
- Andrea Kollath, DVM, North America Regulatory Lead

Bayer Attendees (Sponsor):

- Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head
- Dagmar Kubitz, MD PhD Global Clinical Pharmacology Project Leader, BSP
- Wolfgang M. Mueck, PhD. Director Clinical Pharmacokinetics
- Andrea Derix, PhD, Sen. Global Regulatory Strategist

The following is a summary of the primary discussion points between the Agency and the Sponsor:

- The Division clarified its rationale for including all the in vivo drug interaction information in Section 7 of the draft labeling rather than splitting between Sections 7 and 12. The Sponsor was concerned that there may be changes as they are working with Cardio-Renal Division on the label. The Division confirmed that Cardio-Renal has been involved in the current labeling review.
- The Division clarified its rationale for omitting PgP potency claims by stating that the Agency is not ready to endorse claims regarding PgP potency in labeling at this time.
- The Division provided clarification regarding its rationale for including Section 7.2 (Complex Drug-Disease Interactions) by stating simulations from both the sponsor and FDA reported the potential for a significant increase in rivaroxaban exposure that the team felt required further assessment as a PMR. Once the PMR has been completed and if the data suggests the label should be revised, the Sponsor can submit a supplement.
- The Division provided clarification regarding its rationale for removing [REDACTED] (b) (4) throughout the draft labeling.
- The Division stated that the Sponsor is free to propose revised wording for the introductory paragraph for Section 7.1. However, the Division stressed the quantitative information regarding the extent of the interaction should remain in the noted list drugs in this section.
- The Division stated that the Sponsor may propose changes regarding the use of the term(s) "Avoid" or "Not recommended" or "Use with caution" as long as they are using "active voice".
- The Division stressed that the sponsor is free to submit proposed language for the draft labeling. These proposals would be carefully reviewed, but it should not be assumed they are acceptable to the Agency.
- The Division has completed the review of the label based on the data received in response to the CR. The Division will not be able to review any new data for this submission.

Please inform me if you have any questions or comments.

Kind regards,

Tyree

Tyree Newman

Regulatory Project Manager

Food and Drug Administration

Division of Hematology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

10903 New Hampshire Ave.

Silver Spring, MD 20993

301-796-3907 (phone)

301-796-9845 (fax)

Tyree.Newman@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL



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

/s/

TYREE L NEWMAN
06/30/2011

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, June 22, 2011 10:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 PMR

Good day Andrea, please see the final proposed post-marketing trial request from our review team regarding NDA 22406. Please review and respond by Friday, June 24, 2011. Please provide your proposed completion dates and we will confirm if we are in agreement with your proposal.

Post-marketing Requirements (PMR) for Rivaroxaban:

Under FDAAA, the FDA has determined that you are required to conduct the following:

A post-marketing study consisting of the mandatory collection and reporting of events of interest with enhanced pharmacovigilance (described below) to monitor, summarize, and report on risk factors, clinical management and outcome of cases of major bleeding in association with Rivaroxaban use post-marketing. (Major bleeding: must be defined noted in the clinical protocols and current drug labeling)

Submit a pharmacovigilance plan to describe how you will collect, follow-up, and analyze pertinent clinical information from all spontaneous, published literature, or solicited case reports of major bleeding.

In the protocol, describe:

The methods to be used for data collection and analysis, including your solicitation of reports of bleeding events
The plan for enhanced follow-up with reporters – You will actively query and ascertain key facts about the bleeding event, including:

- Demographics (age, gender, race, location of bleeding.....)
- Underlying diagnoses including specific reason for Rivaroxaban treatment
- Other relevant risk factors for bleeding
- Dose and duration of Rivaroxaban therapy
- Concomitant medications
- Treatment given for the bleeding (names of products, doses and duration of treatment)
- Any laboratory monitoring tests performed

Outcome information on:

- Bleeding outcome – time to cessation and opinion on the role of therapy given on the bleeding cessation
- Survival / disability / further complications

Submit summary information (total cases and summary of key facts in those cases, with pertinent expert analysis of clinically relevant information from the case series and any potential regulatory implications such as label changes) quarterly for 3 years then annually.

Provide expected completion dates

- * Final Protocol Submission: _____
- * Study Trial Completion: _____
- * Final Report Submission: _____

If you have any questions, please let me know.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products

Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
06/23/2011

Newman, Tyree

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, June 21, 2011 2:40 PM
To: Newman, Tyree
Cc: Lu, Min; Robie Suh, Kathy M
Subject: RE: NDA 22406 teleconference
Attachments: emfalert.txt

Hi Tyree,

Thank you for the minutes. We appreciate the opportunity to discuss these topics. Just let us know when you have a time slot for the telecon for the next topic. Our team is on standby this whole week.

Best regards,
 Andrea

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Tuesday, June 21, 2011 2:31 PM
To: Kollath, Andrea [PRDUS]
Cc: Lu, Min; Robie Suh, Kathy M
Subject: NDA 22406 teleconference

Good afternoon Andrea, per our teleconference this morning to discuss the issue of "Major bleeding" in Table 1 of the label for NDA 22406. The following attendees were present:

FDA Attendees (Agency):

- Dr. Min Lu - Clinical Reviewer
- Dr. Kathy Robie-Suh - Clinical Team Leader
- Tyree Newman - Regulatory Project Manager

Johnson and Johnson (Sponsor) attendees:

- Gary Peters , MD, VP, Cardiovascular and Metabolism Clinical Development
- Paul Burton MD PhD FACC, VP Franchise Medical Leader
- Leonard Oppenheimer, PhD. Statistical Sciences
- Juliana Ianus, Ph.D. Statistical Sciences
- Judy Kinaszczuk, R.Ph. Director, Global Labeling
- Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead
- Andrea Kollath, DVM, North America Regulatory Lead

Bayer Attendees:

- Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head,.
- Martin Homering PhD, Statistical Sciences

During the meeting, the following was agreed:

- Only "Major Bleeding" and "Any Bleeding" will be addressed in Table 1 of the label and "Any Bleeding" will be defined by the Sponsor in a foot note.
- The Agency will remove the comment, (b) (4) from the label".

Action items

- The Sponsor requested a separate teleconference with the Clinical and Clinical Pharmacology reviewers to discuss concerns regarding comments noted in the label.
- The Sponsor requested a separate teleconference with DSI and the Clinical Reviewers to discuss data in

Records 1-4.

Please inform me if you have any questions or comments.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
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/s/

TYREE L NEWMAN
06/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION											
TO (Division/Office): Mail: OSE				FROM: Tyree Newman, RPM, Division of Hematology Products										
DATE June 16, 2011	IND NO. N/A	NDA NO. 22406	TYPE OF DOCUMENT PMR		DATE OF DOCUMENT N/A									
NAME OF DRUG Xarelto (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant		DESIRED COMPLETION DATE June 20, 2011									
NAME OF FIRM: Johnson and Johnson														
REASON FOR REQUEST														
I. GENERAL														
<div><div><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</div><div><input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT</div><div><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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW):</div></div>														
II. BIOMETRICS														
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH											
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III. BIOPHARMACEUTICS														
<div><input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES</div>			<div><input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST</div>											
IV. DRUG EXPERIENCE														
<div><input type="checkbox"/> PHASE IV 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</div>			<div><input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS</div>											
V. SCIENTIFIC INVESTIGATIONS														
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL											
<p>COMMENTS/SPECIAL INSTRUCTIONS:</p> <p>We in DHP think we will want a registry post-marketing study for this new NDA now under review. The drug inhibits clotting factor X in its activated form, this inhibiting blood clotting. There is no "antidote" - treatment that can directly reverse the anticoagulant effects, thus bleeding can be a problem to stop.</p> <p>2 possible clinical studies to characterize drug safety better after approval:</p> <ul style="list-style-type: none">Registry of major bleeding events occurring on drug therapyDevelopment of a means of "reversing" - or mitigating - major bleeding in patients receiving the drug <p>(Nothing like these possible proposals was done on Dabigatran.)</p> <p>DRUG NAME: Xarelto™ (Rivaroxaban) Tablets TYPE OF MEETING: Internal Team mtg INDICATION: for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery PURPOSE: edit/discuss labeling EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx</p> <p>NDA 22406: Xarelto (Rivaroxaban) Tablets: - Sponsor - J&J. for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery.</p> <p>Anticipated Action: TBD Press Release: TBD BURST: TBD</p> <table><tr><td>Project Manager</td><td>Clinical Team</td><td>Medical Officer</td><td>Statistics Reviewer</td><td>Chemistry/Biopharm</td><td>Pharm/Tox Reviewer</td><td>Microbiology Reviewer</td><td>Clin.Pharm. Reviewer</td></tr></table>							Project Manager	Clinical Team	Medical Officer	Statistics Reviewer	Chemistry/Biopharm	Pharm/Tox Reviewer	Microbiology Reviewer	Clin.Pharm. Reviewer
Project Manager	Clinical Team	Medical Officer	Statistics Reviewer	Chemistry/Biopharm	Pharm/Tox Reviewer	Microbiology Reviewer	Clin.Pharm. Reviewer							

	Leader			Reviewer				
Newman Tyree	Kathy Robie-Suh	Min Lu	Xu, Qing	Crich, Joyce Ghosh, Tapash	Chopra, Yash M	N/A	Grillo, Joseph	
Letter Date:				December 30, 2010		AC Mtg TBD		
Receipt Date:				January 3, 2011				
Date to DD:				June 23, 2011				
PDUFA Date:				July 3, 2011				
Action Package Delivery Date:				TBD				
SIGNATURE OF REQUESTER Tyree Newman					METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND			
SIGNATURE OF RECEIVER					SIGNATURE OF DELIVERER			

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/s/

TYREE L NEWMAN
06/16/2011

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, June 14, 2011 12:58 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 PMR/PMC

Good day Andrea, please see the proposed post marketing trial requests from our review team regarding NDA 22406. Please review and respond by Friday, June 17, 2011, if you have any questions or comments. We have also proposed completion dates. If you cannot meet the proposed dates, please propose alternative dates and we will confirm if we are in agreement with your proposal. Also, you can expect additional post marketing requests. Once I receive these requests, I will forward immediately.

Postmarketing Commitments (PMC) for Rivaroxaban:

Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet in physical characteristics. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement.

Rationale

A 5 mg dosing form (tablet) or scored 10 mg tablet will allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically significant changes in rivaroxaban exposure. These include patients with Child Pugh class B hepatic impairment without coagulopathy, patients concurrently taking rivaroxaban with a Pgp and strong CYP3A4 inhibitor, and patients concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment. The availability of lower dose strengths of rivaroxaban is the best option to allow a larger patient population to receive this treatment.

Proposed completion dates

- Final Protocol Submission: 8/17/2011
- Study Trial Completion: 3/3/2012
- Final Report Submission: 4/3/2012

Postmarketing Requirements (PMR) for Rivaroxaban:

Evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation.

Rationale

You reported that based on simulations using a population pharmacokinetic approach, you anticipate that combined use of a drug that would inhibit non-renal clearance by 30% and inhibit active renal clearance by 45% in patients with mild or moderate renal impairment may result in an approximate 2 and 2.4 fold increase in plasma AUC, respectively, when compared to subjects which is considered significant. Using a physiologically based (PBPK) modeling approach FDA reached similar results, but also found that this complex DDI may be more pronounced in the elderly.

Proposed completion dates

- Final Protocol Submission: 7/18/2011
- Study Trial Completion: 2/3/2012
- Final Report Submission: 3/3/2012

If you have any questions, please let me know.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

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TYREE L NEWMAN
06/15/2011

Newman, Tyree

From: Newman, Tyree
Sent: Monday, June 13, 2011 11:35 AM
To: 'Kollath, Andrea [PRDUS]'
Cc: 'Jalota, Sanjay [PRDUS]'
Subject: RE: NDA 22406 FDA label review
Attachments: NDA 22406 (b) (4) 100-count-blister-pack.pdf; NDA 22406 draft-carton-and-container-labels-bottle.pdf; NDA 22406 draft-carton-and-container-labels (b) (4) bl.pdf

Hi Andrea, please also see our comments regarding the container carton and blister pack labels. Please accept changes you agree to and for changes you do not, keep in track changes.

Please provide your response by Thursday, COB, June 16, 2011.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

From: Newman, Tyree
Sent: Monday, June 13, 2011 11:22 AM
To: Kollath, Andrea [PRDUS]
Cc: Jalota, Sanjay [PRDUS]
Subject: NDA 22406 FDA label review

Good morning Andrea, please see the attached redlined version of the label regarding NDA 22406 for your review and comments. Please accept changes you agree to and for changes you do not, keep in track changes.

Please provide your response by Thursday, COB, June 16, 2011.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
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Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN

06/15/2011

Newman, Tyree

From: Newman, Tyree
Sent: Monday, June 13, 2011 11:22 AM
To: Kollath, Andrea [PRDUS]
Cc: Jalota, Sanjay [PRDUS]
Subject: NDA 22406 FDA label review
Attachments: NDA 22406 label comments_6 13 11.doc

Good morning Andrea, please see the attached redlined version of the label regarding NDA 22406 for your review and comments. Please accept changes you agree to and for changes you do not, keep in track changes.

Please provide your response by Thursday, COB, June 16, 2011.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
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/s/

TYREE L NEWMAN
06/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION																			
TO (Division/Office): Mail: OSE				FROM: Tyree Newman, RPM, Division of Hematology Products																		
DATE May 25, 2011	IND NO. N/A	NDA NO. 22406	TYPE OF DOCUMENT Label		DATE OF DOCUMENT May 25, 2011																	
NAME OF DRUG Xarelto (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant		DESIRED COMPLETION DATE June 13, 2011																	
NAME OF FIRM: Johnson and Johnson																						
REASON FOR REQUEST																						
I. GENERAL																						
<div><div><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</div><div><input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT</div><div><input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input checked="" 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):</div></div>																						
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V. SCIENTIFIC INVESTIGATIONS																						
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL																			
<p>COMMENTS/SPECIAL INSTRUCTIONS:</p> <p>We request any comments on the labeling regarding possible <u>hepatic effects</u> specifically to the sponsor's proposed labeling sections 6.2 and 8.7. Also, we are willing to accept comments regarding any other sections of the label.</p> <p>The label is currently being reviewed by the review team.</p> <p>DRUG NAME: Xarelto™ (Rivaroxaban) Tablets</p> <p>TYPE OF MEETING: Internal Team mtg</p> <p>INDICATION: for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery</p> <p>PURPOSE: edit/discuss labeling</p> <p>EDR Location: \CDSESUB1\EVSPROD\NDA022406\0059</p> <p>Global Submit: \CDSESUB1\EVSPROD\NDA022406\022406.enx</p> <p>NDA 22406: Xarelto (Rivaroxaban) Tablets: - Sponsor - J&J. for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery.</p> <p>Anticipated Action: TBD Press Release: TBD BURST: TBD</p> <table><tr><td>Project Manager</td><td>Clinical Team Leader</td><td>Medical Officer</td><td>Statistics Reviewer</td><td>Chemistry/Biopharm Reviewer</td><td>Pharm/Tox Reviewer</td><td>Microbiology Reviewer</td><td>Clin.Pharm. Reviewer</td></tr><tr><td>Newman Tyree</td><td>Kathy Robie-Suh</td><td>Min Lu</td><td>Xu, Qing</td><td>Crich, Joyce Ghosh, Tapash</td><td>Chopra, Yash M</td><td>TBD</td><td>Grillo, Joseph</td></tr></table>							Project Manager	Clinical Team Leader	Medical Officer	Statistics Reviewer	Chemistry/Biopharm Reviewer	Pharm/Tox Reviewer	Microbiology Reviewer	Clin.Pharm. Reviewer	Newman Tyree	Kathy Robie-Suh	Min Lu	Xu, Qing	Crich, Joyce Ghosh, Tapash	Chopra, Yash M	TBD	Grillo, Joseph
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Newman Tyree	Kathy Robie-Suh	Min Lu	Xu, Qing	Crich, Joyce Ghosh, Tapash	Chopra, Yash M	TBD	Grillo, Joseph															

Letter Date:	December 30, 2010	AC Mtg TBD
Receipt Date:	January 3, 2011	
Date to DD:	June 23, 2011	
PDUFA Date:	July 3, 2011	
Action Package Delivery Date:	TBD	
SIGNATURE OF REQUESTER Tyree Newman	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

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/s/

TYREE L NEWMAN
05/25/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022406

**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: Andrea F. Kollath, DVM
Director, Regulatory Affairs

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated July 22, 2008, received July 29, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rivaroxaban Tablets, 10 mg.

We also refer to your February 25, 2011, correspondence, received February 25, 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 25, 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 Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Tyree Newman at (301) 796-3907.

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 22-406

INFORMATION REQUEST

Johnson and Johnson Pharmaceutical Research and Development

Attention: Andrea F. Kollath, DVM

Director, Regulatory Affairs

920 Route 202, P.O. Box 300

Raritan, NJ 08869

Dear Dr. Kollath:

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 December 30, 2010, submission, containing a Class 2 response to our May 27, 2009, action letter.

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 by May 4, 2011, in order to continue our evaluation of your NDA.

Relating to DMF 21580 in support of Johnson & Johnson Pharmaceutical Research & Development's drug product application (NDA):

1. Your primary and secondary stability studies include the use of a matrix design for the different containers and closures and a bracketing approach for the number of tablets filled to support your proposed shelf life. Submit in a tabular format comparative evaluation of the containers/closures and fill volumes to support your matrix and bracketing design. Include comparative data for the container/closure composition, moisture vapor transmission rate, strengths, container size, container fill and other parameters critical to support the stability of your drug product.
2. Provide a complete comparison of the HDPE bottle configurations, (b) (4) per tablet to demonstrate package equivalence in the primary stability studies and to support the proposed marketed bottle configurations.
3. Submit data demonstrating that the hardness and water content changes observed during the stability studies do not affect the dissolution with a recommended dissolution acceptance criterion ($Q = (b) (4)$ at 15 minutes).

4. Provide the correlation between (b) (4) per tablet and hardness/water content change for each packaging configuration.
5. Clarify the temperature and humidity ranges used in the primary stability studies. Provide additional justification if the conditions for the long term stability studies are not the same as the controlled conditions mentioned in ICH Q1 (e.g. 25°C +/- 2°C/60%RH +/- 5%RH).

Relating to DMF 21592 in support of Johnson & Johnson Pharmaceutical Research & Development's drug product application (NDA):

1. The proposed release specifications for Rivaroxaban Film-Coated Tablets manufactured by Johnson & Johnson Janssen Ortho are inconsistent with the specifications used for Rivaroxaban Film-Coated Tablets in primary stability studies by Bayer HealthCare. Correct any inconsistencies and submit a single specification for both proposed manufacturing sites.
2. Skip lot testing for microbial purity is not acceptable. Revise accordingly.
3. Clarify the temperature and humidity ranges for the site specific stability studies, to demonstrate that the site specific stability data adequately support the proposed storage conditions. Provide additional justification if the conditions employed for the site specific stability studies are not the same as the controlled room temperature conditions mentioned in ICH Q1 (e.g. 25°C +/- 2°C/60%RH +/- 5%RH).
4. Provide justification for omitting hardness and water content in the proposed specifications for the drug product.

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}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
04/21/2011

From: Mesmer, Deborah
Sent: Thursday, April 21, 2011 9:42 AM
To: 'Kollath, Andrea [PRDUS]'
Cc: Lambert, Tu-Van
Subject: NDA 22-406- LOA

Dear Dr. Kollath,

As discussed in our phone conversation this morning, please submit to NDA 022406 a proper LOA for DMF 21592.

Sincerely,

Debbie Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 1627
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023
deborah.mesmer@fda.hhs.gov

From: Kollath, Andrea [PRDUS] [<mailto:AKollath@its.jnj.com>]
Sent: Thursday, April 21, 2011 9:38 AM
To: Mesmer, Deborah
Subject: NDA 22-406

Dear Deborah,
e-mail as discussed.
Kind regards,
Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

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/s/

DEBORAH M MESMER
04/21/2011



NDA 22-406

INFORMATION REQUEST

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

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 December 30, 2010 submission, containing a Class 2 response to our May 27, 2009 action letter.

We are reviewing the Chemistry, Manufacturing and Control - Biopharmaceutics 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.

In light of the release data of the pilot and commercial batches, the Agency proposes the following in-vitro dissolution specification for both Bayer and Johnson & Johnson manufacturing facilities:

Q = (b) (4) at 15 minutes using the following dissolution methodology:

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 ± 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry
	Both analytical procedures lead to the same results and may thus be used interchangeably.

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}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
04/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			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) Marcus Cato, RPM, Division of Hematology Products					
REQUEST DATE February 11, 2011	IND NO.	NDA/BLA NO. NDA-022406	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Resub/Class 2 (Labeling)					
NAME OF DRUG XARELTO™ (Rivaroxaban)	PRIORITY CONSIDERATION Rush		CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) June 3, 2011				
NAME OF FIRM: J&J			PDUFA Date: July 3, 2011					
TYPE OF LABEL TO REVIEW								
<table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top; width: 33%;"> TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE (IFU) </td> <td style="vertical-align: top; width: 33%;"> TYPE OF APPLICATION/SUBMISSION <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 </td> <td style="vertical-align: top; width: 33%;"> REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION </td> </tr> </table>						TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <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	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <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	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION						
EDR link to submission: EDR Location: \CDSESUB1\EVSPROD\NDA022406\0059 Global Submit: \CDSESUB1\EVSPROD\NDA022406\022406.enx								
<p>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.</p>								
COMMENTS/SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review, provide comment and attend any related meetings (from your discipline perspective). EDR Location: \CDSESUB1\EVSPROD\NDA022406\0059 Global Submit: \CDSESUB1\EVSPROD\NDA022406\022406.enx Please contact Marcus Cato for any questions 301-796-3903 <table style="width: 100%; border: none; margin-top: 10px;"> <tr> <td style="width: 33%; vertical-align: top;"> Clinical Reviewer Regulatory Project Manager </td> <td style="width: 33%; vertical-align: top;"> Reviewer Lu, Min Cato, Marcus </td> <td style="width: 33%; vertical-align: top;"> Team Leader Robie Suh, Kathy M Jamison, Janet </td> </tr> </table>						Clinical Reviewer Regulatory Project Manager	Reviewer Lu, Min Cato, Marcus	Team Leader Robie Suh, Kathy M Jamison, Janet
Clinical Reviewer Regulatory Project Manager	Reviewer Lu, Min Cato, Marcus	Team Leader Robie Suh, Kathy M Jamison, Janet						
PDUFA Goal Date: July 3, 2011								
SIGNATURE OF REQUESTER								
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND					

Reference ID: 2904479

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>			
TO (Office/Division): Pediatric and Maternal Health Staff (PMHS)			FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Hematology Products		
DATE February 11, 2011	IND NO.	NDA NO. NDA-022406	TYPE OF DOCUMENT Resubmission/Class 2	DATE OF DOCUMENT January 3, 2011	
NAME OF DRUG XARELTOTM (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE TBD	
NAME OF FIRM: J&J					
REASON FOR REQUEST					
I. GENERAL					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>					
II. BIOMETRICS					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <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): </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>					
III. BIOPHARMACEUTICS					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div> </div>					
IV. DRUG SAFETY					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <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 </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </div> </div>					
V. SCIENTIFIC INVESTIGATIONS					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> CLINICAL </div> <div style="width: 50%;"> <input type="checkbox"/> NONCLINICAL </div> </div>					
<p>COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTOTM (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (labeling), provide comment and attend any related meetings (from your discipline perspective).</p> <p>EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059</p> <p>Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx</p> <p>Please contact Marcus Cato for any questions 301-796-3903</p> <div style="display: flex; justify-content: space-between;"> <div> <p>Reviewer Team Leader</p> <p>Clinical Reviewer Lu, Min Robie Suh, Kathy M</p> <p>Non-Clinical Reviewer Chopra, Yash M Saber, Haleh</p> <p>Regulatory Project Manager Cato, Marcus Jamison, Janet</p> <p>Clinical Pharm. Reviewer Grillo, Joseph Bullock, Julie</p> </div> <div style="text-align: right;"> <p>Reference ID: 2904484</p> </div> </div>					

PDUFA Goal Date: July 3, 2011	
SIGNATURE OF REQUESTOR Marcus Cato	METHOD OF DELIVERY (Check one) <input checked="" 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/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Office/Division): Quantitative safety team in the Office of Biostatistics/through Mandi Yu			FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Hematology Products	
DATE February 11, 2011	IND NO.	NDA NO. NDA-022406	TYPE OF DOCUMENT Resubmission/Class 2	DATE OF DOCUMENT January 3, 2011
NAME OF DRUG XARELTO™ (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE March 30, 2011
NAME OF FIRM: J&J				
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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Resub/Class 2				
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 type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (the ROCKET study for liver safety evaluation and verification), provide comment and attend any related meetings (from your discipline perspective). EDR Location: \\CDSESUBI\EVSPROD\NDA022406\0059 Global Submit: \\CDSESUBI\EVSPROD\NDA022406\022406.enx Please contact Marcus Cato for any questions 301-796-3903				
Clinical Reviewer Non-Clinical Reviewer Regulatory Project Manager Clin.Pharm. Reviewer		Reviewer Lu, Min Chopra, Yash M Cato, Marcus Grillo, Joseph	Team Leader Robie Suh, Kathy M Saber, Haleh Jamison, Janet Bullock, Julie	
PDUFA Goal Date:		July 3, 2011		
SIGNATURE OF REQUESTOR Marcus Cato			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER Reference ID: 2904471			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>		
TO (Office/Division): GOOD CLINICAL PRACTICES BRANCH II OC/CDER/OC/DSI/GCPBII/		FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Hematology Products		
DATE February 11, 2011	IND NO.	NDA NO. NDA-022406	TYPE OF DOCUMENT Resubmission/Class 2	DATE OF DOCUMENT January 3, 2011
NAME OF DRUG XARELTO™ (Rivaroxaban)	PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE March 30, 2011	
NAME OF FIRM: J&J				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Resub/Class 2 </div> </div>				
II. BIOMETRICS				
<div style="display: flex;"> <div style="width: 50%;"> <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): </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>				
III. BIOPHARMACEUTICS				
<div style="display: flex;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div> </div>				
IV. DRUG SAFETY				
<div style="display: flex;"> <div style="width: 50%;"> <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 </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </div> </div>				
V. SCIENTIFIC INVESTIGATIONS				
<div style="display: flex;"> <div style="width: 50%;"> <input type="checkbox"/> CLINICAL </div> <div style="width: 50%;"> <input type="checkbox"/> NONCLINICAL </div> </div>				
COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review, provide comment and attend any related meetings (from your discipline perspective). EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx Please contact Marcus Cato for any questions 301-796-3903				
Clinical Reviewer Non-Clinical Reviewer Regulatory Project Manager Clin.Pharm. Reviewer		Reviewer Lu, Min Chopra, Yash M Cato, Marcus Grillo, Joseph	Team Leader Robie Suh, Kathy M Saber, Haleh Jamison, Janet Bullock, Julie	
PDUFA Goal Date:		July 3, 2011		
SIGNATURE OF REQUESTOR Marcus Cato		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER Reference ID: 2904461		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): DIVISION OF RISK MANAGEMENT (OC/CDER/OSE/DRISK/)		FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Hematology Products		
DATE February 11, 2011	IND NO.	NDA NO. NDA-022406	TYPE OF DOCUMENT Resubmission/Class 2	DATE OF DOCUMENT January 3, 2011
NAME OF DRUG XARELTO™ (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE March 30, 2011
NAME OF FIRM: J&J				
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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Resub/Class 2				
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 type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (for possible liver monitoring), provide comment and attend any related meetings (from your discipline perspective). EDR Location: \\CDSESUBI\EVSPROD\NDA022406\0059 Global Submit: \\CDSESUBI\EVSPROD\NDA022406\022406.enx Please contact Marcus Cato for any questions 301-796-3903				
Clinical Reviewer Non-Clinical Reviewer Regulatory Project Manager Clin.Pharm. Reviewer		Reviewer Lu, Min Chopra, Yash M Cato, Marcus Grillo, Joseph		
		Team Leader Robie Suh, Kathy M Saber, Haleh Jamison, Janet Bullock, Julie		
PDUFA Goal Date:		July 3, 2011		
SIGNATURE OF REQUESTOR Marcus Cato		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER Reference ID: 2904459		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION																	
TO (Office/Division): DIVISION OF MEDICATION ERROR PREVENTION & ANALYSIS (OC/CDER/OSE/DMEPA/)		FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Hematology Products																	
DATE February 11, 2011	IND NO.	NDA NO. NDA-022406	TYPE OF DOCUMENT Resubmission/Class 2	DATE OF DOCUMENT January 3, 2011															
NAME OF DRUG XARELTO™ (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE March 30, 2011															
NAME OF FIRM: J&J																			
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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Resub/Class 2																			
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 type="checkbox"/> NONCLINICAL																			
COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (Labeling/Trade Name), provide comment and attend any related meetings (from your discipline perspective). EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx Please contact Marcus Cato for any questions 301-796-3903 <table border="0"> <tr> <td>Clinical Reviewer</td> <td>Reviewer</td> <td>Team Leader</td> </tr> <tr> <td>Non-Clinical Reviewer</td> <td>Lu, Min</td> <td>Robie Suh, Kathy M</td> </tr> <tr> <td>Regulatory Project Manager</td> <td>Chopra, Yash M</td> <td>Saber, Haleh</td> </tr> <tr> <td>Clin.Pharm. Reviewer</td> <td>Cato, Marcus</td> <td>Jamison, Janet</td> </tr> <tr> <td></td> <td>Grillo, Joseph</td> <td>Bullock, Julie</td> </tr> </table>					Clinical Reviewer	Reviewer	Team Leader	Non-Clinical Reviewer	Lu, Min	Robie Suh, Kathy M	Regulatory Project Manager	Chopra, Yash M	Saber, Haleh	Clin.Pharm. Reviewer	Cato, Marcus	Jamison, Janet		Grillo, Joseph	Bullock, Julie
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	Grillo, Joseph	Bullock, Julie																	
PDUFA Goal Date: July 3, 2011																			
SIGNATURE OF REQUESTOR Marcus Cato		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND																	
PRINTED NAME AND SIGNATURE OF RECEIVER Reference ID: 2904456		PRINTED NAME AND SIGNATURE OF DELIVERER																	

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): DIVISION OF EPIDEMIOLOGY (OC/CDER/OSE/DEPI): c/o Dr. John Senior, Dr. Kate Gelperin		FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Hematology Products		
DATE February 11, 2011	IND NO.	NDA NO. NDA-022406	TYPE OF DOCUMENT Resubmission/Class 2	DATE OF DOCUMENT January 3, 2011
NAME OF DRUG XARELTO™ (Rivaroxaban)		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE March 30, 2011
NAME OF FIRM: J&J				
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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Resub/Class 2				
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IV. DRUG SAFETY				
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V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review data related to liver toxicity. provide comment and attend any related meetings (from your disciple perspective). EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx Please contact Marcus Cato for any questions 301-796-3903				
Clinical Reviewer Non-Clinical Reviewer Regulatory Project Manager Clin.Pharm. Reviewer		Reviewer Lu, Min Chopra, Yash M Cato, Marcus Grillo, Joseph		Team Leader Robie Suh, Kathy M Saber, Haleh Jamison, Janet Bullock, Julie
PDUFA Goal Date:		July 3, 2011		
SIGNATURE OF REQUESTOR Marcus Cato		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER Reference ID: 2904455		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

MARCUS A CATO
02/11/2011

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, January 27, 2011 11:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request
Importance: High
Attachments: eDISHdataRequirement.xls; narrative_enter_by_hand.sas

Dear Andrea,

We would like you to submit clinical narratives in a SAS data set and send to us by direct mail (FedEx or UPS), rather than to the EDR system.

Attached are:

1. An Excel file detailing data requirements including why and how to create reviewable clinical narratives by your company's physicians (not by computer technicians and no data dumps to the Agency)
2. A SAS program that enables your SAS program to create the narratives we want.

The files can be sent to me at the address below.

Marcus Cato
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5241
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

We are requesting a response by **12:00 PM Friday February 4, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Reference ID: 2901538

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

2/5/2011

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/s/

MARCUS A CATO
02/05/2011



NDA 22406

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

We acknowledge receipt on January 3, 2011, of your December 30, 2010, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) Tablets.

We consider this a complete, Class 2 response to our May 27, 2009, action letter. Therefore, the user fee goal date is July 3, 2011.

If you have any questions, call me at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

MARCUS A CATO
01/14/2011

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE: October 14, 2010 – April 15, 2011
APPLICATION NUMBER: NDA 22406

BETWEEN:

Name: Andrea Kollath, DVM,
Global Regulatory Affairs
e-mail: akollath@its.jnj.com
Representing: Johnson & Johnson Pharmaceutical Research &
Development, L.L.C.

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

SUBJECT: Information Requests/General Correspondence

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, April 15, 2011 4:44 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus,

Regarding these questions, we wanted to know if the Reviewer was aware of the responses sent to CardioRenal Division ? On Feb 28 Sequence #23- an updated combined dataset was sent to CardioRenal. Does the Reviewer have access to that database?

Do the NDA 22-406 Reviewers have access to the responses sent to CardioRenal in general?

Thanks

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, April 14, 2011 1:29 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request

Dear Andrea,

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

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We are requesting a response by **12:00 PM Monday April 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, April 14, 2011 1:34 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus,
I will review this with our statisticians right away.
Kind regards,
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, April 14, 2011 1:29 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request

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

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We are requesting a response by **12:00 PM Monday April 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Thursday, April 14, 2011 1:23 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Attachments: Liver Safety Review Issues v2.doc

Dear Andrea,

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

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.



Liver Safety Review
Issues v2....

We are requesting a response by **12:00 PM Monday April 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Thursday, April 14, 2011 1:29 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Attachments: Liver Safety Review Issues v2.doc

Dear Andrea,

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

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.



Liver Safety Review
Issues v2....

We are requesting a response by **12:00 PM Monday April 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, April 06, 2011 10:12 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 202439 seq 0036

Hi Andrea,

Thanks, will do

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, April 05, 2011 11:26 PM
To: Cato, Marcus
Subject: NDA 202439 seq 0036

Dear Marcus,

The attached cover letter was filed with a submission to the Division of Cardiovascular and Renal products with a cc to the Division of Hematology.

If you have any questions please let me know.

Best regards

Andrea

<<...>>

Date Dispatched: 5 April 2011

E-Sub Server Path/Gateway Receipt and Core ID Information (one for each submission/sequence):

Note: The dispatch notification process has been enhanced to decrease the size of emails and increase efficiencies. All Gateway dispatch notices now note the Core ID Number which is found within the Gateway receipt. This information is also included within the WRAT entry of Gateway submissions. Please contact any US GSO Publisher with questions regarding this update.

Archive\leCTD\NDA\202439\0036\m1\us

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, March 31, 2011 11:40 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 PUDUFA action date

Hi Andrea,

Sorry for the delay in reply, the action date is technically July 3rd 2011. It may be best to treat the action date as July 1st.

Thanks
~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, March 28, 2011 10:58 AM
To: Cato, Marcus
Subject: NDA 22-406 PUDUFA action date

Hi Marcus

We have a question on when the action date for this current application is. We submitted our complete response to FDA on Dec 30th, the 31st was a holiday, and the FDA receipt is from Jan 3rd.

The action date is the 3rd of July, which is a Sunday, Monday is July 4th holiday, so when can we expect a response? July 1st or July 5th?

It may seem trivial but it has an impact on the company.

Thank you and Kind regards
Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, March 28, 2011 10:58 AM
To: Cato, Marcus
Subject: NDA 22-406 PUDUFA action date

Hi Marcus

We have a question on when the action date for this current application is. We submitted our complete response to FDA on Dec 30th, the 31st was a holiday, and the FDA receipt is from Jan 3rd.

The action date is the 3rd of July, which is a Sunday, Monday is July 4th holiday, so when can we expect a response? July 1st or July 5th?

It may seem trivial but it has an impact on the company.

Thank you and Kind regards

Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, February 28, 2011 1:03 PM
To: Kang, Sue; Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Attachments: ORS_Cover_Letter_Proprietary Name Request__2_.pdf; ORS NDA request tradename review Feb 25 2011.pdf; emfalert.txt



ORS_Cover_Letter_Proprietary N...
_Proprietary N...
ORS NDA request tradename revi...
emfalert.txt (659 B)

Dear Ms. Kang and Marcus,

Attached please find a copy of the cover letter and the request for proprietary name review submitted through Gateway on Friday February 25, 2011 to the Division of Medication Error Prevention and Analysis.

If you have any questions please contact me any time.
Kind regards,

Andrea

From: Kollath, Andrea [PRDUS]
Sent: Friday, February 25, 2011 11:46 AM
To: Kang, Sue
Cc: Marcus.Cato@fda.hhs.gov
Subject: RE: NDA 22406 (rivaroxaban)

Dear Ms. Kang,

I will be send out the letter today or Monday.
I can cc you on the Gateway submission cover letter and attachment.
We recently send a similar request for the new NDA submitted to Division of Cardiovascular and Renal Products. I will use the same format and information. See below.
Best regards,
Andrea

“REQUEST FOR PROPRIETARY NAME REVIEW” with regard to the New Drug Application (NDA) 202,439 for rivaroxaban, an oral anticoagulant, which is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Friday, February 25, 2011 10:47 AM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Dr. Kollath,

Can you provide me with an update as to when you plan on submitting your request to review a proprietary name?

Kind regards,
Sue Kang
Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]

Sent: Tuesday, February 15, 2011 3:53 PM

To: Kang, Sue

Cc: Cato, Marcus

Subject: RE: NDA 22406 (rivaroxaban)

Dear Sue,

We will provide the requested amendment.

Thank you.

Andrea

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]

Sent: Tuesday, February 15, 2011 3:37 PM

To: Kollath, Andrea [PRDUS]

Cc: Cato, Marcus

Subject: NDA 22406 (rivaroxaban)

Dr. Kollath,

As a follow-up to our phone conversation this afternoon regarding your proprietary name review, you will need to submit an amendment to your NDA and code this amendment as a request for review of a proprietary name. This submission will trigger a 90 day review clock. In your submission, if no product characteristics have changed since the original NDA submission, you may reference the proprietary name information from your original NDA submission.

If you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Sue Kang
Project Manager

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

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email or telephone.**

Cato, Marcus

From: Cato, Marcus
Sent: Monday, February 28, 2011 12:52 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

ok, Thanks
~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, February 28, 2011 12:35 PM
To: Cato, Marcus
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Marcus.

Correct. We are planning on submitting the clinical narratives around the end of this week to Division of Cardiovascular and Renal Products and a copy of the cover letter to you.

Is that sufficient?
Kind regards
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, February 28, 2011 8:51 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Andrea,

Thanks. Were you all still planning to submit clinical narratives in a SAS (version 9.2) data by direct mail (FedEx or UPS). I heard a few different things, last I heard was you were in early March?
Thanks
~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study
Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

If you have any questions please contact me.
Kind regards
Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, February 28, 2011 12:35 PM
To: Cato, Marcus
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Attachments: emfalert.txt



emfalert.txt (659 B)

Hi Marcus.

Correct. We are planning on submitting the clinical narratives around the end of this week to Division of Cardiovascular and Renal Products and a copy of the cover letter to you.

Is that sufficient?
Kind regards
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, February 28, 2011 8:51 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

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Thanks. Were you all still planning to submit clinical narratives in a SAS (version 9.2) data by direct mail (FedEx or UPS). I heard a few different things, last I heard was you were in early March?
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~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study

Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

Cato, Marcus

From: Cato, Marcus
Sent: Monday, February 28, 2011 8:51 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Andrea,

Thanks. Were you all still planning to submit clinical narratives in a SAS (version 9.2) data by direct mail (FedEx or UPS). I heard a few different things, last I heard was you were in early March?

Thanks
~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study

Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

If you have any questions please contact me.
Kind regards
Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study

Attachments: CL response to IR eDISH datasets Feb 25 2011.pdf



CL response to IR
eDISH datasete...

Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

If you have any questions please contact me.

Kind regards

Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 11:46 AM
To: Kang, Sue
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Dear Ms. Kang,

I will be send out the letter today or Monday.

I can cc you on the Gateway submission cover letter and attachment.

We recently send a similar request for the new NDA submitted to Division of Cardiovascular and Renal Products. I will use the same format and information. See below.

Best regards,
Andrea

“REQUEST FOR PROPRIETARY NAME REVIEW” with regard to the New Drug Application (NDA) 202,439 for rivaroxaban, an oral anticoagulant, which is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Friday, February 25, 2011 10:47 AM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Dr. Kollath,

Can you provide me with an update as to when you plan on submitting your request to review a proprietary name?

Kind regards,
Sue Kang
Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]

Sent: Tuesday, February 15, 2011 3:53 PM

To: Kang, Sue

Cc: Cato, Marcus

Subject: RE: NDA 22406 (rivaroxaban)

Dear Sue,

We will provide the requested amendment.

Thank you.

Andrea

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]

Sent: Tuesday, February 15, 2011 3:37 PM

To: Kollath, Andrea [PRDUS]

Cc: Cato, Marcus

Subject: NDA 22406 (rivaroxaban)

Dr. Kollath,

As a follow-up to our phone conversation this afternoon regarding your proprietary name review, you will need to submit an amendment to your NDA and code this amendment as a request for review of a proprietary name. This submission will trigger a 90 day review clock. In your submission, if no product characteristics have changed since the original NDA submission, you may reference the proprietary name information from your original NDA submission.

If you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Sue Kang

Project Manager

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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Tel: 301-796-4216

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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, February 15, 2011 3:53 PM
To: Kang, Sue
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Dear Sue,
We will provide the requested amendment.
Thank you.
Andrea

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Tuesday, February 15, 2011 3:37 PM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: NDA 22406 (rivaroxaban)

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If you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Sue Kang
Project Manager

Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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Bldg. 22; Room 3475
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Tel: 301-796-4216
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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, February 07, 2011 11:36 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus,
No problem, just wanted to make sure.
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, February 07, 2011 11:12 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22406 Information Request

Hi Andrea,

It is for Rivaroxaban, forgive me it was a typographical error...

Thanks
~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, February 07, 2011 8:22 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Hi Marcus,
I am confirming receipt of this message and I have a question. I am wondering why you quoted "section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection."
? This is for Rivaroxaban? An oral tablet.
Kind regards
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Saturday, February 05, 2011 2:04 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request

Dear Andrea,

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

We are reviewing the clinical pharmacology section in 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. Submit the study report, control streams and datasets used for the simulations to assess appropriateness of 5 mg rivaroxaban dose in subjects receiving strong inhibitors of both CYP3A4 and P-gP. All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt).

2. Your document "Rivaroxaban: Complete Response to FDA Letter of May 27, 2009" on Page 27 under "Patients with Child-Pugh class B hepatic impairment without coagulopathy" states that: "Furthermore, PT both at baseline and during treatment with rivaroxaban was more pronounced in Child Pugh class B subjects due to the underlying hepatic disease which impairs the ability of the liver to synthesize clotting factors. This led to a increased pharmacodynamic response and a steeper PK/PD relationship between rivaroxaban plasma concentrations and PT in Child Pugh class B patients (7.8 seconds/(100 µg/L) for C-P class B patients versus 3.1 seconds/(100 µg/L) for healthy subjects with normal hepatic function)."

Submit the data and report to support these findings or direct us to the document that provides more detail about these findings.

We are requesting a response by **12:00 PM Friday February 18, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Saturday, February 05, 2011 2:04 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Dear Andrea,

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

We are reviewing the clinical pharmacology section in 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. Submit the study report, control streams and datasets used for the simulations to assess appropriateness of 5 mg rivaroxaban dose in subjects receiving strong inhibitors of both CYP3A4 and P-gP. All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt).
2. Your document "Rivaroxaban: Complete Response to FDA Letter of May 27, 2009" on Page 27 under "Patients with Child-Pugh class B hepatic impairment without coagulopathy" states that: "Furthermore, PT both at baseline and during treatment with rivaroxaban was more pronounced in Child Pugh class B subjects due to the underlying hepatic disease which impairs the ability of the liver to synthesize clotting factors. This led to a increased pharmacodynamic response and a steeper PK/PD relationship between rivaroxaban plasma concentrations and PT in Child Pugh class B patients (7.8 seconds/(100 µg/L) for C-P class B patients versus 3.1 seconds/(100 µg/L) for healthy subjects with normal hepatic function)."

Submit the data and report to support these findings or direct us to the document that provides more detail about these findings.

We are requesting a response by **12:00 PM Friday February 18, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, March 16, 2011 4:44 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Dear Andrea,

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

We are reviewing the clinical section in 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. Provide a summary of the incidence of ischemic stroke during on and off (within 30 days) treatment period in each of following studies: Rocket, J-Rocket, Einstein DVT, PE, and Extension, Atlas ACS Timi 46, 11223, and 11528.

2. Provide a summary of clinical outcomes of patients who had hepatic disorder adverse events leading to permanent study drug discontinuation in each of following studies: Rocket, J-Rocket, and Einstein DVT, PE, and Extension.

We are requesting a response by **12:00 PM Friday March 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, February 03, 2011 3:03 PM
To: Cato, Marcus
Subject: Telecon Feb 4 2011 3:30 to 4 PM

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus,
We are available for the telecon at this time.

Please use this call in number:

North American Dial-In Number: **(888) 627-7005**
Conference Code: **619833 #**

Kind regards
Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126*

akollath@its.jnj.com

Cato, Marcus

From: Cato, Marcus
Sent: Monday, January 31, 2011 10:32 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22406 Information Request

Hi Andrea,

Will share with the team and get back to you.

Thanks

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, January 31, 2011 10:23 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Dear Marcus,

We met with our team on Friday and are hoping we have a better understanding of what you are asking for.

The e-Dish datasets for the ROCKET study can be provided within the next few days.

The narratives which are in the HEAC packets were manually generated for the HEAC members to review and therefore cannot be provided in SAS program.

Local lab values which were relevant were included in the narratives.

Again, if this is not what you were asking please contact me.

Best regards

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 2:18 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22406 Information Request

Hi Andrea,

Yes. we were able to find the narratives. We would like you to clarify if the submitted ISLS has included LFTs from local labs in all completed phase 3 studies (2 ROCKET studies and 2 EINSTEIN studies) in the safety analysis including HEAC evaluations.

Thanks

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 27, 2011 12:44 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Hi Marcus,

We have a question.

Is this request specific to liver-related narratives or all narratives. If liver-related, are there specific cases or is this for all the 201 HEAC reviewed cases?

Kind regards,

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:36 AM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request
Importance: High

Dear Andrea,

We would like you to submit clinical narratives in a SAS data set and send to us by direct mail (FedEx or UPS), rather than to the EDR system.

Attached are:

1. An Excel file detailing data requirements including why and how to create reviewable clinical narratives by your company's physicians (not by computer technicians and no data dumps to the Agency)
2. A SAS program that enables your SAS program to create the narratives we want.

The files can be sent to me at the address below.

Marcus Cato

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22, Room: 5241

10903 New Hampshire Avenue

Silver Spring, Maryland 20903

We are requesting a response by **12:00 PM Friday February 4, 2011.**

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, January 31, 2011 10:31 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus,

No problem,

Please the latest message from today.

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, January 31, 2011 10:29 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22406 Information Request

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Attachments: emfinfo.txt



emfinfo.txt (582 B)

Dear Marcus,

We met with our team on Friday and are hoping we have a better understanding of what you are asking for.

The e-Dish datasets for the ROCKET study can be provided within the next few days.

The narratives which are in the HEAC packets were manually generated for the HEAC members to review and therefore cannot be provided in SAS program.

Local lab values which were relevant were included in the narratives.

Again, if this is not what you were asking please contact me.

Best regards

Andrea

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2. A SAS program that enables your SAS program to create the narratives we want.

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, January 27, 2011 11:53 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22406 Information Request

FYI - the request is to create a version 9 SAS data set for the narratives.

Thanks

~Marcus

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From: Cato, Marcus
Sent: Thursday, January 27, 2011 11:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request
Importance: High

Dear Andrea,

We would like you to submit clinical narratives in a SAS data set and send to us by direct mail (FedEx or UPS), rather than to the EDR system.

Attached are:

1. An Excel file detailing data requirements including why and how to create reviewable clinical narratives by your company's physicians (not by computer technicians and no data dumps to the Agency)
2. A SAS program that enables your SAS program to create the narratives we want.

The files can be sent to me at the address below.

Marcus Cato

Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5241
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

We are requesting a response by **12:00 PM Friday February 4, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, January 27, 2011 11:44 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus,

I have received the request and we will start on this.

Kind regards,

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:36 AM
To: Kollath, Andrea [PRDUS]
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Subject: NDA 22406 Information Request

Importance: High

Attachments: eDISHdataRequirement.xls; narrative_enter_by_hand.sas



eDISHdataRequire ment.xls (37 K... narrative_enter_by _hand.sas (6...

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From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, January 27, 2011 11:32 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 Complete Response location of HEAC Packets

Attachments: emfalert.txt



emfalert.txt (659 B)

Hi Marcus,

Thanks for the advance notice. Just let us know what you need and we are happy to help.

Kind regards

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:24 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 Complete Response location of HEAC Packets

Hi Andrea,

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~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, January 24, 2011 9:15 AM
To: Cato, Marcus
Subject: NDA 22-406 Complete Response location of HEAC Packets

Hi Marcus,

I just want to make sure that the information I sent was helpful or not. Has the Reviewer been able to locate the HEAC packets of information including the narratives?

Kind regards

Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs*

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

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

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

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Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs*

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920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, January 18, 2011 12:17 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Attachments: Response to FDA Q Jan 11 2011 on location of HEAC Packets_3_.pdf; emfinfo.txt



Response to FDA Q emfinfo.txt (582 B)
Jan 11 2011 ...

Hi Marcus,

Attached please see a list of the detailed location for the Hepatic Assessment Committee (HEAC) packets. Please note the HEAC packets include the patient narratives, the evaluation pages by the HEAC members and the patient profiles as well as the CIOMS.

If you have any questions please contact me.

Best regards

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 13, 2011 3:58 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea

Our reviewer was unable to locate the patient narratives/CRFs based on the pages from the table. As you have submitted many separated PDF files. Could you please include specific names of files and pages for patient narratives, CRFs, and HPAC assessment in the table below.

Warmly,

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 13, 2011 12:18 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

- 1) The patient narratives and case report forms (HEAC packets) for the patients reviewed by the hepatic event assessment committee (HEAC) are located in the following sections for each study, please see table below:
- 2) The HEAC causality assessment summary for each patient can be found listed by the HEAC member name under the HEAC packet.

In general:

Discussion of cases with combined ALT >3x ULN and total bilirubin >2 x ULN with

HEAC causality assessments of majority possible or higher and for other HEAC criteria

cases with majority probable or higher is provided for each individual study in Appendix 1.1 (starting on page 91 of the ISLS) and summarized across the program in Sections 2.4.1 and 2.4.2.

Cases of interest are defined as “at least 2 possible or higher HEAC causality assessments”

Study

Rivaroxaban

Comparator

Total

Source

ROCKET AF 11630

75

76

151

ISLS page 130

All cases located in ROCKET CSR Appendix 4

J-ROCKET 12620

9

5

14

ISLS page 170

All cases located in HEAC packets for J-ROCKET

EINSTEIN 11702 (DVT)

8

12

20

ISLS page 193

All cases located in EINSTEIN DVT CSR/MRR Appendix 16.4.1.3

EINSTEIN Extension (11899)

1

0

1

ISLS page 210

All cases located in EINSTEIN Ext CSR/MRR Appendix 16.4.1.3 and 16.4.1.4

EINSTEIN PE (11702)

(ongoing but open-label)

9

6

15

ISLS page 296

Only 2 cases of interest in ISLS Appendix 7.1.1.5

(other cases not included as this is a ongoing study)

TOTAL

102

99

201

ISLS: pages 64 and 65

ATLAS ACS 2 TIMI 51

Please note that ATLAS ACS 2 TIMI 51 study 13194 is not unblinded and therefore we do not know the number of rivaroxaban and comparator cases. There were a total of 18 subjects with ALT >3xULN and total bilirubin >2xULN concurrently and/or non-concurrently at any time in the study (see Table ISLS1.4 and Table ISLS1.3 in Appendix 7.1.2.1). (page 303 of the ISLS)

The HEAC packets are available in App 7.1.2.5 (four cases of interest)

-

Spontaneous reports

A total of 22 cases of interest were reviewed by HEAC. HEAC packets sent for review and the HEAC reviewer clinical evaluation forms and narratives for cases in Table 8.2.-5 can be found in Appendix 8.2.1.

-

If it would be helpful for us to meet with the Reviewer and walk through the location of any of the data

we would be happy to do so.

Let me know if there are any other questions.

Best regards

Andrea

-
-
-
-
-

From: Cato, Marcus
Sent: Tuesday, January 11, 2011 9:00 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea,

We need patient narratives and case report forms for all patients (about 200 cases) who were reviewed by hepatic event assessment committee (HEAC). An HEAC causality assessment summary for each patient should also be submitted for review.

Our reviewer was unable to find all the information in the submission. She could only see CRFs for cases (only 20 cases) of the combined ALT>3xULN with total bilirubin >2x ULN cases with at least 2 possible or higher HEAC causality assessments from the Phase 3 clinical program in the submission.

Please submit this information or let us know the location if you have submitted.

Warmly

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 06, 2011 12:56 PM
To: Cato, Marcus
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

Please note that in the Sponsor Complete response all liver-related safety information is provided in a separate document, the Integrated Summary of Liver Safety (ISLS) which is located in Mod 5.3.5.3.

The *datasets* for the ISLS are provided to FDA in *NDA 202439*, submitted to the Cardio Renal Division yesterday January 5th for the indication of prevention of stroke and non CNS systemic embolism in patients with non-valvular atrial fibrillation.

If you have any questions regarding the ISLS datasets please contact me.

Kind regards

Andrea

From: Kollath, Andrea [PRDUS]
Sent: Monday, January 03, 2011 11:18 AM
To: 'Cato, Marcus'; susan.thompson1@fda.hhs.gov
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Dr. Thompson and Marcus,

Happy New Year to both of you.

Attached please find the cover letter of the sponsor complete response submitted Dec 30th last week.

Marcus,

If you have any questions regarding the submission please contact me.

Kind regards

Andrea

*Andrea Kollath, DVM,
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.*

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

From: Kollath, Andrea [PRDUS]
Sent: Wednesday, December 29, 2010 11:21 AM
To: Cato, Marcus
Subject: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Marcus,

Happy Holidays to you!

I wanted to let you know we are providing our sponsor complete response on December 30th to the FDA action letter received in May of 2009 for XARELTO[®] (rivaroxaban) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

I will send you a copy of the cover letter.

Kind regards

Andrea

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Global Regulatory Affairs*

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

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

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Cato, Marcus

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To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

ok

Thanks

~Marcus

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Total

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ISLS page 130

All cases located in ROCKET CSR Appendix 4

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EINSTEIN 11702 (DVT)

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ISLS page 193

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(ongoing but open-label)

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ISLS page 296

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~Marcus

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Silver Spring, MD 20903. Thank you.

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 13, 2011 12:18 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

- 1) The patient narratives and case report forms (HEAC packets) for the patients reviewed by the hepatic event assessment committee (HEAC) are located in the following sections for each study, please see table below:
- 2) The HEAC causality assessment summary for each patient can be found listed by the HEAC member name under the HEAC packet.

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cases with majority probable or higher is provided for each individual study in Appendix 1.1 (starting on page 91 of the ISLS) and summarized across the program in Sections 2.4.1 and 2.4.2.

Cases of interest are defined as “at least 2 possible or higher HEAC causality assessments”

Study

Rivaroxaban

Comparator

Total

Source

ROCKET AF 11630

75

76

151

ISLS page 130

All cases located in ROCKET CSR Appendix 4

J-ROCKET 12620

9

5

14

ISLS page 170

All cases located in HEAC packets for J-ROCKET

EINSTEIN 11702 (DVT)

8

12

20

ISLS page 193

All cases located in EINSTEIN DVT CSR/MRR Appendix 16.4.1.3

EINSTEIN Extension (11899)

1

0

1

ISLS page 210

All cases located in EINSTEIN Ext CSR/MRR Appendix 16.4.1.3 and 16.4.1.4

EINSTEIN PE (11702)

(ongoing but open-label)

9

6

15

ISLS page 296

Only 2 cases of interest in ISLS Appendix 7.1.1.5

(other cases not included as this is a ongoing study)

TOTAL

102

99

201

ISLS: pages 64 and 65

ATLAS ACS 2 TIMI 51

Please note that ATLAS ACS 2 TIMI 51 study 13194 is not unblinded and therefore we do not know the number of rivaroxaban and comparator cases. There were a total of 18 subjects with ALT >3xULN and total bilirubin >2xULN concurrently and/or non-concurrently at any time in the study (see Table ISLS1.4 and Table ISLS1.3 in Appendix 7.1.2.1). (page 303 of the ISLS)

The HEAC packets are available in App 7.1.2.5 (four cases of interest)

-

Spontaneous reports

A total of 22 cases of interest were reviewed by HEAC. HEAC packets sent for review and the HEAC reviewer clinical evaluation forms and narratives for cases in Table 8.2.-5 can be found in Appendix 8.2.1.

-

If it would be helpful for us to meet with the Reviewer and walk through the location of any of the data we would be happy to do so.

Let me know if there are any other questions.

Best regards

Andrea

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From: Cato, Marcus

Sent: Tuesday, January 11, 2011 9:00 AM

To: 'Kollath, Andrea [PRDUS]'

Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Importance: High

Hi Andrea,

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Our reviewer was unable to find all the information in the submission. She could only see CRFs for cases (only 20 cases) of the combined ALT>3xULN with total bilirubin >2x ULN cases with at least 2 possible or higher HEAC causality assessments from the Phase 3 clinical program in the submission.

Please submit this information or let us know the location if you have submitted.

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 06, 2011 12:56 PM
To: Cato, Marcus
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

Please note that in the Sponsor Complete response all liver-related safety information is provided in a separate document, the Integrated Summary of Liver Safety (ISLS) which is located in Mod 5.3.5.3.

The *datasets* for the ISLS are provided to FDA in *NDA 202439*, submitted to the Cardio Renal Division yesterday January 5th for the indication of prevention of stroke and non CNS systemic embolism in patients with non-valvular atrial fibrillation.

If you have any questions regarding the ISLS datasets please contact me.

Kind regards

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Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Dr. Thompson and Marcus,
Happy New Year to both of you.

Attached please find the cover letter of the sponsor complete response submitted Dec 30th last week.

Marcus,

If you have any questions regarding the submission please contact me.

Kind regards

Andrea

*Andrea Kollath, DVM,
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.*

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

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Sent: Wednesday, December 29, 2010 11:21 AM

To: Cato, Marcus

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Dear Marcus,

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I wanted to let you know we are providing our sponsor complete response on December 30th to the FDA action letter received in May of 2009 for XARELTO[®] (rivaroxaban) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

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akollath@its.jnj.com

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, January 13, 2011 3:58 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea

Our reviewer was unable to locate the patient narratives/CRFs based on the pages from the table. As you have submitted many separated PDF files. Could you please include specific names of files and pages for patient narratives, CRFs, and HPAC assessment in the table below.

Warmly,

~Marcus

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EINSTEIN Extension (11899)

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(ongoing but open-label)

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Importance: High

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Attachments: emfinfo.txt



emfinfo.txt (582 B)

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Rivaroxaban

Comparator

Total

Source

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Do you think a response would be possible by 12:00 today?

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Hi Marcus,

There has not been a manufacturing facility change since the action letter.

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Kind regards

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To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea,

Another question: we need to know if there has been manufacturing facility changes since our action letter. Is this information in the resubmission.

Thanks

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To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Attachments: emfinfo.txt



emfinfo.txt (582 B)

Hi Marcus

I have a question on the list I put together so I will send by noon.

Yesterday we had a “snow” day here so everyone was out. Sorry.

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
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To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
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Attachments: emfinfo.txt



emfinfo.txt (582 B)

Yes. I will send it by 10 AM

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Attachments: emfinfo.txt



emfinfo.txt (582 B)

Dear Marcus

I'm checking to see if my new encryption works.

Please let me know if you can read this?

Just hit reply and send back please.

Thanks

Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs*

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

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NDA 22-406 Dec 27
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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, November 09, 2010 11:30 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Attachments: emfalert.txt



emfalert.txt (1 KB)

Thank you.

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Tuesday, November 09, 2010 10:48 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Hi Andrea,

Your proposal is acceptable.

Thanks

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, November 08, 2010 2:51 PM

To: Cato, Marcus

Subject: RE: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Hi Marcus

Can you let me know if this is an acceptable proposal?

Thanks

Andrea

From: Kollath, Andrea [PRDUS]

Sent: Wednesday, October 27, 2010 1:34 PM

To: Cato, Marcus

Subject: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Dear Marcus,

We are preparing our Complete Response to FDA CR Letter of May 27, 2009.

Under Safety Update, Question 8, we are asked to provide English translations of current approved foreign labeling not previously submitted.

The current list of international approvals for rivaroxaban is over 100 countries. Please see attached list.

We propose to provide English translations for the following countries which we think provide a representative example for the major geographic regions and major markets.

1. European Union
2. Switzerland (non-EU country in Europe)
3. Russia
4. Canada
5. Mexico
6. Brazil
7. Australia

8. New Zealand
9. China
10. India
11. Kenya
12. U.A.E.
13. South Africa

Is this acceptable to the Division of Hematology Products?

Best regards,

Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs*

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

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

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AAPEARS THIS WAY ON ORIGINAL

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Sent: Wednesday, October 27, 2010 1:34 PM
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Attachments: Xarelto (rivaroxaban) regulatory approval status _16062010.pdf; emfalert.txt



Xarelto
varoxaban) regulat



emfalert.txt (1 KB)

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Andrea

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Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, October 15, 2010 10:30 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Attachments: emfalert.txt



emfalert.txt (1 KB)

Thank you.

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Friday, October 15, 2010 9:42 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Hi Andrea

It is acceptable to link to the information, no need to submit twice. We have been discouraging submission of duplicate information.

Thanks

~Marcus

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, October 14, 2010 3:29 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Hi Marcus,

I just want to make sure it is acceptable to FDA? We do not wanted to get cited for missing information.

Thanks

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, October 14, 2010 3:22 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Hi Andrea,

I am not sure the exact details but if its been submitted to the gateway previously... you should be able to link to it in your response... do you have a target date for your response?

Thanks

~Marcus

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This will help with our planning.

Thank you and Best regards,

Andrea

*Andrea Kollath, DVM,
Global Regulatory Affairs*

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

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Raritan NJ 08869

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Attachments: emfalert.txt



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akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, October 14, 2010 3:26 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Attachments: emfalert.txt



emfalert.txt (1 KB)

Hi Marcus,

We plan to submit towards the end of December this year.

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, October 14, 2010 3:22 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

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akollath@its.jnj.com

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

/s/

MARCUS A CATO
06/07/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-406

MEETING MINUTES

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2009. The purpose of the meeting was to discuss the potential planned unblinding of data related to your application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Clinical, Guidance

Meeting Date and Time: November 13, 2009, 10:00 AM - 11:00 AM EST
Meeting Location: CDER WO Building 22, conference room 1419

Application Number: NDA 22-406
Product Name: Xarelto™ (Rivaroxaban) Tablets
Indication: Prophylaxis of Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) in hip or knee surgery
Sponsor/Applicant Name: Johnson & Johnson Pharmaceutical Research and Development (J&J)

Meeting Chair: Dr. Dwaine Rieves
Meeting Recorder: Mr. Marcus Cato

FDA ATTENDEES

OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., M.P.H., Clinical Reviewer
Diane Leaman, Safety Regulatory Project Manager
Ira Krefting, M.D., Safety Deputy Director

OFFICE OF DRUG EVALUATION I/DIVISION OF CARDIOVASCULAR & RENAL
PRODUCTS

Stephen Grant, M.D., Deputy Director
Robert Temple, M.D., Director Office of Drug Evaluation I/Office of Medical Policy

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF
EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer
Gwen Zornberg, M.D., Medical Team Leader
Mark Avigan, M.D., Office Associate Director

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

John R. Senior, M.D., Medical Officer (Hepatotoxicity)
Carr, Catherine, M.S., Regulatory Health Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader
Robert O'Neill, Ph.D., Office Director

OFFICE OF TRANSLATIONAL SCIENCES

Marc Walton, M.D., Associate Director

SPONSOR ATTENDEES

J&J

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters, MD Franchise Medical Leader
Lloyd Haskell, MD, Compound Development Team leader
Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Harry Flanagan, DO, Post-Marketing Benefit Risk Management
G.K. (Dina) Anand MD, Post-Marketing Safety Franchise Leader
Sigmond Johnson, MS, MBA Program Coordination
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs

Bayer

Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head, Thrombosis and Hemostasis
Aasia Bhatti, MD, Deputy Director, Global Pharmacovigilance
Andrea Nadel PhD, Statistical Sciences
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Harald Kallabis, Ph.D., Global Project Leader

1.0 BACKGROUND

In a letter dated May 29, 2009, J&J requested a meeting to obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter (CR). On June 19, 2009, FDA and J&J met to discuss the CR.

In a letter dated July 2, 2009, J&J submitted a proposed liver adjudication panel (LAP) procedural charter, as follow-up to the Type A meeting held on June 19, 2009. On July 31, 2009, FDA met with J&J, to discuss their proposed LAP charter. At the meeting, FDA agreed to meet with J&J again, to discuss the possible unblinding of potential *Hy's Law* cases and other safety conveyance topics, after further internal discussions could be held.

MEETING OBJECTIVES:

To discuss the potential planned unblinding of data related to the application.

2. DISCUSSION

FDA recommends that J&J submit the LAP output to the NDA in a complete response to the Agency action letter. All of the data in the submission should be unblinded (including treatment assignment codes). Alternatively, the sponsor could submit a letter to the application authorizing an unblinded statistician to submit the information to the NDA.

J&J noted that three new reviewers have been selected for the liver adjudication panel and that adjudication will not be by consensus process but rather each adjudicator will adjudicate each case independently. Using a cut-off date of September 15, 2009, it has identified 72 potential *Hy's Law* cases. J&J anticipates submitting the following:

- The fully blinded data package reviewed by the LAP
- The evaluation forms from the LAP review
- Summary Tables

J&J is planning to submit all information blinded. FDA informed J&J that this plan is not acceptable. FDA inquired about J&J's reluctance to unblind the data.

J&J stated that it does not want to jeopardize the four large ongoing trials. It is concerned that unblinding may introduce operational bias and it would like to unblind as few cases and people (including as few FDA reviewers) as possible. Approximately 10 of the 72 subjects are still on study drug as they have not met the discontinuation criteria. FDA clarified that it has to know the safety data and outcomes for these patients and it has to look at the data to make a determination: FDA will be reviewing the data and performing its own analyses. J&J responded that its proposed plan was to submit the full LAP data package along with adjudications from the panel and to have FDA identify cases of interest it would like to discuss at a meeting with the cross study Data and Safety Monitoring Board (DSMB). FDA stated that meeting with J&J's DSMB would not be helpful, since the unblinded safety data for the potential *Hy's law* cases

need to be submitted to the NDA. FDA will be reviewing the data and doing its own analyses independently.

J&J stated that very few of its potential *Hy's Law* cases have been unblinded because they have not meet the per protocol criteria to be unblinded. J&J is very concerned about introducing operational bias and this concern is based on previous interactions with FDA.

FDA is concerned that the Rivaroxaban NDA has an incompletely developed safety database. FDA is concerned that there are 72 potential *Hy's Law* cases and can not approve the pending NDA without full access to the safety data.

FDA clarified that the proposal to limit the number of FDA reviewers who have access to unblinded data is not acceptable. FDA reminded J&J that an alternative to submitting the unblinded data is to wait until the ongoing studies have been completed before responding to the Agency action letter. However, FDA is not encouraging J&J to delay responding. FDA acknowledges that generally sponsors are encouraged to unblind as few subjects in ongoing trials as possible. FDA stated that the situation is unusual in that FDA needs to review safety data from ongoing trials in order to evaluate the safety of rivaroxaban as part of a NDA for another indication.

FDA acknowledges that, in general, it does not anticipate that all 72 cases will actually be *Hy's Law* cases; however, it does need to be able to unblind data for identified cases of interest. J&J wanted assurance that unblinding the data would not negatively impact the FDA perception of the integrity of the ongoing trials. FDA responded that the proposed limited unblinding should not result in a judgment that the integrity of the studies had been compromised, provided the process was pre-specified and carried out according to plan. J&J responded that, if the unblinding of this data will not compromise the studies; it would submit the data itself rather than have an unblinded statistician submit the information on its behalf.

FDA requested that J&J submit the following data in its complete response where ALT, TB and ULN refer to alanine aminotransferase, total bilirubin and upper limit of normal, respectively:

- A. Combined ALT >3xULN and TB >2xULN case information with treatment codes blinded (i.e., the clinical information pertaining to those patients the company has previously identified as potential *Hy's Law* cases based upon plans submitted to the FDA)
- B. Tabular distribution of ALT >3x ULN , ALT > 5X, ALT > 10X data presented by study, by threshold and by treatment group- (A vs. B)
- C. Tabular distribution of concurrent ALT > 3X x ULN and TBL > 2x ULN (within one month) presented by study and by treatment group (A vs. B)
- D. FDA would review the combined ALT + TB cases (potential *Hy's Law* cases) and request treatment codes for specific cases. It would also request unblinded tabular data (i.e., A and B group identified as to specific treatment assignment) if needed during its review of the liver data.

J&J agreed to A. through D. (above).

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
J&J to submit safety data in its Complete Response as specified above	Sponsor	N/A

5.0 ATTACHMENTS AND HANDOUTS

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	ORIG-1	JOHNSON AND JOHNSON PHARMACEUTICA L RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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

/s/

MARCUS A CATO
12/10/2009

RAFEL D RIEVES
12/10/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22406

MEETING MINUTES

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

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 the teleconference between representatives of your firm and the FDA on October 14, 2010. The purpose of the meeting was to discuss the design of a proposed study to evaluate the pharmacokinetics of rivaroxaban in patients with either mild or moderate renal impairment.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure:

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: 11:00 AM – 12:00 PM EST
Meeting Location: White Oak Building 22, Conference Room: 2376

Application Number: NDA 22406
Product Name: Xarelto™ (Rivaroxaban) Tablets
Indication: Prophylaxis of venous thromboembolism (VTE)
Sponsor/Applicant Name: J&JPRD

Meeting Chair: Dr. Julie Bullock
Meeting Recorder: Mr. Marcus Cato

FDA ATTENDEES

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS DIVISION OF HEMATOLOGY PRODUCTS

Edvardas Kaminskas, M.D., Deputy Director (Acting)
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., M.P.H., Clinical Reviewer
Marcus Cato, M.B.A, Regulatory Health Project Manager

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Julie Bullock, Pharm. D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm. D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Johnson and Johnson PRD Attendees

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters, MD Franchise Medical Leader
Paul Burton MD PhD FACC, Senior Medical Director, Clinical Leader
Alexei Plotnikov MD, Project Physician
Troy Sarich PhD, Compound Development Team Leader
Kenneth Todd Moore, MS, Clinical Pharmacology Leader Rivaroxaban
Sigmond Johnson, MS, MBA Program Management Leader
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Sanjay Jalota, MRPharmS, Global Regulatory Lead

Andrea Kollath, DVM, NA Regulatory Lead

Bayer Attendees

Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head, Thrombosis and Hemostasis
Karola Flocke, PhD, Global Regulatory Strategist

1.0 BACKGROUND

In the Complete Response letter of May 27, 2009, the Agency requested J&J PRD provide a description of the plans to develop a lower strength formulation to be used for dose modification in specific populations of patients. FDA indicated that this clinical pharmacology request is not a basis for its inability to approve the sponsor application. However, it requested a response to facilitate its review of the proposed labeling and the need for any post-marketing expectations.

The purpose of this meeting is to obtain guidance from the Agency on the design of a proposed study to evaluate the pharmacokinetics of rivaroxaban in patients with either mild or moderate renal impairment taking rivaroxaban concomitantly with a moderate CYP3A4 and/or P-gp inhibitor. The sponsor intends to address labeling recommendations for those patients concurrently taking rivaroxaban with strong CYP3A4 and/or P-gp inhibitors, and patients under the category of Child-Pugh class B hepatic impairment without coagulopathy in its reply to the Agency's Complete Response.

In a letter dated September 2, 2010, J&J requested a meeting to discuss its proposal. This request included the meeting background package. On October 7, 2010, FDA sent J&J, via e-mail, draft responses to the questions raised in the September 2, 2010, background materials (See below). The responses sent on October 7, 2010, were not the final FDA preliminary responses and were inadvertently sent to the sponsor. On October 13, 2010, FDA sent J&J, via e-mail, the corrected preliminary responses to the questions raised in the September 2, 2010, background materials (See questions and responses below).

2. DISCUSSION

2.1. Category/Discipline A

Question 1: *Does the Agency agree with the general study design for the proposed renal impairment / drug-drug interaction study and J&J PRD's proposal for the use of erythromycin, 500 mg tid as the probe drug in this clinical trial?*

FDA Response to Question 1:

Yes the general design appears acceptable. However, we are concerned about the safety of the 10 mg dose you propose for Period 3 in patients with moderate renal impairment taking a concurrent CYP3A4 inhibitor. You should review the PK and safety data from Period 2 before initiating Period 3. If exposures from this group in Period 2 are similar to, or exceed exposures (e.g. > 2 fold) from Period 1, patients with moderate renal impairment should not continue to Period 3. Incorporate stopping rules for safety into the design of the study.

The use of erythromycin as the probe appears reasonable; however, you should dose erythromycin to the last rivaroxaban sampling day in periods 2 and 3.

You should add 0.5 hr and 48 hr rivaroxaban sampling times to your PK and PD sampling schedules.

You should also evaluate Factor Xa, aPTT, and Heptest activity since your dedicated renal study #11002 reports rivaroxaban related changes in these PD parameters.

Discussion:

The sponsor will add extra doses of erythromycin and additional PK/PD samples (and parameters) as requested above. The sponsor voiced some justifications for using a 10mg dose in moderate patients in Period 3. The Agency requested that the sponsor supply their justification for using this dose in these patients for review at the time of protocol submission.

Question 2: *Does the Agency agree with the classification of subjects by renal function based on the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis and Impact on Dosing and Labeling (May 1998), in addition to including the estimated glomerular filtration rate (eGFR) using the Modification of Diet in renal disease (MDRD) equation?*

FDA Response to Question 2:

Yes.

Discussion:

None

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor to submit a modified protocol as described above.	Sponsor	N/A

5.0 ATTACHMENTS AND HANDOUTS

- October 7, 2010, draft responses to the questions raised.

Meeting Date: October 14, 2010

Time: 11:00 AM – 12:00 PM EST

Type: Type C, Guidance

Product: Rivaroxaban Tablets

Sponsor: Johnson & Johnson PRD

Purpose: To obtain guidance from the Agency on the design of a proposed study to evaluate the pharmacokinetics of rivaroxaban in patients with either mild or moderate renal impairment taking rivaroxaban concomitantly with a moderate CYP3A4 and/or P-gp inhibitor. Labeling recommendations for those patients concurrently taking rivaroxaban with strong CYP3A4 and/or P-gp inhibitors, and patients under the category of Child-Pugh class B hepatic impairment without coagulopathy will be addressed in J&J PRD's reply to the Agency's Complete Response.

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **October 14, 2010**, between **Johnson & Johnson** and the Division of Hematology Products. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Sponsor Questions and FDA Response:

Question 1 -

Does the Agency agree with the general study design for the proposed renal impairment / drug-drug interaction study and J&J PRD's proposal for the use of erythromycin, 500 mg tid as the probe drug in this clinical trial?

FDA Response:

No. We are concerned about the safety of the 10 mg dose you propose for Period 3 in patients with renal impairment taking a concurrent CYP3A4 inhibitor. You should review the PK and safety data from Period 2 before initiating Period 3. If exposures from Period 2 are similar to, or exceed exposures from Period 1 patients should not continue to Period 3.

The use of erythromycin as the probe appears reasonable; however, you should dose erythromycin to the last rivaroxaban sampling day in periods 2 and 3.

You should add 0.5 hr and 48 hr rivaroxaban sampling times to your PK and PD sampling schedules.

You should also evaluate Factor Xa, aPTT, and Heptest activity since your dedicated renal study #11002 reports rivaroxaban related changes in these PD parameters.

Question 2

Does the Agency agree with the classification of subjects by renal function based on the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis and Impact on Dosing and Labeling (May 1998), in addition to including the estimated glomerular filtration rate (eGFR) using the Modification of Diet in renal disease (MDRD) equation?

FDA Response:

Yes.

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/s/

EDVARDAS KAMINSKAS
10/15/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22406

MEETING GRANTED

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your July 28, 2008, 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 September 2, 2010, correspondence requesting a meeting to discuss the design of a proposed study to evaluate the pharmacokinetics of rivaroxaban in patients with either mild or moderate renal impairment. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

The teleconference is scheduled as follows:

Date: October 14, 2010

Time: 11:00 AM – 12:00 PM EST

Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER Participants:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS
DIVISION OF HEMATOLOGY PRODUCTS

Ann Ferrell, M.D., Director (Acting)
Edvardas Kaminskas, M.D., Deputy Director (Acting)
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., M.P.H., Clinical Reviewer
Marcus Cato, M.B.A., Regulatory Health Project Manager

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION
OF CLINICAL PHARMACOLOGY 5

Julie Bullock, Pharm. D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm. D., Clinical Pharmacology Reviewer

Submit background information for the meeting (one electronic copy to the application and 12 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by September 14, 2010, we may cancel or reschedule the meeting.

Submit the **12 desk copies** to the following address:

Marcus Cato
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5241
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, call me at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	GI-1	JOHNSON AND JOHNSON PHARMACEUTICA L RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

MARCUS A CATO
09/13/2010



NDA 22406

INFORMATION REQUEST

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

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 March 5, 2010, submission, containing your briefing document.

We are reviewing the 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. Your March 5, 2010, submission, states that no subject in the RECORD 1, 2, or 3 studies was randomized postoperatively. However, it is unclear what source was used to document this statement. Please detail the process by which Johnson and Johnson determined that no subjects in the RECORD 1, 2, or 3 trials were randomized postoperatively and by which the percentage of subjects randomized postoperatively was determined.
2. Subjects at the clinical investigator sites listed in Items a-h below had irregularities noted during the (b) (4) audits regarding documentation of study drug administration. The information provided in the audits is insufficient to allow for an assessment of the audit findings. Please provide information that can adequately address the issues described below.
 - a. (b) (4) Study coordinators used logs to document drug accountability and dosing for all subjects, but entries in the logs were not signed and dated/initialed; medications and infusions administered to the study subjects were recorded inconsistently; no documentation of subject training on injection techniques, dosing instructions, proper storage of study drug.
 - b. (b) (4): Study drug administration times were exactly the same of each of the 34 subjects audited; exact dosing times were not documented.

- c. (b) (4): For all 35 subjects audited, documentation of study drug administration during the inpatient phase is captured only on progress notes as "administered dose of study 11354 medication per protocol at XXX [time]". It is not clear whether the tablet or syringe were administered, or both. In addition, 8 of 35 subjects audited lacked documentation of a single dose of study drug; 1 additional subject lacked documentation for Days 1-6.
- d. (b) (4): 10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation. In addition, no source documentation to support the date and time of the preoperative self administered injection of enoxaparin/placebo by the subjects or the date and time of the last outpatient dosing for all subjects.
- e. (b) (4): Study drug administration times were exactly the same for each subject for all subjects audited; exact times could not be documented.
- f. (b) (4): Documentation of study drug administration during the inpatient phase of the study was missing or deficient: 8 subject records contained very few notations that the study drug had been given, and the remaining 16 records contained none. Doses of study medication documented only on the SDW were not signed/initialed or dated, so it is unclear whether they are primary source entries.
- g. (b) (4): The exact time of drug administration was rarely recorded on the inpatient medication administration for any of the 27 subjects – the times were recorded only on a grid with times of 0800, 1200, 1600, and 2000. Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheets. In addition, the drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability.
- h. (b) (4): Source documentation for 1-6 days of study drug medication was missing for 8 of 35 subjects.
3. At (b) (4), the study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/times, and laboratory draw times. Please provide this information, if available.

Please respond to the above request on or before close of business August 30, 2010.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	GI-1	JOHNSON AND JOHNSON PHARMACEUTICA L RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

ANN T FARRELL
08/02/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22406

GENERAL ADVICE

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

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 April 29, 2010, submission, requesting that the time to resubmit your complete response to our action letter dated May 27, 2009, be extended to May 27, 2011.

The Agency has considered your request and is granting you an extension until May 27, 2011, by which time you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions we will consider your lack of response a request to withdraw the application under 21 CFR 314.65.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director (Acting)
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22406

GI-1

JOHNSON AND
JOHNSON
PHARMACEUTICA
L RESEARCH AND
DEVELOPMENT
LLC

XARELTO (RIVAROXABAN)
ORAL 10 MG

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/s/

ANN T FARRELL
05/10/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22406

MEETING MINUTES

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

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 the meeting between representatives of your firm and the FDA on April 7, 2010. The purpose of the meeting was to discuss the third party audit of the RECORD studies.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Clinical

Meeting Date and Time: 10:00 – 11:00 AM EST
Meeting Location: White Oak Campus, Conference Room 1415

Application Number: NDA 22406
Product Name: Xarelto™ (Rivaroxaban) Tablets
Sponsor/Applicant Name: Johnson and Johnson (J&J)

Meeting Chair: Dr. Ann Ferrell
Meeting Recorder: Mr. Marcus Cato

FDA ATTENDEES

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS
DIVISION OF HEMATOLOGY PRODUCTS

Ann Farrell, M.D., Director (Acting)
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., M.P.H., Clinical Reviewer
Marcus Cato, M.B.A, Regulatory Health Project Manager

OFFICE OF TRANSLATIONAL SCIENCES/ OFFICE OF BIOSTATISTICS/ DIVISION OF
BIOMETRICS V

Jyoti Zalkikar, Ph.D., Biostatistics Team Leader
Qing Xu, Ph.D., Biostatistics Reviewer
Mark Rothmann, Ph.D., Biostatistics Team Leader

OFFICE OF COMPLIANCE/ DIVISION OF SCIENTIFIC INVESTIGATIONS/ GOOD
CLINICAL PRACTICES BRANCH II

Susan Thompson, M.D., Medical Officer
Tejashri Purohit-Sheth, M.D., Branch Chief
Leslie Ball, M.D., Division Director
Winifred Meeker-Oconnell, M.S., Consumer Safety Officer

SPONSOR ATTENDEES

J&JPRD PARTICIPANTS

Peter DiBattiste, MD	Vice President, Cardiovascular Development Head
Gary Peters MD	Vice President, Franchise Medical Leader
Lloyd Haskell, MD, MBA	Vice President, Compound Development Team Leader
Paul Burton MD PhD	Senior Medical Director/ Clinical Leader
Leonard Oppenheimer, PhD	Senior Director, Statistical Sciences
Steven Miller	Vice President, Regulatory Affairs Cardiovascular and Metabolism
Sanjay Jalota	Senior Director, Global Regulatory Affairs
Andrea Kollath, DVM	Director, Regulatory Affairs
Andrea Masciale	Senior Director, Regulatory Affairs, FDA Liaison Office
Susan Katz MS	Senior Director, Global Clinical Operations
Alysia Baldwin-Ferro	Senior Director, Therapeutic Area Clinical Quality Assurance

BAYER PARTICIPANTS

Scott D. Berkowitz, MD	Vice President and Head, Thrombosis & Hemostasis Group
Martin Homering MSPH	Principal Statistician, Hematology/Cardiology
Andrea Derix PhD	Senior Global Regulatory Strategist
Max Wegner	Vice President, Global Regulatory Affairs
Julie Roeschen, MSSW	Head, Global Monitoring and Study Management
Andy Hargreaves	Head GCP Study Audit Management
Robert Kraemer, PhD	Global Project Leader, Global Development Project Management

1.0 BACKGROUND

In a letter dated January 18, 2010, J&J requested a meeting to discuss the third party audit of the RECORD studies. In a submission dated March 5, 2010, J&J submitted the meeting background package. On March 31, 2010, FDA sent J&J, via e-mail, draft responses to the questions raised in the March 5, 2010, background materials (see questions and responses below).

2. DISCUSSION

J&J presented slides (see J&J slides below).

J&J acknowledged the FDA position and comments and stated its interest is in exhausting the options to maintain the value of the data from the RECORD 1 through 4 studies.

Slides 1-3

J&J inquired about specific audit findings and if they would necessarily invalidate the data obtained. FDA clarified that the role of DSI is to evaluate the integrity of safety and efficacy data. DSI inspects a sample of clinical investigator sites and makes a recommendation to the review division regarding the potential impact of the inspectional findings on the database as a whole. It does not necessarily invalidate data based on individual audit or inspectional findings but makes an assessment of how audit results impact overall safety and efficacy for a given study. FDA stated that the full (b) (4) audit report is required for a complete assessment of the audit results, and a summary report is insufficient to make such a determination. FDA will review the (b) (4) audit finding and make its own assessment regarding the audit results with resultant DSI recommendations to the review division.

Slides 4

J&J shared its assessment of the impact of post surgery randomization on clinical outcomes in RECORD 4. FDA stated that the major concern with post surgery randomization in violation of the RECORD 4 protocol was that it may result in enrichment of the patient population for such characteristics as bleeding tendency. The result may be a study population not accurately represented by the product label. Ultimately the decision as to the significance of postoperative randomization will be a review issue. J&J stated that 97% of patients who were screened were randomized in RECORD 4 compared to 99% in RECORD 1-3. J&J also described subsequent analysis it has done to assess the impact of postoperative randomization on the RECORD 4 study results. FDA responded that the assessment of the significance of postoperative randomization will be a review issue. The review division will perform its own analysis working closely with DSI to evaluate the impact of this finding on the study population and results. FDA emphasized its assessment of the (b) (4) audits will not be limited to post surgery randomization but will include other issues such as the lack of records documenting the administration of the study drug in some cases, protocol violations, etc.

Slides 5-9

FDA expressed concern regarding the 603 additional adverse events not reported but identified during the (b) (4) audits (listed in Table 5 of the briefing book). FDA stated that these events were

not specific to RECORD 4, but also were identified in RECORD 1, 2, and 3. J&J stated that it focused on RECORD 4 as a problematic study because it appeared to be the most egregious.

J&J asked what it could do to provide reassurance of the robustness of the data. FDA advised that at this time, the full (b) (4) audit report should be submitted for review. FDA remarked that, in its experience, it has had audits that have addressed concerns as well as audits that underscored the need for additional studies. FDA stated that further decisions are dependent upon the details of the (b) (4) audit report and its findings. J&J agreed to provide the (b) (4) audit reports (~30) as well as the (b) (4) audit reports conducted while the RECORD studies were ongoing (~74) as soon as possible.

J&J stated that rather than eliminating sites from safety and/or efficacy, its preferred approach is to rank sites by performance and to conduct sensitivity analyses. J&J stated its aim is:

- to obtain an accurate assessment of the drug risk-benefit profile
- to fully account for adverse events
- to perform sensitivity analyses to evaluate impact of audit findings on data

FDA stated this approach seems reasonable, but final agreement between FDA and J&J on the path forward will not be possible until the (b) (4) audit results are reviewed by FDA. FDA requested that J&J provide a summary of its proposed methodology as well as what data it finds acceptable and why or why not.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
J&J agreed to provide the (b) (4) audit reports (~30) as well as the (b) (4) audit reports (~74) as soon as possible.	Sponsor	April 21, 2010
J&J to provide a summary of its proposed methodology as well as what data it finds acceptable and why or why not.	Sponsor	N/A

5.0 ATTACHMENTS AND HANDOUTS

- Sponsor Questions and FDA responses
- J&J slides

Meeting Date: April 7, 2010

Time: 10:00 – 11:00 AM EST

Type: Type C, Clinical,

Product: Xarelto™ (Rivaroxaban) Tablets

Sponsor: Johnson and Johnson (J&J)

Purpose: The objective of the meeting is to obtain feedback from the Agency regarding the independent third party audits conducted to date and the planned data verification activities to provide assurance of the data quality and reliability of the RECORD studies

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **April 7, 2010** between **J&J** and the Division of Hematology Products. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Sponsor Questions and FDA Response:**FDA Comments:**

Johnson & Johnson concludes in their briefing package that the (b) (4) Audit findings support the integrity of the data from RECORD 1, 2, and 3, and that Johnson & Johnson acknowledge that there were issues of concern with RECORD 4. Therefore, Johnson & Johnson has submitted proposals for data verification plans and sensitivity analyses specific for RECORD 4. However, based on the summary of the (b) (4) audits, DSI is unable to concur with Johnson & Johnson's assessment regarding the integrity of the data from RECORD 1, 2, and 3. Without DSI's review of the full (b) (4) Audit Reports, DSI is unable make any definitive conclusions regarding data reliability from any of the RECORD studies, RECORD 1, 2, 3, and 4, at this time. The responses to Johnson & Johnson's specific questions follow.

QUESTION 1:***Data Verification Plan***

Does the Agency agree with the plan to perform data verification at the sites participating in the RECORD 4 study to identify any unreported AEs and SAEs?

FDA Response:

Without reviewing the full (b) (4) Audit reports, DSI is unable to evaluate the impact of the findings on data reliability, and comment upon this plan at this stage. Given the number and type of violations revealed by the audit summary, DSI are concerned that the data in RECORD 4 may not be reliable; however, a definitive assessment will not be feasible until after Agency evaluation of the RECORD 4 (b) (4) audit results. DSI's examination of the sponsor's summary from five of the nine additional audit sites performed for RECORD 4 leads DSI to conclude that data from these sites may not be reliable even from the summary information presented. This is in addition to the data considered unreliable from the three sites classified as OAI in RECORD 4 (Drs. (b) (4)) inspected previously by DSI, as well as the data from the sites of Drs. (b) (4) which were previously identified concerning which respect to data reliability. In light of the number of monitoring and study conduct defects including deficiencies in adverse event reporting and randomization of a significant number of subjects postoperatively in violation of the protocol, DSI cannot make any definitive statements at this time regarding the RECORD 4 data in support of the safety and efficacy of Xarelto in NDA 22-406.

QUESTION 2:

***Site Performance Metric Data and Monitoring Quality Analysis
Strategy for RECORD 4***

a) Does the Agency agree with the proposed strategy to assess site performance by collecting and reviewing key site performance metric data, as outlined in Section 4 of this briefing book?

FDA Response:

DSI is unable to comment upon this proposed strategy at this juncture. Before final decisions are made regarding further J&J proposals, DSI must receive and review the (b) (4) Audit Reports from RECORD 4, as well as from RECORD 1-3.

b) Does the Agency agree with the proposed sensitivity analyses to assess the impact of site performance on the key efficacy and safety outcomes?

FDA Response:

DSI is unable to comment upon this proposed strategy at this juncture. Before final decisions are made regarding further J&J proposals, DSI must receive and review the (b) (4) audit reports from RECORD 4, as well as from RECORD 1-3.

c) Does the Agency further agree that the proposed analyses adequately address the Agency's areas of concern as described in Question 1 of the CR letter?

FDA Response:

The proposed analyses do not adequately address DSI's areas of concern. Johnson & Johnson focuses on RECORD 4 data; however, DSI is concerned that there may be issues with data reliability from RECORD 1, 2, and 3. However, as stated previously, DSI is unable to make any conclusions regarding data reliability for RECORD 1, 2, and 3 at this time. Determination of the validity of the data from these studies will be contingent upon DSI's detailed review of (b) (4) Audit Reports. DSI remains concerned that the number of findings categorized as Critical and Major in these studies are significant and represent findings that could have an impact on study safety and efficacy. DSI notes that for the new audits of RECORD 4, 9 Critical findings were noted in the 312 subjects audited, as well as 47 major findings (0.18 Critical and Major findings/subject audited). For the remaining RECORD studies:

- **RECORD 1 = 0.12 Critical/Major findings per subject**
- **RECORD 2 = 0.15 Critical/Major findings per subject**
- **RECORD 3 = 0.18 Critical/Major findings per subject**

These results show that the number of Critical and Major findings noted per subject audited is similar across studies, and not limited to RECORD 4. Additionally, DSI's review of Johnson & Johnson's summary information demonstrates that two RECORD 2 sites ((b) (4)) produced data that may not be reliable given the number and range of deficiencies identified; however, a definitive assessment cannot be made until review of the (b) (4) Audit Reports.

In summary, DSI requires that the (b) (4) i Audit Reports for the RECORD 1, 2, 3, and 4 for the audited sites be submitted to the Agency for review prior to determination of whether or not further auditing and analyses as proposed in the sponsor's briefing package will be necessary and/or beneficial.

DSI Questions and Comments for Johnson & Johnson

1. On page 22 of the background package, the sponsor states: "...and the audits identified only a few subjects that were potentially unblinded through the measurement of local coagulation parameters...". Please explain this finding: What was the number of subjects unblinded? How did the coagulation measurement unblind these subjects?
2. For RECORD 1, 2, and 3, the sponsor states that (b) (4) determined that monitoring was effective at 60-75% of audited sites. What is the percentage for each individual study? We note that effective monitoring was assessed at 35% of RECORD 4 sites. Inadequate monitoring at 25-65% of clinical sites is concerning, and may call for further measures to assure data integrity before any or all of the data from RECORD 1, 2, 3, and 4 are determined to be acceptable.
3. Regarding the sponsor's proposal for further auditing of RECORD 4: How was (b) (4) chosen? How was the proposed methodology validated? What would the sponsor consider an acceptable outcome of these additional studies?

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	GI-1	JOHNSON AND JOHNSON PHARMACEUTICA L RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

MARCUS A CATO
05/07/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-406

MEETING GRANTED

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your July 28, 2008, 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 18, 2010, correspondence requesting a meeting to discuss your RECORD study audit results and your planned data verification activities. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

The meeting is scheduled as follows:

Date: March 5, 2010
Time: 11:00 AM – 12:00 PM EST
Location: White Oak Campus, Building 22, Conf. Room 1415
10903 New Hampshire Ave., Silver Spring, MD 20903

CDER participants:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwayne) Rieves, M.D., Director
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., M.P.H., Clinical Reviewer
Marcus Cato, M.B.A, Regulatory Health Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

OFFICE OF COMPLIANCE/ DIVISION OF SCIENTIFIC INVESTIGATIONS/ GOOD
CLINICAL PRACTICES BRANCH II

Susan Thompson, M.D., Medical Officer
Tejashri Purohit-Sheth, M.D., Branch Chief

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at Marcus.Cato@fda.hhs.gov so that our security staff has sufficient time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Marcus Cato at 301-796-3903 or Brent Adkins at 301-796-1366.

Provide the background information for the meeting (three copies to the application, one electronic copy to the above e-mail address and 12 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by February 5, 2010, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22406

GI-1

JOHNSON AND
JOHNSON
PHARMACEUTICA
L RESEARCH AND
DEVELOPMENT
LLC

XARELTO (RIVAROXABAN)
ORAL 10 MG

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/s/

MARCUS A CATO

01/22/2010

RECORD OF TELEPHONE CONVERSATION

DATE: October 26, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Sanjay Jalota, MRPharmS
Regulatory Global Regulatory Lead

e-mail: SJalota@its.jnj.com

Representing: Johnson and Johnson Pharmaceutical Research and
Development (J&J)

AND

Name: Rafel (Dwayne) Rieves, M.D., Director
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: hepatic safety data analyses

DISCUSSION:

FDA called J&J to find out what statistician they have planned to do the assorted unblinded hepatic safety data analyses that have been generally agreed to.

J&J stated:

-they have not made a final selection of the statistician who will review and analyze the unblinded liver safety data but it "likely will be Dr. (b) (4), who is also the statistician for the (b) (4) "

-each of the ongoing studies has a unique statistician assigned to it

Attachments:

- Cross Study Data Monitoring Board (CS DSMB) Charter Cover letter.
- A list of the cross study DSMB members/which includes Dr. (b) (4), as assigned statistician



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

Date: 16 October 2009

R. Dwaine Rieves, M.D., Director
Division of Medical Imaging and Hematology Drug
Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-406
XARELTO™ (rivaroxaban)

New Drug Application
General correspondence

Cross Study Data Monitoring Board
(CS DSMB) Charter

Dear Dr. Rieves:

Reference is made to the original New Drug Application (**NDA**) for **XARELTO™** (rivaroxaban) immediate release tablets for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery, filed July 28th, 2008 by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI). This submission was provided electronically in Common Technical Document (eCTD) format.

We received a request from the Project Manager Mr. Marcus Cato for a copy of the Cross Study Data Monitoring Committee Charter. Enclosed please find the charter titled: **Johnson & Johnson Pharmaceutical Research & Development, Rivaroxaban Independent Cross Study Data Safety Monitoring Board Charter, Objectives and Procedures for the Independent Cross Study Data Safety Monitoring Board (CS-DSMB) Rivaroxaban/BAY 59-7939 (JNJ39039039)**

Should you have any questions regarding this submission or require additional information, please contact me directly at (908) 927-6522.

Sincerely,

Andrea Kollath, DVM,
Director, Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

cc. Marcus Cato, MBA, FDA Project Manager, Division of Medical Imaging and
Hematology Drug Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	GI-1	JOHNSON AND JOHNSON PHARMACEUTICA L RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

MARCUS A CATO
11/02/2009

RAFEL D RIEVES
11/02/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 31, 2009. The purpose of the meeting was to discuss your proposed liver adjudication panel procedural charter submitted as follow-up to the Type A meeting with the Agency on June 19, 2009; held to obtain clarification the May 27, 2009, FDA Complete Response Letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: July 31, 2009
TIME: 10:00 AM - 11:00 AM EST
LOCATION: CDER WO 2201 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson & Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., M.P.H., Clinical Reviewer

OFFICE OF NEW DRUGS/ OFFICE OF DRUG EVALUATION I/DIVISION OF
CARDIOVASCULAR & RENAL PRODUCTS

Stephen M. Grant, M.D., Clinical Team Leader

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

John R. Senior, M.D., Medical Officer (Hepatotoxicity)

EXTERNAL ATTENDEES:

J&J

Martin Fitchet, MD, Global TA Head, CV & Metabolism
Gary Peters , MD Franchise Medical Leader

Lloyd Haskell , MD, Compound Development Team leader
Mehul Desai MD, Clinical
Debra Karvois, Clinical Project Scientist
Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Harry Flanagan, DO, Post-Marketing Safety Expert, Benefit Risk Management
G.K. (Dina) Anand MD, Post-Marketing Safety Franchise Leader
Sigmond Johnson, MS, MBA Program Coordination
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Andrea Kollath, DVM, Regulatory Affairs

BAYER

Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis, Hemostasis, CV and Coagulation
Sabine Dittmar MD, Global Pharmacovigilance
Andrea Derix, PhD, Sen. Global Regulatory Strategist
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Alice Benson PhD, Principal Statistician, Global Clinical Statistics,
Martin Homering PhD, Statistical Sciences

BACKGROUND:

In a letter dated May 29, 2009, J&J requested a meeting to obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter (CR). On June 19, 2009, FDA and J&J meet.

In a letter dated July 2, 2009, J&J submitted a proposed liver adjudication panel procedural charter, as follow-up to the Type A meeting with the Agency on June 19, 2009. On July 29, 2009, FDA sent J&J, via e-mail, draft responses to the questions raised in the June 2, 2009, submission (See FDA preliminary comments below).

MEETING OBJECTIVES:

To discuss the J&J proposed liver adjudication panel procedural charter, submitted as follow-up to the Type A meeting with the Agency on June 19, 2009.

DISCUSSION POINTS:

J&J clarified that (b) (6) was not a part of the original liver adjudication panel (LAP). He performed a separate adjudication and presented these findings at the March 19, 2009, advisory committee meeting (AC). J&J did not intend to include (b) (6) in the new liver adjudication panel but intended to use him as a consultant.

FDA commented that its objection is to (b) (6) participating in the adjudication process and not to him participating as a consultant or reviewing the LAP output. With regard to other members from the previous LAP, FDA emphasized that its concern is objectivity; previous members have publicly expressed an opinion on the existence of liver toxicity. The FDA objection is not based on the qualifications of the panel members but is to ensure objectivity.

FDA reminded J&J that it has outlined what it believes to be the most persuasive proposal in previous communications. J&J stated that its current proposal is to send the data to three different reviewers to perform an independent five-scale assessment. The reviewers would independently examine and record their opinion and then meet to build consensus.

FDA emphasized that it would like a clear, independent, output, without the reviewers discussing amongst themselves. J&J proposed collapsing the design to a locked *yes/no* output for each reviewer (as to whether the enzyme elevations appear drug related) prior to collecting the five-scale assessment. FDA stated it is important to preserve the original output/opinions of the LAP reviewers, to lock a *yes/no* vote and to ensure that FDA have available all data that the LAP relievers had. FDA emphasized that it needs a *forced-opinion* for each case.

J&J inquired about what studies to include. FDA stressed that all potential *Hy's Law cases* from all studies, up to the safety update, be included.

FDA expressed concern about patients who dropped out of the study and were not followed by the central and local laboratories. FDA requested that J&J identify and follow-up with the central and local laboratories for all patients that dropped who were not per-protocol (some patients had an alanine aminotransferase (ALT) reach three times the upper limit of normal (ULN) but dropped-out from the trial). FDA requested full accounting and an active query for patients that discontinued. J&J agreed to query these patients and provide summary tables, though they will not be adjudicated.

J&J requested FDA concurrence with the proposal to adjudicate only the ongoing studies, and to not re-adjudicate RECORD potential *Hy's Law cases*. FDA concurred.

J&J stated it intended to submit all information on potential *Hy's Law cases* and the same blinded data reviewed by the LAP as part of the complete response to the FDA action letter.

FDA stated it envisions a process in which it would receive:

- The original LAP adjudication output
- A complete LAP adjudication summary report
- The full blinded data package reviewed by the LAP

FDA would review the LAP output and re-adjudicate cases-of-interest as needed. FDA expects that the DSMB would produce a report; however, there would be no joint overview (FDA & DSMB) of the adjudication output.

FDA noted that the process for conveying the liver safety data to the agency remains under discussion and under one scenario, FDA envisions receiving only blinded data for potential *Hy's Law cases* while the adjudication output would also go to the DSMB. FDA would meet with the DSMB to discuss the results (in a controlled environment) and FDA will not archive unblinded data to the application. FDA will archive the conclusion of whether drug-induced liver injury is present or not.

FDA emphasized that it may only need to archive the DSMB decision.

The sponsor agreed with the FDA outline and considerations.

FDA and J&J discussed the number of potential *Hy's Law cases* to be adjudicated (approximately 50-60). FDA commented that with so few cases J&J may wish to consider unblinding all the potential *Hy's Law cases*, particularly if these cases would be unblinded anyway. J&J expressed concern about unblinding these cases. FDA agreed to meet with J&J again, to discuss potential unblinding, after further internal discussion. No conclusion was reached regarding the unblinding/process for conveying safety data from the ongoing studies to the NDA.

DECISIONS (AGREEMENTS) REACHED:

- J&J proposed collapsing the design to a locked “yes/no” output for each reviewer prior to collecting the five-scale assessment. FDA emphasized that it needs a *forced-opinion* for each case.
- FDA stressed that all potential *Hy's Law cases* from all studies, up to the safety update, be included in the LAP adjudication. J&J agreed
- J&J to adjudicate only the ongoing studies, and not re-adjudicate RECORD cases.
- J&J agreed to submit all information on potential *Hy's Law cases* and the same blinded data reviewed by the LAP as part of the complete response to the FDA action letter.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- FDA agreed to meet with J&J again, to discuss potential unblinding of potential *Hy's Law cases* and other safety conveyance topics, after further internal discussion.

ACTION ITEMS:

- FDA to meet with J&J after internal discussion.

ATTACHMENTS/HANDOUTS:

- FDA preliminary comments

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **July 31, 2009** between **Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&J)** and the FDA. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Draft Preliminary Comments for J&J July 31 teleconference regarding Liver Adjudication Panel

1. The documentation of Liver Advisory Panel (LAP) procedures appears much more developed, compared to those used in the prior adjudication process.
2. Several of our prior recommendations were not incorporated into the LAP procedures. We continue to believe that incorporation of our prior recommendations is more likely to provide a definitive outcome and encourage you to reconsider our prior major recommendations. In particular we reiterate that the new adjudication should be conducted solely by individuals who were not involved in the previous liver adjudication panel. Most notably, we are very concerned that the inclusion (b) (6) within the new adjudication process is inappropriate, based upon his conclusions voiced at the Advisory Committee. At a minimum, we encourage you to exclude (b) (6) from the adjudication/review process.
3. We have the following specific comments:
 - a. We do not concur with the plan for documentation of individual clinical adjudicator conclusions, followed by the formation of a consensus conclusion for each patient. We continue to believe that adjudication should be conducted independently by two individuals with adjudication by a third if there is disagreement.
 - b. We recommend you modify section 4 of the LAP procedural document to also state that applicable "cases" from the post-marketing experience will be adjudicated. We recognize that available data may be more limited for these "cases" but inclusion of these cases within the final report will help verify that all available data have been analyzed for signals of severe liver injury.

c. We acknowledge that you plan to modify the LAP procedural document to expand the case selection criteria to include cases that occur within 4 weeks "after the ALT elevation."

d. We are particularly unclear about the process outlined on pages 9 and 10 of your cover letter. For example, we do not understand the point of inclusion of FDA participants in a blinded review of index cases (item 1). Additionally, we are unclear of the individuals representing "the designated clinical reviewers" (item 5). We request revision of these procedures following our discussion. In general, we expect:

i. Within your complete response, submission of copies of all source information and case report forms used in the adjudication process. Submission of this information will allow FDA to perform a detailed review/readjudication of any cases that appear of particular concern, based upon a preliminary review of the information.

ii. Development of procedures in which FDA representatives will meet with members of the Data Safety and Monitoring Board in order to have the members convey their unblinded review findings, conclusions and the basis for their conclusions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	ORIG-1	JOHNSON AND JOHNSON PHARMACEUTICA L RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

MARCUS A CATO
10/13/2009



NDA 22-406

GENERAL ADVICE

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

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

We also refer to your July 8, 2009 submission, containing your proposed supplemental audit plan.

We have reviewed the referenced material and have the following comments and recommendations:

1. We agree with the number of sites selected and the number of subjects to be audited at each site.
2. We agree that you will submit individual site reports as well as a separate summary report as outlined in the proposal.
3. The Data Verification Tool appears acceptable to capture all necessary information.
4. The summary report should include the exact role of the Bayer representative in the audit.
5. We request that you submit an updated timeline for the supplemental audit completion.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, MD
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES

08/14/2009

RECORD OF TELEPHONE CONVERSATION

NDA: 22-406

Product: Rivaroxaban

Today's date: August 10, 2009

Speakers:

For FDA: Dwaine Rieves and Marcus Cato

For Johnson and Johnson: Gary Peters and Peter Debateste

FDA called the company today to request perspectives regarding the following items:

1. How many patients do they anticipate will need adjudication and of these, how many have already been unblinded to treatment assignment?

Response: The company plans adjudication of patients from five on-going clinical studies:

- Magellan
- Rocket
- Rocket/Japan
- Einstein
- Atlas AC

The company noted that enrollment in Atlas AC is early/enrollment in other studies in near completion/or completed. The company "roughly" estimates about 60 patients will need adjudication. Of these, the company estimates that no more than 10% (6 patients) will have been unblinded since the protocols generally did not anticipate unblinding.

2. Could the company restate its position regarding unblinding of all index cases for adjudication? FDA notes that, since these patients will have stopped drug and the sample sizes in the studies are so very large, it seems reasonable to unblind all patients who are to undergo adjudication.

Response: The company stated they remain strongly opposed to unblinding of the index cases because:

a. Unblinding presents logistical challenges/need for protocol amendments or cleared "exceptions" to satisfy European and US expectations since the unblinding had not been a component of the protocol plans.

b. Concern that ad hoc unblinding might reveal findings that necessitate protocol modifications, particularly for Atlas AC and performance of this form of safety

monitoring outside of the DSMB/protocol plans may ultimately raise questions of study conduct.

The company also emphasized that the assessment of important liver signals relies not only on the adjudication results for index patients but also upon the active/control comparisons of the distribution of patients with excessive aminotransferase elevations (as they had outlined in their plans). For this reason, they had proposed that the "cross study DSMB" have the main responsibility for examining unblinded adjudicated case distributions as well as tabular summaries of the distribution of patients with excessive aminotransferase levels. The company noted that the DSMB charter allows "consultants" to be added to the DSMB review proceedings and, in this context, the DSMB may choose to allow a small number of FDA staff to join the meeting to review the unblinded data (if necessary).

FDA closed the conversation by stating that discussions are on-going within the agency regarding the plans and follow-up from these discussions will be provided to the company.

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/s/

RAFEL D RIEVES

08/13/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your July 28, 2008, 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 the teleconference between representatives of your firm and the FDA on June 19, 2009. The purpose of the meeting was to obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: June 19, 2009
TIME: 3:00 PM - 4:30 PM EST
LOCATION: CDER WO 1311 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., M.P.H., Clinical Reviewer
Diane Leaman, Safety Regulatory Project Manager
Ira Krefting, M.D., Safety Deputy Director

OFFICE OF NEW DRUGS/ OFFICE OF DRUG EVALUATION I/DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS

Stephen M. Grant, M.D., Clinical Team Leader
Alison Blaus, Regulatory Health Project Manager

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Nitin Mehrotra, Ph.D., Clinical Pharmacology Reviewer
Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF PHARMACEUTICAL SCIENCE / OFFICE OF NEW DRUG QUALITY
ASSESSMENT/DIVISION OF PRE-MARKETING ASSESSMENT AND
MANUFACTURING SCIENCE BRANCH V

Josephine M Jee, Ph.D., CMC Reviewer

Richard Lostritto, Ph.D., Director

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/ DIVISION OF
PHARMACOVIGILANCE II

Timothy Lape, Pharm.D., Senior Regulatory Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer

Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

OFFICE OF COMPLIANCE/ DIVISION OF SCIENTIFIC INVESTIGATIONS/ GOOD
CLINICAL PRACTICES BRANCH II

Susan Thompson, M.D., Medical Officer

Tejashri Purohit-Sheth, M.D., Branch Chief

EXTERNAL ATTENDEES:

J&J

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV

Gary Peters, MD Franchise Medical Leader

Martin Fitchet, MD, Global TA Head, CV & Metabolism

Lloyd Haskell, MD., VP, Compound Development Team Leader

Leonard Oppenheimer, PhD. Statistical Sciences

Mehul Desai MD, Clinical

Deborah Karvois, Clinical

Lisa Schmitt, VP, Therapeutic Area Clinical Quality Assurance

Alysia Baldwin-Ferro, Senior Director, Therapeutic Area Clinical Quality Assurance

Nancy Micalizzi, J&J CMC RA

An Thyssen, PhD, Clinpharm Leader Rivaroxaban

Harry Flanagan, DO, Post-Marketing Safety Expert, Benefit Risk Management

Sigmond Johnson, MS, MBA, Program Coordination

Andrea Masciale, Regulatory Affairs, FDA Liaison Office

Michael Kronig, MD, VP Cardiovascular Regulatory Affairs

Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead

Michael Kronig, MD, VP Cardiovascular Regulatory Affairs

Andrea Kollath, DVM, Regulatory Affairs, US Lead

BAYER

Frank Misselwitz, MD, PhD, VP, Head Therapeutic Area CV and Coagulation
Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis and Hemostasis CV and Coagulation
Dagmar Kubitzka, MD PhD Global Clinical Pharmacology Project Leader, BSP
Andrea Derix, PhD, Sen. Global Regulatory Strategist
Alice Benson PhD, Principal Statistician, Global Clinical Statistics,
Martin Homering PhD, Statistical Sciences
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Torsten Westermeier PhD Therapeutic Area Expert Statistician CC
Robert Kelly CMC RA
Harald Kallabis, Ph.D., Global Project Leader

BACKGROUND:

In a letter dated May 29, 2009, Johnson and Johnson Pharmaceutical Research and Development (J&J) requested a meeting to obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter (CR). In a submission dated June 8, 2009, J&J submitted the specific question for clarification to serve as the meeting background package. On June 19, 2009, FDA sent J&J, via e-mail, draft responses to the questions raised in the June 8, 2009, background materials (See questions and responses below).

MEETING OBJECTIVES:

To obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter.

DISCUSSION POINTS:

Regarding the audit requested by FDA, J&J noted that while it is typical to audit five percent of sites, it has actually audited ten percent of its sites. J&J proposed to audit 15 percent. FDA acknowledged that although it may be typical to audit five percent of sites as part of standard procedures, the audits being requested by FDA are to ensure data integrity of the data submitted in support of the application given that data integrity concerns have arisen as a result of inspectional findings from FDA audits. FDA further clarified that, when inspecting a site, it expects that 100 percent of patients would be inspected and that it may be more useful to audit higher enrolling sites compared to lower enrolling sites. J&J expressed concern that an audit of 20 percent of sites and 100 percent of patients appeared to be above normal practice and might represent a prohibitive number of patients to audit in a timely manner. FDA advised J&J to submit an appropriate alternate proposal to include a complete audit plan, including any statistical support information that would help address FDA concerns about the representativeness of the limited number of sites to be audited. FDA outlined the items to be included in the audit plan in the June 19, 2009 FDA response to the background material. FDA emphasized the need to review the plan prior to its implementation. The sponsor inquired if

FDA would require statistical power. FDA responded that it would need the exact proposal to evaluate the statistics appropriately and proposed the following hypothetical example:

Selection of sites from all four RECORD studies with a total enrollment of 60 or higher results in identification of 26 sites: 9 in RECORD 1 (2 already inspected by the Agency), 4 in RECORD 2, and 13 in RECORD 4 (6 already inspected by the Agency). If 5% is the margin of error for tolerance of unreliable sites detected by the audit, then audit of 30 sites is necessary to show with 95% confidence that the percentage of unreliable sites does not exceed 5%, assuming that 25% of sites are actually unreliable. Therefore, 18 high enrolling sites (with ≥ 60 subjects) not previously inspected could be included in the audit plan, which represents 11% of enrolled subjects. If 30 total sites are to be audited, an additional 12 sites could be included in the audit, which represent a random sample of sites which enrolled 40-60 subjects and sites which enrolled 10-30 subjects.

FDA commented that it would review and provide comment on the proposed audit plan. J&J inquired about the criteria FDA used to determine that data from a site was unreliable. FDA stated that the criteria used are pertinent to adherence to the protocol, adherence to key eligibility criteria, conducting key efficacy and safety assessments as prespecified in the protocol, etc. and the impact of any violations noted on data integrity and subject safety. The sponsor inquired if randomly selecting lower enrolling sites would be of benefit. FDA commented that it may not be productive to audit lower enrolling sites, such as sites enrolling less than 10 subjects. J&J asked about inspecting 100 percent of patients per site. FDA reminded J&J that the purpose of this audit program was different from routine sponsor monitoring since FDA has detected signals raising concerns with respect to data integrity. FDA inspections found four of ten sites to be problematic. The proposed sponsor audits are required to provide assurance that FDA can remain sufficiently confident in the data integrity of the data from the rest of the sites to support the NDA. FDA noted that the audits should be conducted by an independent third party and the justification for the choice of the third party auditor be provided. FDA expects that it could review a proposal from the sponsor in 2-4 weeks depending on its size and complexity. FDA would also potentially consider a plan that contained stopping rules which would allow an audit to be stopped if a prespecified percentage of patients are audited without significant violations being identified. After the audit plan's implementation, FDA would prefer receiving a summary of audit findings rather than interim, sequential, and/or partial reporting. J&J is welcome to submit the completed audit findings; however, FDA will not provide comments until all results have been submitted.

Regarding the request by FDA for an assessment of the potential signal for severe liver toxicity in the on-going *ROCKET* studies, J&J commented that FDA had not requested case adjudications in the original CR letter. J&J stated that it had discussed formal adjudication internally and intended to submit a plan for review. J&J ask for the FDA rationale in requesting that the new adjudication panel exclude any members who had either previously adjudicated findings from their clinical development program or who had participated in the studies in any role. FDA advised that its intent was to generate an original data set rather than build on the previous data set; FDA stated that a systematic adjudication review that adjudicated all applicable cases in the same manner would minimize questions about variability in the case adjudications. FDA

commented that the previous adjudication had apparently been performed in a relatively unsystematic manner. FDA did not want the prior adjudicators' experience to influence their review of the newer cases. FDA commented that in Medical Imaging experience, readjudication is commonly referred to as a re-read and to support the usefulness of the re-read findings there should be no carryover of previous experience or biases. FDA commented that this is its recommendation; hence, FDA is open to review an alternative plan. J&J inquired if FDA wanted re-adjudication of previous studies. FDA responded that it believes that its recommendation (inclusion of all applicable cases within the new adjudication, including those previously adjudicated) is likely to generate the most persuasive data. J&J is welcome to submit an alternate plan along with an appropriate rationale. FDA reminded J&J that alternatives may be acceptable provided they are thoroughly justified.

J&J inquired about the potential re-adjudication of cases from the *RECORD* studies. FDA stated that there have been some concerns about use of a consensus process (versus individual opinions) in the previous panel. Additionally, the separate adjudication presented at the March 19, 2009, advisory committee meeting raised additional unanswered questions regarding the *RECORD* program.

J&J requested that FDA clarify if it was interested in the *ROCKET* studies only. FDA responded that the CR letter did place emphasis on the *ROCKET* studies, however, the team is thinking in terms of evaluating all available data. FDA re-emphasized that it is interested in the most persuasive data possible and has outlined its recommended plan to generate that data. J&J is welcome to submit an alternate plan and FDA will evaluate it.

J&J inquired about the FDA request for a final adjudication panel report. FDA stated that each case would have a specific outcome and it would expect, in addition to the individual outcomes, a final comprehensive review document that summarizes the interpretation of the adjudicator findings.

FDA and J&J discussed the number of potential *Hy's Law* cases to be adjudicated (less than 50). FDA emphasized that the sponsor should not unblind subjects in the *ROCKET* program who meet the definition of a *Hy's Law* case. Rather, unblinding and assessment of the findings should be solely the responsibility of the Data Safety Monitoring Board (DSMB). FDA and J&J discussed alternative processes for conveying the adjudication findings and DSMB findings to the FDA. FDA encouraged J&J to consider the systematic aspects of the process and to describe them in the proposed adjudication panel procedural charter.

With regard to the safety update, J&J noted that a cut-off date of one month prior to submission of the complete response is not feasible and proposed a two month cut off. FDA agreed. FDA also noted that its draft response to this question (QUESTION 5 (SAFETY UPDATE)):

“all subjects in any study with ALT > 3x ULN and total bilirubin > 2X ULN within four weeks of each other, as outlined above.”

Should read:

“all subjects in any study with an ALT value > 3x ULN and a total bilirubin value > 2x ULN at the same time as the ALT signal detected OR within four weeks after the ALT signal was detected, OR -discontinued the study drug due to liver test abnormalities or symptoms of liver disease.”

DECISIONS (AGREEMENTS) REACHED:

- FDA has outlined its recommended plan in its response to the meeting. J&J is welcome to submit an alternate provided there is justification for deviations.
- J&J will submit a safety update with a cut-off date two months prior to submission of the complete response

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None.

ACTION ITEMS:

- J&J to submit a QA audit plan proposal for FDA review
- J&J to submit an adjudication panel procedural "charter" proposal for FDA review
- J&J to submit a safety update with a cut-off date two months prior to submission of the complete response

ATTACHMENTS/HANDOUTS:

- Sponsor Questions and FDA responses

Meeting Date: June 19, 2009

Time: 3:00 – 4:30 PM EST

Type: Clinical, Post-Action Guidance, (Type A)

Product: Xarelto™ (Rivaroxaban) Tablets

Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
(J&J)

Proposed Indication: Prevention of Venous Thromboembolism

Purpose: To obtain clarification on items detailed in the Complete Response Letter:

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **June 19, 2009** between **Johnson & Johnson Pharmaceutical Research & Development, L.L.C.** and the Division of Medical Imaging and Hematology Products. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Sponsor Questions and FDA Response:

QUESTION 1 (GENERAL):

The sponsor proposes submitting a complete response to the Complete Response Letter by the end of June 2009. The June 2009 submission will include final responses to all Items identified in the Complete Response Letter except additional audit results [see Item 1c (iii)] will be submitted by end of October 2009, and the Safety Update will be submitted by end of August 2009. The sponsor respectfully requests that the Agency classify our June 2009 submission a complete response and base the review cycle on such submission. This procedure will facilitate review by the Agency, and permit expeditious final review of the NDA for rivaroxaban for patients undergoing total hip or knee replacement surgery.

Does the Agency concur with this proposal?

FDA Response:

No. A complete response should address all items identified in our Complete Response Letter, including the additional audit results from RECORD studies and a Safety Update.

The results of the audit results are integral to the Agency's assessment of the application. The results of these audits are critical to determination of the adequacy of sponsor monitoring and integrity of data from the clinical sites. The audit results must be reviewed and evaluated by the Agency prior to a final determination of the validity of the safety and efficacy data submitted in support of the Xarelto NDA.

QUESTION 2 (CLINICAL):

Sponsor Inspection: *From a general perspective, would the Agency provide the sponsor with the criteria that were used to determine the data from Drs. (b) (4) sites were unreliable?*

FDA Response:

The unreliability determination was based on the results of the inspections conducted by the FDA at Drs. (b) (4) clinical sites. Please refer to the CR letter for the reasons why data from the 5 clinical investigators, including Dr. (b) (4), are considered unreliable.

Item 1a (ii): *The sponsor wishes to clarify that 69 routine and 5 for-cause/directed sponsor conducted audits were performed across the RECORD program. The sponsor also wishes to clarify that Dr. (b) (4) was not included in the sponsor audit program. As requested in Item 1a (ii), a report will be generated identifying the audit findings. A table will be provided showing all Class 1 and Class 2 observations, corrective actions, and outcome.*

Does the Agency concur?

In view of the above, does the Agency consider additional audits necessary?

FDA Response:

The Agency notes that 69 routine and 5 for-cause/directed sponsor-conducted audits were performed across the RECORD program and understands that Dr. (b) (4) was not included in the sponsor audit program. You state that a report will be generated identifying the sponsor's audit findings, as directed in the CR letter. The report is to include all Class 1 and Class 2 observations, corrective actions, and outcome. The Agency concurs with this planned report of completed sponsor-conducted audits. In addition, the original audit reports should be provided within the complete response. Please see our subsequent comments regarding the need for auditing of additional clinical sites.

We reiterate that the following items should be provided within the response to the CR letter:

a.i. A report of your QA audit plan, including your plan for securing compliance from non-compliant clinical investigators. Include copies of any Standard Operating Procedures (SOPs) that were in place during conduct of the study to address means by which corrective actions were to be taken if or when you or the contract research organization (CRO) identified noncompliant clinical investigators.

a. iii. A description of any clinical investigators terminated for non-compliance. If so, please provide a list of the clinical investigators, their sites, the specific violations, and whether the data were included in the NDA submission.

We also direct your attention to item b from the CR letter:

b. Please describe Bayer's QA program with respect to the oversight of CROs that were hired to monitor the clinical sites, including (b) (4) for RECORD 4. Please describe the procedures implemented to make sure that the CROs adequately monitored the clinical sites. In your response, include the following information:

i. How was Bayer kept apprised by the CROs concerning monitoring of the clinical sites during the course of the study? Specifically, what information did the CROs provide? Please provide a list of non-compliant clinical study sites reported by the CROs.

ii. How did Bayer review the information obtained from the CROs, during the course of the study and at the end of the study? What monitoring information was kept at the end of the study?

iii. What actions did Bayer take based on the monitoring reports?

Given the results of the clinical investigator and sponsor inspections conducted by FDA in support of this NDA, additional audits are essential to documentation of the integrity of the safety and efficacy data submitted to the Agency. In particular, we regard confirmation of the adequacy of sponsor monitoring by Bayer of the conduct of the RECORD program studies as essential to assure data integrity. Performance of additional audits by an independent third party is an integral component of this process.

Item 1c (i): If the Agency determines that the 69 audits and the 5 for cause audits are not sufficient, the sponsor proposes an additional targeted audit of 24 clinical sites. The proposed targeted audit plan does not include visits to the sites already inspected by DSI or Bayer. The site selection will be proportional to the percentage of patients in each of the RECORD studies contributed by each country. The audit will cover twenty (20) percent of the subjects enrolled at the selected sites, not to exceed a maximum of 10 subjects per site. The total planned sample size is 181 subjects.

Does the Agency concur with the proposed audit plan in terms of the number of sites and method of site selection?

FDA Response:

We do not concur with your proposed audit plan. Given that 4 of 10 FDA inspections of the RECORD study sites resulted in issues with data integrity, the additional audits are considered critical in our assessment of data integrity. Please provide the statistical analysis used to justify your selection of 24 additional sites with a total planned sample size of 181 subjects, as proposed in your targeted audit plan. In addition, please provide the justification for selection of sites based on the percentage of patients contributed by each country.

Since a primary goal of the additional site audits is to determine the adequacy of sponsor monitoring, the audits conducted by Bayer themselves are not sufficient for this goal. It is extremely important that sufficient number of sites and patients be included in the audit plan such that there is sufficient statistical power to assure the absence of systematic monitoring deficiencies.

We recommend that you submit a detailed audit plan for the proposed third party audits for Agency concurrence prior to finalization. The audit plan should identify the statistical analyses used to determine the sites for audit. In addition, you should prepare and submit a description of how a third party auditor is to be chosen.

We recommend that you conduct an audit of sites based on high patient enrollment in the RECORD program, with an additional group of sites selected randomly to sample lower enrolling sites. Sites which enroll very few patients should be excluded from selection for audit. Rather than covering a subset of subjects at each selected site, we propose that all patients at a selected site be included in the audit. We agree that sites previously audited by the Agency should not be included in your proposed audit plan.

Item 1c (ii): The sponsor will finalize the plan following the meeting and intends to begin the additional targeted audits through the use of an independent third-party by the end of June 2009. It is anticipated that these 24 audits will be completed and reported to the Agency by the end of October 2009.

Does the Agency find these timelines acceptable?

Does the Agency agree that the results from the additional audits can be submitted as an addendum to the Complete Response?

FDA Response:

No. We reiterate the importance of a complete response. The timeline for completion of our review of your complete response will not begin until we have determined that your submitted response is complete. We do not concur with your plan to submit an incomplete response.

Item 2a: As of May 29, 2009, 14,252 subjects have been randomized in the ROCKET-AF study (#11630) and 1,280 in the Japan ROCKET-AF study (#12620). The number of subjects with concurrent elevations of ALT > 3X upper limit normal (ULN) with total bilirubin > 2X ULN is 27 and 5, respectively. Warfarin is the active control comparator agent in both studies. In order to provide the most information with the least risk to these ongoing blinded studies the sponsor proposes that unblinded liver safety data be reviewed only for the ROCKET-AF (#11630) study as follows:

- 1. All concurrent combined ALT > 3X ULN with total bilirubin > 2X ULN cases that are in the clinical study database from both central and local laboratory data with a cutoff date of May 29, 2009 will be reviewed in a blinded fashion individually by the ROCKET-AF DSMB chair (Dr. Joseph Alpert- University of Arizona) and a hepatology consultant not on the DSMB (Dr. Paul Watkins- University of North Carolina).*
- 2. Data for this blinded individual case review will include patient profiles for each individual case (prepared from the clinical study database without treatment group identification) and the most current serious adverse event report (CIOMS form).*
- 3. In parallel, the unblinded DSMB statistician at the (b) (4) will prepare a listing of the treatment assignments for the identified combined ALT > 3X ULN with total bilirubin > 2X ULN cases and summary tabular information by treatment group (including two sided 95% confidence intervals for the difference between groups) for all subjects in the safety population for the prevalence of combined ALT > 3X ULN with total bilirubin > 2X ULN.*
- 4. The unblinded DSMB statistician will also prepare summary tabular information by treatment group (including 95% two sided confidence intervals for treatment group differences) for all subjects in the safety population for ALT values at various thresholds (3X, 5X, 8X, 10X, 20X ULN) and a Kaplan Meier figure and corresponding table of the cumulative incidence of ALT > 3X ULN over time by treatment group for all postbaseline abnormalities.*
- 5. After completion of the blinded individual case reviews the two reviewers will meet (face to face at (b) (4) or another suitable location) along with the (b) (4) statistician to unblind the cases and review the summary table and figure information.*

6. *The reviewers will then complete and sign a summary report indicating that the liver data have been reviewed along with the binary outcome (liver signal not present /liver signal present). This report will not contain any unblinded or blinded data. Dr. Joseph Alpert will forward the report directly to FDA only (i.e. no copies to the sponsor or the study executive committee).*

7. *After this meeting, all the information reviewed (including the blinded individual patient profiles) will be returned to the (b) (4) statistician and archived at (b) (4) along with other DSMB documents.*

This activity will be conducted under strict confidentiality for all participants and no data or results from the unblinded review will be shared verbally or in writing with any outside parties (e.g. FDA, sponsor, ROCKET-AF Executive Committee, ROCKET-AF investigators).

Does the Agency concur with the proposal to address review of unblinded liver safety data from the ROCKET AF study (#11630) only? This proposal will also need to be discussed and agreed with the DSMB, FDA Cardiovascular and Renal Drugs Division, and ROCKET-AF Executive Committee prior to implementation to make sure that this analysis will not compromise the analytical integrity of the study.

FDA Response:

No. We recommend you to develop and submit an Adjudication Panel procedural "charter" for our review. A well-constructed procedural charter document will enhance the ability (for you as well as FDA) to verify the soundness of the findings from the adjudication process and hopefully minimize the potential for misunderstandings and/or misinterpretations. In addition to any other information, we recommend the charter to describe the following items:

a. The requisite qualifications for the members of the Adjudication Panel. We request that the criteria exclude any potential members who previously adjudicated findings from your clinical development program or who participated in the studies in any role (e.g., safety monitor).

b. The number of members of the panel. In general, we anticipate the panel will consist of at least 3 members. For example, you may wish to have 2 members assigned the responsibility for adjudicating each case and, if the two review conclusions are not consistent in their findings, then a third panel member will review the case data and form the final adjudication outcome, based upon concurrence with one of the initial 2 adjudicators.

c. The types of data to be presented to the Panel. We request the review of all available clinical data from any patients who meet one of the following criteria:

- had an ALT value > 3x ULN and a total bilirubin value > 2x ULN at the same time as the ALT signal detected OR within four weeks after the ALT signal was detected, OR
- discontinued the study drug due to liver test abnormalities or symptoms of liver disease.

d. The specific types of data to be presented for review by each adjudicator (e.g., case report forms, medical records, autopsy results, histopathology slides, etc). We request adjudication of information from all patients who experienced one of the adjudication criteria (above); including (re)adjudication of the cases from your completed studies. With respect to the on-going Rocket studies, we request a data lock as close as feasible to the current date.

e. The specific process for data adjudication. We recommend:

- use of a "sequential, locked" adjudication process in which each adjudicator reviews the information individually/sequentially and assigns a specific, final outcome (e.g., "study drug associated," "not study drug associated," "possibly study drug associated")
- description of the process for determination of a final outcome from the entire panel's review findings (see plan outlined in b, above or you may wish to consider a "majority" outcome process); we discourage a consensus approach to resolution of inconsistent findings. We emphasize the importance of having a final (single) outcome finding from the panel's review of each case.
- development of case report forms for documentation of adjudicator findings.
- a description of the expectations of the adjudicators, guidelines (as feasible) for decision-making in the adjudication process and the planned training in the expectations and procedures.

f. The plan (including possibly a template) for the development of a final Adjudication Panel report.

g. The plan for archiving of the Panel findings and conveyance of this information to you, the Rocket studies' Data Safety and Monitoring Board(s) and FDA.

h. The process for the DSMB review of the Adjudication Panel findings, including access to the treatment code assignments, anticipated analyses (focused mainly upon detecting an imbalance in the occurrence of liver safety signals between the study drugs) and the "output" recommendations to you (the sponsor) from the DSMB review (e.g., "continue study without alteration"--consistent with the existing DSMB charter for data review).

We also request you to outline the process for conveyance of the adjudication findings as well as the DSMB findings to the FDA. We recommend submission of the following items as components of the Complete Response:

- a. The final Adjudication Panel report along with tabular listings of each adjudicator's locked assessment. Also submit a text that summaries your interpretation of the adjudicator findings, particularly highlighting the cases in which discordance occurred among the individual adjudicators.
- b. Narratives (or cross reference to previously submitted narratives) for the adjudicated cases. Include a tabular listing of the cases and the location of the narratives within the Complete Response.
- c. The final recommendation to you from the DSMB review of the Adjudication Panel findings.
- d. A plan for representatives of the DSMB to meet with us (the FDA review team) at which time the DSMB will provide FDA with the treatment assignment codes for each of the adjudicated cases. This plan should minimize the potential for any individual to have access to the treatment code assignments, exclusive of the statistician already assigned to the DSMB, the members of the DSMB and the FDA review team. FDA will not archive the treatment code assignment as a component of the NDA. However, FDA conclusions and review findings are anticipated to become components of review documents. As usual, we anticipate discussing our overall review findings with you. This discussion will not include information pertaining to treatment code assignments.

Item 2d: The ATLAS ACS TIMI 46 final study report (CSR) was submitted to IND (b) (4) on May 07, 2009 (IND Serial No 0803). Data for the 6-month safety update were based on the final database, so they are part of the safety results in the CSR.

Given that ATLAS ACS TIMI 46 study safety data were provided in the 4-month and 6-month safety updates and liver safety data during the NDA review, does the Agency require the CSR to be submitted to NDA 22-406?

If so, the sponsor seeks clarification on whether efficacy data are required since (b) (4) NDA 22-406?

FDA Response:

Yes, the full study report of ATLAS ACS TIMI 46 study with datasets should be submitted to this NDA. The totality of the study's data (including efficacy) are important for a thorough review. Submission of selected data (e.g., only "safety") is inappropriate.

QUESTION 3 (PRODUCT QUALITY):

Item 3,4 and 5: The sponsor understands, after speaking with Don Henry, (ONDQA project manager) that the responses to the DMF deficiency letters which were submitted on May 1, May 12 and May 14, 2009 have not yet been reviewed by the Agency. This would include our response to Product Quality Item 9, which has been addressed in the May 12 and May 14, 2009 DMF responses.

Provided the Agency's review of these responses finds them acceptable, can the Agency confirm that there are no other DMF deficiencies?

FDA Response:

The DMF deficiencies are those identified in the DMF letters. That there are no continuing DMF deficiencies is contingent on our finding that the information provided in the amendments to the DMF's fully resolve the issues that were the basis for issuance of the DMF letters.

Items 6, 7, 8, 10 and 11: The sponsor intends to submit the required information (drug substance information, drug product specification, container closure information and stability data) from the respective DMFs to Module 3 of the NDA. However any future post-approval changes to these sections will be made only to the DMFs and reported by cross reference in the NDA according to the appropriate reporting notifications established in 21 CFR 314.

Is this proposal acceptable to the Agency?

FDA Response:

Future post-approval changes to the manufacture and controls of drug substance and drug product may be submitted to the DMF's. However, it is the responsibility of Johnson & Johnson Pharmaceutical Research & Development to monitor such changes in accordance to the Change Control Protocol to assess and assure that any such changes will not have an adverse effect on the identity, strength, quality, purity or potency of the product marketed. Be advised that changes, such as those to the specifications of the drug substance and drug product, formulation, container closure and stability that relate to the safety and effectiveness of the product require submission of a supplement to the approved NDA with the appropriate reporting categories as to whether the changes are deemed to have a major or moderate impact.

QUESTION 4 (CLINICAL PHARMACOLOGY):

Item 12: The sponsor seeks clarification on special population(s) that the Agency believes would warrant a lower strength formulation for dose modification.

FDA Response:

As stated in our previous letter of May 27, 2009, our request was not a basis for the inability to approve your application, but rather to facilitate our review of the proposed labeling and the need for any post-marketing expectations. In this context we anticipate the ultimate need for development of a lower strength tablet is warranted for patients with Child Pugh (C-P) class B hepatic impairment without coagulopathy and patients concurrently taking rivaroxaban with 1) strong CYP3A4 and/or P-gp inhibitors or 2) moderate or strong CYP3A4 and/or P-gp inhibitors with mild-moderate renal impairment. In the interim, the use of rivaroxaban in these populations should be avoided.

The sponsor's understanding based on previous interactions with the Agency is that there is agreement that there is sufficient efficacy and safety data from the RECORD program to support the use of the 10 mg dose in patients with moderate renal impairment (calculated creatinine clearance 30 to < 50 mL/min).

Does the Agency agree with this statement?

FDA Response:

Based on the findings from a subgroup analysis of the pooled RECORD Studies, it appears that the 10 mg dose is acceptable in patients with moderate renal impairment (calculated creatinine clearance 30 to < 50 mL/min); however, close monitoring will be required.

The sponsor (b) (4) patients with hepatic disease associated with coagulopathy (i.e. prolonged prothrombin time) since these patients are already auto-anticoagulated and the addition of any additional impairment of hemostasis (including a lower rivaroxaban dose) may compromise the safety of the patient(s).

Does the Agency agree with this approach?

FDA Response:

See the first clinical pharmacology comment above. In addition, we agree that rivaroxaban should be contraindicated at any level of hepatic impairment associated with coagulopathy. In addition, rivaroxaban use should also be contraindicated in Child-Pugh (C-P) class C hepatic impairment (We refer you to the Guidance "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling"

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>).

Several situations exist where rivaroxaban exposures would be modestly increased but for which there is limited clinical efficacy and safety data to directly support the use of the 10 mg dose (e.g. strong inhibition of both CYP3A4 and PgP, moderate renal impairment with strong CYP3A4 inhibition, severe renal impairment with CYP3A4 inhibition, severe renal impairment alone, etc). Depending on the specific situation the sponsor recommends either (b) (4) in the proposed label.

Does the Agency agree with this approach?

FDA Response:

See the first clinical pharmacology comment above.

QUESTION 5 (SAFETY UPDATE):

The sponsor proposes providing this safety update in a similar format to the 4-month and 6-month safety updates. The proposed cut-off date for this safety update is May 29, 2009. As previously agreed with the Agency, case report forms and narrative summaries are not provided for patients who died or discontinued due to an adverse event from ongoing studies. Narratives will be provided for all patients with concurrent elevations of ALT > 3X ULN with total bilirubin > 2X ULN.

Does the Agency concur with this proposal?

FDA Response:

The format you suggest is acceptable, with modifications. A cut-off date 1 month prior to submission of your complete response is acceptable. Narratives should be provided for all patients (spontaneous, post-marketing reports of serious adverse reactions) in countries in which rivaroxaban is marketed and all subjects in any study with ALT > 3x ULN and total bilirubin > 2X ULN within four weeks of each other, as outlined above.

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/s/

Marcus Cato

7/14/2009 04:13:09 PM

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: June 3, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Andrea F. Kollath, DVM
Director, Regulatory Affairs
Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: Type A meeting request Granted

Dr. Kollath Called to discuss the May 29, 2009, letter from Johnson and Johnson requesting a Type A meeting with FDA.

The below information was conveyed to Dr. Kollath:

Meeting Date: June 19, 2009
Time: 3:00 – 4:30 PM EST
Type: Clinical, Post-Action Guidance, (Type A)
Product: Xarelto™ (Rivaroxaban) Tablets
Sponsor: Johnson & Johnson Pharmaceutical Research & Development,
L.L.C. (J&J)
Proposed Indication: Prevention of Venous Thromboembolism
Purpose: To obtain clarification on items detailed in the Complete Response
Letter:
North American Dial-In Number: (888) 627-7005
Conference Code: 619833 #

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/s/

Marcus Cato

6/26/2009 04:53:28 PM

Memorandum

To: NDA 22-406
CC: Eldon Leutzinger, Josephine Jee, Rik Lostritto, Ph.D.
From: Sarah C. Pope, Ph.D.
Date: 5/27/2009
Re: Final CMC recommendation for NDA 22-406

NDA 22-406 was initially submitted on 28-JUL-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 29-MAR-2009) identified several Chemistry, Manufacturing and Controls (CMC) deficiencies which should be conveyed in the action letter.

Resolution of these CMC deficiencies is necessary prior to a CMC recommendation for approval of NDA 22-406. Additionally, at the time of finalization of the 29-MAR-2009 CMC review, an overall recommendation from the Office of Compliance had not been received.

This memo serves to update that determination. The Office of Compliance issued an overall acceptable recommendation for this application on 26-MAY-2009. However, from a CMC perspective, approval of NDA 22-406 cannot be recommended until the outstanding CMC deficiencies are adequately resolved.

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/s/

Sarah Pope
5/27/2009 12:15:48 PM
CHEMIST

Richard Lostritto
5/27/2009 12:24:31 PM
CHEMIST

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	May 12, 2009
TIME:	12:30 – 13:00 ET
LOCATION:	White Oak Conference Room 2560
APPLICATION:	NDA 22-406
SPONSOR:	Johnson & Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME:	Xarelto (Rivaroxaban) tablets
TYPE OF MEETING:	Teleconference
MEETING CHAIR:	Sarah Pope, Ph.D.
MEETING RECORDER:	Don Henry

FDA PARTICIPANTS:

Sarah Pope, PhD., Branch Chief
Eldon Leutzinger, Ph.D., Pharmaceutical Team Leader
Josephine Jee, Ph.D., Chemist
Marcus Cato, Regulatory Project Manager
Don Henry, Regulatory Project Manager

EXTERNAL PARTICIPANTS:**Bayer attendees**

Robert Kelly, Director CMC and Marketed Products, Bayer HealthCare
Deborah Flint, Associate Director CMC, Bayer HealthCare
Larry Winick, MA, Global Regulatory Strategist; Hematology/Cardiology

J&J attendees

Nancy Micalizzi, Associate Director, CMC Regulatory
Donald Doyle, MS, Director, ChemPharm Leader
Frank J DeLuccia, Ph.D. , Vice President, Global CMC Regulatory Affairs
Sanjay Jalota, MRPharmS, Senior Director, Global Regulatory lead
Andrea Kollath, DVM, Director, Regulatory Affairs

BACKGROUND:

The FDA filed deficiency notifications for Drug Master Files 21580, 21581, and 21592 in support of this application (NDA 22-406) for Xarelto (Rivaroxaban) tablets. Based on the letters, J&J requested a teleconference meeting to discuss the following deficiency:

- Based on the 9 months of long-term stability data at 25°C/60% RH and 6 months at 30°C/75% RH submitted of rivaroxaban tablets in HDPE bottles and (b) (4) blisters, a (b) (4) expiration dating period is the maximum that can be granted at this time.

J&J provided the following background information for the meeting:

J&J respectfully notes that the (b) (4) expiry is not acceptable for the Gurabo finished product. Please reconsider the expiry based on the following:

1. The primary stability data for the tablets was generated on batches manufactured at Bayer's Leverkusen site as described in 3.2.P.8 of J&J PRD DMF 21592. Manufacturing site equivalence was established based on a comparison of tablet manufacturing processes, batch release data and stability data. This was agreed with the Agency during the Pre-NDA Meeting correspondence. (Agency responses dated Nov 7, 2008 to our briefing document questions).
2. Also, it is our understanding based on the pre-NDA meeting (FDA response to question 3 in the briefing document) that the expiry would be granted based on a combination of the primary stability data, the Bayer supportive data, as well as the site data. The Bayer DMF supportive data also included (b) (4) open container data. The J&J Gurabo site stability data confirms the stability profile of the product. It should not be the sole dataset to base expiry on.
3. The February 23, 2009 amendment to J&J DMF 21592 contained a 9-mos stability update on the Gurabo site stability batches. We currently also have 12-month stability data and the statistical analysis for both the 9 month and the 12 month data, which could be provided. However, we would like to know if this would be considered a major amendment, necessitating additional review time.

THE TELECONFERENCE DISCUSSION

1. FDA indicated that upon review of the information presented above, an expiry of (b) (4) would be granted for the bottle configurations. Only (b) (4) expiry could be granted for the blisters since they represented worst case and there was only 9-months real-time data for the commercial configurations. However, J&J indicated that the cross-referenced DMF 21580 provides a statistical evaluation of the data that would support a (b) (4) expiry. FDA asked J&J to confirm the location of the statistical analysis and agreed to re-evaluate that data in relationship to the expiration dating period for the blister configuration.
2. Additional Meeting Discussion: J&J indicated that during a previous teleconference with the Division of Medical Imaging and Hematology, they were informed that there were major CMC issues with the applications. J&J asked whether there were issues, in addition to the deficiencies identified in the DMF. FDA expressed that the CMC review is still ongoing and that J&J will be notified of any issues in a timely manner.

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/s/

Don Henry
5/14/2009 09:28:59 AM
PROJECT MANAGER FOR QUALITY

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE: May 12, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Sanjay Jalota, MRPharmS
Regulatory Global Regulatory Lead

Andrea F. Kollath, DVM
Director, Regulatory Affairs

e-mail: AKollath@its.jnj.com
SJalota@its.jnj.com

Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: Final study report for ATLAS ACS TIMI 46

Cato, Marcus

From: Cato, Marcus
Sent: Tuesday, May 12, 2009 4:44 PM
To: 'Jalota, Sanjay [PRDUS]'
Cc: Kollath, Andrea [PRDUS]
Subject: RE: ATLAS ACS TIMI 46 - RE: Questions on NDA 22-406

Dear Sanjay,

My apologies for my delayed response. The reviewers regard the ATLAS study as important. It is at your discretion whether or not to submit it to the NDA at the present time. As discussed in the telephone conversation of May 11 between FDA and Dr. Kronig, the review team is finalizing all reviews at the present time and the division plans to close out this review cycle shortly. Hence, the division does not envision reviewing the ATLAS study during this review cycle. In general, we suggest you await the results of this review cycle prior to submitting additional data (including the ATLAS study).

Thanks

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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From: Jalota, Sanjay [PRDUS] [mailto:SJalota@its.jnj.com]
Sent: Thursday, May 07, 2009 3:51 PM
To: Cato, Marcus; Kollath, Andrea [PRDUS]
Subject: ATLAS ACS TIMI 46 - RE: Questions on NDA 22-406

Hi Marcus,

Hope all is well. We submitted the ATLAS ACS TIMI 46 to IND 75,931. Attached is the cover letter As per the March 20, 2009 AdCom discussions where DMIHP mentioned they had not seen the final study report, please let me know if we need to formally submit the cover letter or the report (~15,000 pages) to the NDA

Thanks and best regards
Sanjay

5/12/2009

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/s/

Marcus Cato
5/14/2009 08:03:24 AM
CSO

RECORD OF TELEPHONE CONVERSATION

NDA 22-406 (Rivaroxaban)

Today's date: May 11, 2009

Speakers: Marcus Cato and Dwaine Rieves for FDA
 Michael Kronig for Johnson and Johnson

FDA returned a phone call to Dr. Kronig (908-727-2526) after Dr. Kronig had left a voice mail on Dwaine Rieves' line. FDA made the following points:

-the NDA is in the "wind down" phase and all primary reviews should have been completed by now

-FDA anticipates completing this review cycle with an action

-FDA anticipates the need for resolution of CMC issues, certain clinical data integrity issues as well as the need for additional clinical data that will help evaluate the risk (if any) for severe liver toxicity

Dr. Kronig acknowledged that they were hoping for a first cycle approval or a major amendment approach but they would deal with other responses.

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/s/

Rafel Rieves
5/11/2009 05:38:16 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 1, 2009
TIME: 1:00 PM - 3:00 PM EST
LOCATION: White Oak CSU Building Room 2047
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Regulatory Briefing

MEETING CHAIR: Dr. John Jenkins

MEETING RECORDER: Mr. Marcus Cato, Ms. Diane Leaman

FDA ATTENDEES:

REGULATORY BRIEFING PANEL

John K Jenkins, M.D., Director, Office of New Drugs
Richard Pazdur, M.D., Director, Office of Oncology Drug Products
Robert Temple, M.D., Director, Office of Medical Policy
Janet Woodcock M.D., Director, Office of the Center
Douglas Throckmorton, M.D., Deputy Director, Center for Drug Evaluation and Research
Gerald Dal Pan, M.D., Director, Office of Surveillance and Epidemiology
Robert O'Neill, Ph.D., Director, Office of Biostatistics
Rosemary Roberts, M.D., Director, Office of Counter-Terrorism and Emergency Coordination
Solomon Sobel, M.D., Associate Director, Science and Research Staff
David Jacobson-Kram, M.D., Associate Director, Office of New Drugs

FDA PRESENTERS

Kathy Robie Suh, M.D., Ph.D., Team Leader, Division of Medical Imaging and Hematology Products
Min Lu, M.D., M.P.H., Medical Officer, Division of Medical Imaging and Hematology Products
Jyoti Zalkikar, Ph.D., Team Leader, Division of Biometrics V
Qing Xu, Ph.D., Reviewer, Division of Biometrics V
Joseph Grillo, Pharm.D., Reviewer, Division of Clinical Pharmacology V
Kate Gelperin, M.D., M.P.H., Medical Officer, Division of Epidemiology I

FDA ATTENDEES

Ian Waxman, Ph.D., Division of Clinical Evaluation & Pharmacology/Toxicology
Keith Burkhart, M.D., Office of New Drugs
Wiley Chambers, M.D., Division of Anti-Infective and Ophthalmology
Jennifer Harris, M.D., Division of Anti-Infective and Ophthalmology
Joseph Stalder, Division of Special Pathogen and Transplant Products
Jane Liedtka, M.D., Division of Dermatology and Dental Products
Melinda McCord, Ph.D., Division of Dermatology and Dental Products
Michael Monteleone, M.D., Division of Cardiovascular and Renal Products
Robert Fiorentino, M.D., Division of Cardiovascular and Renal Products
Steven Grant, M.D., Division of Cardiovascular and Renal Products
Ann Farrell, M.D., Division of Drug Oncology Products
Ke Liu, M.D., Division of Drug Oncology Products
Robert Justice, M.D., Division of Drug Oncology Products
Mohab Alexander, M.D., Division of Medical Imaging and Hematology Products
Diane Leaman, Division of Medical Imaging and Hematology Products
Ira Krefting, M.D., Division of Medical Imaging and Hematology Products
Marcus Cato, M.B.A., Division of Medical Imaging and Hematology Products
Timothy Lape, Pharm.D., Office of Surveillance and Epidemiology
Tselaine Jones-Smith, Pharm.D., Division of Medical Error and Preventions Analysis
Kathryn O'Connell, M.D., Division of Risk Management
Phuong Nina Ton, Pharm.D., Review Management Staff
Lisa Kubaska, Division of Drug Information
Ram Tiwari, Ph.D., Office of Biostatistics
Kate Dwyer, Ph.D., Division of Biometrics III
Rima Izem, Ph.D., Division of Biometrics IV
Aloka Chakravarty, Ph.D., Division of Biometrics V
Chava Zibman, Ph.D., Division of Biometrics I
Min Min, Ph.D., Division of Biometrics I
Li Zhang, Ph.D., Office Of Clinical Pharmacology
Lanyan Fang, Ph.D., Division of Clinical Pharmacology III
John Lazor, Ph.D., Division of Clinical Pharmacology IV
Nam Atiqur Rahman, Ph.D., Division of Clinical Pharmacology V
Young Moon Choi, Ph.D., Division of Clinical Pharmacology V

EXTERNAL ATTENDEES:

None

BACKGROUND:

NDA 22-406 is an application for Xarelto (rivaroxaban), an anticoagulant, for short-term use in prophylaxis of venous thromboembolism (VTE) in patients undergoing elective hip replacement surgery and in patients undergoing elective knee replacement surgery. On March 19, 2009, FDA held an Advisory Committee (AC) meeting regarding the clinical data in NDA 22-406, where the FDA emphasized that, in regard to efficacy, data from four clinical studies demonstrated statistically significant outcomes, predominantly due to asymptomatic venographic findings. The AC discussion focused upon safety considerations such as bleeding, the potential for liver toxicity, and considerations of whether or not the long-term data were essential for the initial short-term risk-benefit assessment. Suggestions of liver toxicity were evident in the short-term studies. To address this concern for a liver toxicity signal, the sponsor presented summary liver test data from a recently completed study (the ATLAS ACS TIMI 46 Clinical Study) in which subjects received six months of rivaroxaban therapy. The final study report and details of this study have not been made available for FDA review. Ultimately, the Advisory Committee provided a favorable recommendation for the risk-benefit assessment based upon considerations of the available clinical data.

MEETING OBJECTIVES:

To discuss the division's plan to issue a Complete Response letter.

DISCUSSION POINTS:

The Division presented slides (see attached).

Prior to the statistical presentation, the Division noted that the primary endpoint of the study [a composite of any deep vein thrombosis (DVT) (venographically demonstrated, symptomatic or non-symptomatic), non-fatal pulmonary embolism (PE), and death from any cause] supported the efficacy of the drug. The statistical presentation would focus on the exploratory pooled analyses of "symptomatic venous thromboembolism (VTE)."

The panel commented that the exploratory analysis of evidence of superiority of rivaroxaban compared to enoxaparin does not meet the regulatory standard for superiority. Proximal VTE is a more clinically meaningful outcome than asymptomatic distal VTE; VTE location should be considered when assessing the benefit/risk. The findings in the RECORD 1 study were favorable for rivaroxaban in regard to occurrence of proximal VTE. Efficacy was demonstrated on the primary endpoint, as well as the main secondary efficacy endpoint of Major VTE. Venographically detected VTE is a surrogate endpoint and has been used for approval of other anticoagulant products for the indications. The Division commented that the venographic evidence of efficacy may provide a sufficient number of events to allow a meaningful statistical comparison. Two of the RECORD studies did not compare rivaroxaban treatment to an approved dose or duration of the comparator. The panel suggested that data from these two studies should not be used in a pooled analysis of treatment effect. The panel noted that when approval is based on a non-clinical endpoint, such as venography, a price is paid with bleeding, a clinical outcome.

After the statistical presentation, the panel inquired about the seven potential Hy's law cases in the enoxaparin control arm. FDA liver experts expressed that not all cases show a signal for liver injury and it is difficult to rule out viruses, alcoholism, and other factors. It requires a thorough review and adjudication which FDA has not been able to do. FDA discussed a recently received adverse event that would require more information.

The panel inquired why follow-up and monitoring of international normalized ratios (INRs) was not necessary. The panel asked for the justification for that. The Division responded that the sponsor did not propose a routine monitoring plan and that routine monitoring was not done in the studies. Also, it is difficult to monitor anti-Factor Xa levels since there is not an accepted standard for the test between institutions. The panel asked how comfortable the Division was with the dose. Clinical Pharmacology noted that it had reviewed safety and efficacy data from phase 2 dose response studies and found a shallow dose response curve for efficacy while a steep dose-response was observed in regard to bleeding, giving support to the selection of a 10mg dose, except for certain special populations at risk for increased exposure (e.g., moderate-severe hepatic impairment, strong CYP3A4/P-gp inhibitor use). The Division informed the panel that body weight as well as other factors such as age, sex, and ethnicity were studied and not deemed to result in clinically relevant exposure changes.

The Division continued its presentations.

Question 1

The Advisory Committee voted 15 to 2 that the "available" clinical data demonstrated a favorable rivaroxaban risk-benefit profile. This vote followed the sponsor's presentation of favorable "liver test" data from the recently completed "ATLAS TIMI 46 Study," for which the Division has received only the study's summary "liver test" data. The Division plans to recommend a Complete Response letter requesting the final ATLAS TIMI 46 study report as well as adjudication of the potential "Hy's cases" in the on-going atrial fibrillation studies. Do you agree?

The panel restated the first question as "Is a signal in short-term data enough to request long-term data before approving a short term indication?"

The panel agreed that the Division is entitled to these data and advised that the Division characterize the potential signal for liver injury. The panel stated that although it does not take 30 days to get liver injury, the Division needs to better characterize the risk; the Division should be able to review the data. The Panel recommended that subjects from the on-going atrial fibrillation studies who had safety issues and stopped medication should be unblinded.

The panel asked if genetic testing was done on the patients. The Division responded that samples were drawn for genetic testing in the Phase 3 studies, but were not analyzed. The Division noted that in its review, it plans to suggest the applicant consider an evaluation of candidate single nucleotide polymorphisms (SNPs) or haplotypes for pharmacogenomic analysis. The panel suggested that the sponsor analyze them as part of the evaluation of potential "Hy's cases."

Question 2

Is completion and full reporting of the “long term, atrial fibrillation” studies essential to assess rivaroxaban’s risks and benefits for the “short term” VTE prophylaxis indication?

The panel asked what the rush was to approve rivaroxaban when it is not a priority application. The study data (from ATLAS and Hy’s cases from ROCKET) would not take long to review. The Division noted that the ROCKET atrial fibrillation data would not be available until next year; however, the sponsor should be able to unblind the Hy’s law cases and submit the data.

The panel recommended a sequential stepwise approach for the decision based on what is observed from the potential “Hy’s cases” and ATLAS TIMI 46 Study.

Question 3

The Division regards the pooling of “clinical outcomes” from the four RECORD studies as inappropriate for hypothesis testing because of important differences in the study designs and analytical deficiencies. Do you agree?

The panel generally regarded the pooling as inappropriate and reminded the Division that FDA has set a high standard in regard to comparative efficacy claims. Regardless of how the studies are combined, it is after the fact and FDA has never allowed sponsors to combine studies to make claims.

SUMMARY OF ADVICE:

- The panel agreed that the Division is entitled to the final ATLAS TIMI 46 study report as well as adjudication and unblinding of the potential “Hy’s cases” in the on-going atrial fibrillation studies to characterize the potential signal for liver injury signal. The panel recommended a sequential stepwise approach for the decision based on what is observed from the potential “Hy’s cases” and ATLAS TIMI 46 Study.
- The pooling of “clinical outcomes” from the four RECORD studies for hypothesis testing is inappropriate.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None

ACTION ITEMS:

- None

ATTACHMENTS/HANDOUTS:

- Division Slides

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Rivaroxaban, NDA 22-406
Johnson and Johnson, Inc.

**Oral anticoagulant for use in the prevention
of VTE among patients undergoing
hip or knee surgery**

Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
May 1, 2009

1

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Background

- Warfarin: approved in 1954
- Ximelagatran:
 - “Short term” & “long term” indications
 - Liver toxicity in “long term” studies
 - NA in US; marketing ceased in non-US
- Rivaroxaban:
 - no structural similarity to ximelagatran
 - for only “short term” initial marketing
 - no dose titration, no coag monitoring ²

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Protecting and Promoting Public Health www.fda.gov

March 19, 2009 AC

- Efficacy: statistical success in 4 studies, mainly on venographic outcomes
- Safety:
 - bleeding
 - potential liver toxicity
 - “long term” study data importance
- Sponsor presented summary “liver” data from a recently completed study
- Favorable AC recommendation based on “available data” ³

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Post-AC

- Unresolved:
 - CMC
 - DSI
- CR Letter anticipated

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Panel Questions

1. Do you agree with planned data request?
 - Final report of study presented at AC
 - Adjudication of possible “Hy’s cases” in long term studies
2. Discuss role of “off-label, long term” considerations in “short term” risk-benefit assessment
3. Discuss the company’s plan to “pool” data from 4 studies to make a labeling claim of “clinical benefit” ⁵

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Overview: Rivaroxaban for Thromboprophylaxis in Patients Undergoing Hip or Knee Replacement Surgery

Kathy Robie Suh, M.D., Ph.D.
Division of Medical Imaging and Hematology Products
CDER Regulatory Briefing

May 1, 2009

1

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FDA Presentations

- **Background for the application**
– Kathy Robie Suh, M.D., Ph.D., OODP
- **Rivaroxaban Efficacy and Safety**
– Min Lu, M.D., OOPD
- **Statistical analysis aspects**
– Qing Xu, Ph.D., OB, DBV
- **Hepatotoxicity Concerns**
– Kate Gelperin, M.D., OSE

2

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Thromboprophylaxis in Orthopedic Surgery

- ~ 800,000 patients in US undergo Hip or knee replacement (2005 AAOS statement)
- VTE rate ~ 40-60% without prophylaxis
- Symptomatic PE or death very uncommon
- Imaging endpoints in clinical trials
- Proximal DVT generally more important than distal DVT

3

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Drugs Approved for VTE Prophylaxis in Hip and/or Knee Surgery Patients

Drug	Indication	Treatment Duration
Enoxaparin	Hip & Knee	7 to 10 days
	Hip, extended prophylaxis	35 days
Dalteparin	Hip	5 to 10 days
Fondaparinux	Hip & Knee	5 to 9 days

4

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Considerations for Evaluation of Rivaroxaban for Thromboprophylaxis in Major Orthopedic Surgery

- **Efficacy:**
 - Imaging (venography) endpoints accepted
 - Missing data common (~ 30%)
- **Safety:**
 - Enoxaparin and liver test abnormalities
 - “Fixed” dose & “special populations”
- **Regulatory:**
 - Drugs currently available, all parenteral
 - First oral anticoagulant since warfarin
 - Potential “extended prophylaxis” or other use
 - On-going studies assess extended use

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Rivaroxaban NDA 22-406

Min Lu, M.D., M.P.H.
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
FDA
May 1, 2009

5/12/2009

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Review Questions

■ Efficacy

- Do the data show efficacy?

■ Safety

- Does rivaroxaban increase bleeding?
- Does rivaroxaban increase the risk for hepatotoxicity?
- Are ongoing studies important for the current application?

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■ Indication:

“for the prophylaxis of DVT and PE in patients undergoing:

- hip replacement surgery
- knee replacement surgery.”

■ Dosing regimen:

- 10 mg orally, once daily
 - 35 days for hip replacement
 - 14 days for knee replacement

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Clinical Development Program

■ Prophylaxis of DVT/PE in hip or knee surgery

■ Prophylaxis of DVT/PE in hospitalized, medically ill

■ DVT/PE secondary prevention

■ Atrial fibrillation

■ Acute coronary syndrome

On-Going

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Clinical Development Program

- ~ 18,000 patients in 64 completed studies
- Four RECORD Studies:
 - main data source
 - 12,729 patients in 41 countries
- Ongoing studies:
 - Limited, preliminary information
 - Six month update:
 - ~ 10,000 exposed for one month
 - ~ 6,000 exposed for six months

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RECORD Studies

- RECORD 1 & 2: hip
- RECORD 3 & 4: knee
- Randomized (1:1) to rivaroxaban or enoxaparin, double-blind, international
- Venography on Day 12 (knee) or Day 35 (hip)
- Follow-up for one additional month
- Central adjudication of major outcomes

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Efficacy Considerations

RECORD 3:

- used unapproved lower enoxaparin dose for knee: 40 mg daily dose
- potential for under-estimation of enoxaparin effect

RECORD 2:

- rivaroxaban for 35 days
- enoxaparin for only 12 days
- potential for under-estimation of enoxaparin effect

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Primary Efficacy Endpoint: RECORD 1 & 2 (hip)

	RECORD 1		RECORD 2	
	Riva n = 1595	Enox n = 1558	Riva n = 864	Enox n = 869
"Total VTE"	18 (1.1%)	58 (3.7%)	17 (2.0%)	81 (9.3%)
<i>Components (numbers of patients with outcome)</i>				
All Death	4	4	2	6
N-F PE	4	1	1	4
Prox DVT	1	31	5	44
Distal DVT	12	27	11	49

p < 0.001 in RECORD 1 and 2

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Primary Efficacy Endpoint: RECORD 3 & 4 (knee)

	RECORD 3		RECORD 4	
	Riva n = 824	Enox n = 878	Riva n = 965	Enox n = 959
"Total VTE"	79 (9.6%)	166 (18.9%)	67 (6.9%)	97 (10.1%)
<i>Components (numbers of patients with outcome)</i>				
All Death	0	2	2	3
N-F PE	0	4	5	8
Prox DVT	9	20	8	14
Distal DVT	74	156	57	82

p < 0.001 in RECORD 3 and p<0.05 in RECORD 4

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Symptomatic VTE (DVT or PE) in RECORD Study Safety Population

RECORD	Riva	Enoxa	Hazard ratio (95% CI)
1	6/2209 (0.3%)	11/2224 (0.5%)	0.5 (0.2, 1.5)
2	3/1228 (0.2%)	15/1229 (1.2%)	0.2 (0.1, 0.7)
3	8/1220 (0.7%)	24/1239 (1.9%)	0.3 (0.2, 0.8)
4	11/1526 (0.7%)	18/1508 (1.2%)	0.6 (0.3, 1.3)

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Safety Results

- Overall Adverse Events
- Bleeding Events
- Hepatic Events

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Adverse Events in RECORD Studies

Adverse events	Riva n =6183	Enoxa n =6200
Any AEs	4179 (67.6%)	4306 (69.5%)
Death	13 (0.2%)	25 (0.4%)
Any SAEs	406 (6.6%)	528 (8.5%)
AE resulting in permanent discontinuation of study drug	230 (3.7%)	288 (4.7%)

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Deaths (treatment and follow-up) in RECORD Study

RECORD	Riva	Enoxa or Enoxa/placebo
1 (hip)	5/2209 (0.2%)	5/2224 (0.2%)
2 (hip)	2/1228 (0.2%)	8/1229 (0.7%)
3 (knee)	0/1220 (0.0%)	6/1239 (0.5%) (40 mg od)
4 (knee)	6/1526 (0.4%)	6/1508 (0.4%)

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"Major Bleeding" in RECORD Studies

Event	Riva n = 6183	Enoxa n = 6200
"Major bleeding"	24 (0.4%)	13 (0.2%)
<i>Components (numbers of patients)</i>		
Fatal	2	0
Bleeding into critical organ	3	5
Bleeding requiring re-op	12	7
Extra-surgical site bleeding with > 2 g/dL Hgb decrease	8	1
Extra-surgical site bleeding with > 2 units blood	8	1

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"Non-major" Bleeding in RECORD Studies

Events	Riva n = 6183	Enoxa n = 6200
Any bleeding	434 (7.0%)	401 (6.5%)
"Clinically relevant" non-major bleeding	177 (2.9%)	145 (2.3%)
Other non-major bleeding	260 (4.2%)	256 (4.1%)

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Possible Signal for Liver Toxicity in RECORD Studies

Small imbalance in:

- Serious hepatic events
- ALT and TB marker:
(ALT > 3X ULN and TB > 2X ULN)

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Incidence of ALT > 3x ULN Concurrent With TB > 2x ULN in RECORD Studies

Result	Rivaroxaban (n=6131)	Enoxaparin (n=6131)
ALT > 3xULN with TB > 2xULN	9 (0.15%)	7 (0.11%)
<i>Drug-relatedness Assessment by LAP* (n)</i>		
Unrelated/excluded	2	4
Possible	6	2
Probable	1	1
Definite	0	0

* "most relatedness" assignment by any adjudicator

5/12/2009

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Incidence of ALT/TB Elevations in RECORD Studies

Result	Riva n = 6131	Enoxa n = 6131
ALT > 3x ULN	2.5%	3.7%
> 5x ULN	0.9%	1.3%
> 8x ULN	0.3%	0.3%
> 10x ULN	0.16%	0.15%
> 20x ULN	0.03%	0.02%
TB > 1.5x ULN	2.8%*	2.6%
> 2x ULN	0.8%*	0.8%

*n = 6133

5/12/2009

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Incidence of Serious "Hepatic" Adverse Events in RECORD Studies		
Preferred term	Riva n = 6183	Enoxa n = 6200
Any event	33 (0.5%)	27 (0.4%)
ALT increased	17 (0.3%)	11 (0.2%)
AST increased	5 (0.1%)	7 (0.1%)
Bilirubin increased	5 (0.1%)	4 (0.1%)
"Hepatic enzyme increased"	6 (0.1%)	7 (0.1%)

Incidence of ALT > 3x ULN Concurrent With TB > 2x ULN in Phase 2 and 1 Studies		
Result	Riva N = 3206	Enoxa n = 847
ALT > 3x ULN with TB > 2x ULN	5 (0.16%)	2 (0.24%)
"Liver-related deaths"	2 (0.06%)	0 (0.00%)

Ongoing Studies (as 12/5/08) ALT > 3x ULN Concurrent With TB > 2x ULN		
Ongoing Studies	Rivaroxaban	Control
ATLAS ACS TIMI 46	0/2270	3/1134
EINSTEIN DVT/PE	3/1562	0/1549
ROCKET-AF	16 (13 blinded, 3 warfarin)/10,472	
J-ROCKET-AF (as 10/30/08)	3 (2 blinded, 1 rivaroxaban)/1,108	
MAGELLAN	2 (1 blinded, 1 enoxaparin)/808	
Total	27 Cases (16 blinded)	
"Liver-related deaths"	3-blinded, 2-rivaroxaban, 1-placebo, 1-enoxaparin	

ATLAS ACS TIMI 46 Study		
■ Randomized, double-blind, placebo-controlled, dose-escalation phase 2 study		
■ Patients with acute coronary syndrome		
■ Rivaroxaban doses: 5, 10, 15, and 20 mg		
■ 1445 (of 2309) received ≥ 6 months		
■ Data submitted: summary in 6-month safety update (2/2/2009) and liver dataset for eDISH		

ATLAS ACS TIMI 46 Study		
Table 3: Incidence of ALT or AST > 3x ULN and Total Bilirubin > 2x ULN (Subjects Available for Safety in ATLAS ACS TIMI 46)		
Laboratory Abnormality Time of Measurement	Rivaroxaban N=2302 n/J (%)	Placebo N=1149 n/J (%)
ALT > 3x ULN total bilirubin > 2x ULN		
Baseline	0/2215 (0.0%)	0/1103 (0.0%)
Postbaseline	0/2270 (0.0%)	3/1134 (0.3%)
Treatment-emergent	0/2172 (0.0%)	2/1082 (0.2%)
AST > 3x ULN, total bilirubin > 2x ULN		
Baseline	2/2120 (0.1%)	1/1054 (0.1%)
Postbaseline	1/302 (0.3%)	4/162 (2.5%)
Treatment-emergent	1/231 (0.4%)	3/131 (2.3%)

ATLAS ACS TIMI 46 Study		
Table 2: Incidence of Treatment-Emergent Abnormal Liver Function Test (ALT and Total Bilirubin) Values (Subjects Available for Safety in ATLAS ACS TIMI 46)		
Laboratory Variable Level of Increase	Rivaroxaban N=2302 n/J (%)	Placebo N=1149 n/J (%)
ALT		
> 3x ULN	55/2093 (2.6%)	37/1056 (3.5%)
> 5x ULN	12/2137 (0.6%)	12/1076 (1.1%)
> 8x ULN	2/2146 (0.1%)	3/1079 (0.3%)
> 10x ULN	1/2148 (<0.1%)	2/1079 (0.2%)
> 20x ULN	0/2148 (0.0%)	0/1079 (0.0%)
Bilirubin, total		
> 1.5x ULN	17/2149 (0.8%)	11/1084 (1.0%)
> 2x ULN	5/2163 (0.2%)	4/1090 (0.4%)
> 3x ULN	0/2166 (0.0%)	0/1092 (0.0%)
> 5x ULN	0/2166 (0.0%)	0/1092 (0.0%)
> 8x ULN	0/2166 (0.0%)	0/1092 (0.0%)

Review Questions

- **Do the data show efficacy?**
 - Yes, based on “Total VTE”
- **Does rivaroxaban increase bleeding?**
 - Yes
- **Does rivaroxaban increase the risk for hepatotoxicity?**
 - Cannot exclude possibility
- **Are ongoing studies important for the current application?**
 - Yes. ATLAS study and Hy's law cases in ROCKET studies.

5/12/2009

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Rivaroxaban, NDA 22-406 Regulatory Briefing

Qing Xu, Ph.D.
Office of Biostatistics, FDA

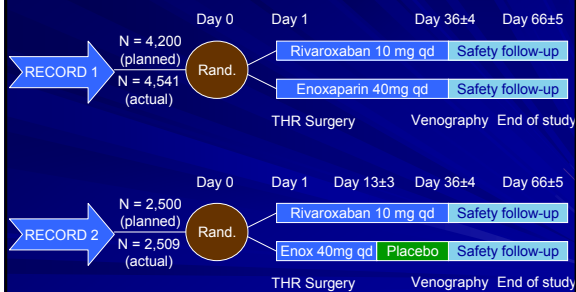
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Outline

- Brief Description of Clinical Development Program
- Integrated Analyses
 - Benefit
 - Bleeding Risk

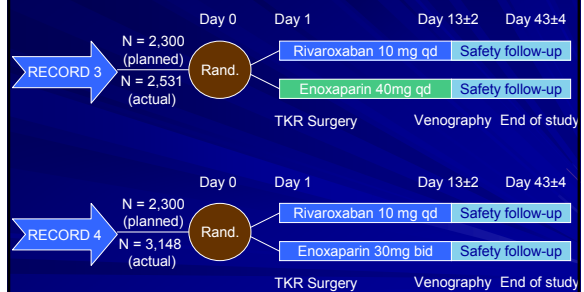
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Record 1 & 2 Study Design-THR



3

Record 3 & 4 Study Design-TKR



4

Results

- Statistical superiority for Rivaroxaban achieved at 5% level
 - For the primary endpoint of "Total VTE"
 - Primarily due to venography based components
 - Low rates of Death and Non-fatal PE
 - Effect of Rivaroxaban on these is unclear
- SAP did not include control of false positive rate for multiple secondary endpoints for anticipated claims based on statistical significance
- Nominal p-values for secondary endpoints
 - < 0.05 ONLY for RECORD 2 and 3, NOT for RECORD 1 and 4
 - Supportive of primary analysis

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Agreement

The data from RECORD studies demonstrate efficacy of Rivaroxaban for prophylactic anticoagulation after THR/TKR surgery

6

What is Extent of Benefit

An Evaluation

7

Symptomatic VTE or Death

- Clinically Important Endpoint
- No allocation of α in the Statistical Analysis plan for each RECORD study
- Any comparison of rivaroxaban with enoxaparin in terms of this endpoint
 - exploratory
 - at best hypothesis-generating

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Symptomatic VTE (DVT or PE) in RECORD Study Safety Population

RECORD	Riva	Enox
1 (hip)	6/2209 (0.3%)	11/2224 (0.5%)
2 (hip) (Short Enox Duration)	3/1228 (0.2%)	15/1229 (1.2%)
3 (knee) (Lower Enox dose)	8/1220 (0.7%)	24/1239 (1.9%)
4 (knee)	11/1526 (0.7%)	18/1508 (1.2%)

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Integrated Analyses

- Prospective plan – Simple pooling
- Important study characteristics are ignored
 - Type of surgery
 - Dose
 - Duration
- No Strong control of Type I error
 - not built into the plan for pooled analyses for anticipated claims based on statistical significance.
- This type of analysis can yield spurious results.

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Sponsor's Results for Symptomatic VTE or Death (In RECORD Study Safety Population)

RECORD	Riva	Enox	Hazard ratio (95% CI)
1	10/2209 0.45%	15/2224 0.67%	0.7 (0.3, 1.5)
2 (Shorter treatment duration for Enox)	5/1228 0.41%	20/1229 1.6%	0.2 (0.1, 0.7)
3 (unapproved dose regimen for Enox)	8/1220 0.66%	26/1239 2.1%	0.3 (0.1, 0.7)
4	12/1526 0.79%	21/1508 1.4%	0.6 (0.3, 1.2)
Pooled	35/6183 0.57%	82/6200 1.3%	0.4 (0.29, 0.63)

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Statistical Methods Used by FDA Integrated Analysis

- **Meta-Analysis**
 - Provides ability to control between-study variation
 - Provides more precise estimate of the overall treatment effect
- **Proportional Hazard Regression adjusted for covariates**
 - Enables adjustment for the covariates or risk factors
 - Gives more precise analysis
 - Increases model power

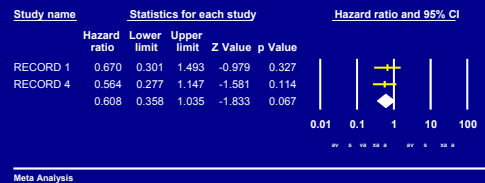
12

FDA : Symptomatic VTE adjust covariate

Study	Hazard Ratio	95% CI	P-value
Record 1 (age surgery)	0.67	(0.30, 1.49)	0.32
Record 2 (age surgery)	0.25	(0.09, 0.67)	0.0055
Record 3	0.309	(0.14, 0.68)	0.0037
Record 4	0.564	(0.28, 1.15)	0.11
Pooled 1 & 4 (treatdur, study)	0.67	(0.39, 1.15)	0.143
Pooled (treatdur, study, age)	0.69	(0.46, 1.04)	0.07
Record 2 (Day 15) (age, surgery)	0.27	(0.06, 1.30)	0.10 (0.18)*

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Meta Analysis for Symptomatic VTE or Death for Pooled 1 & 4 Study

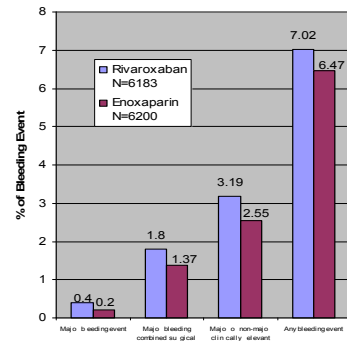


Bleeding Risk

An Evaluation

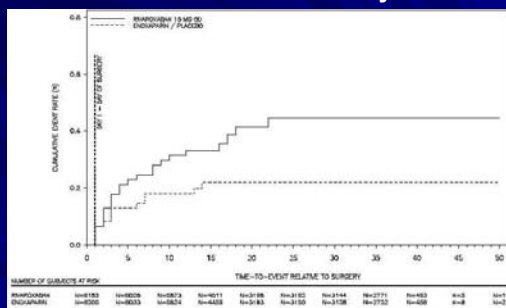
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% of Bleeding Event for Total Duration in Pooled Study



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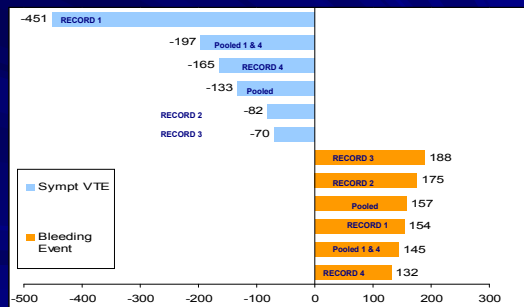
Cumulative Rate of Major Bleeding Events – Pooled Study



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Benefit & Risk

Number needed to treat -Symptomatic VTE
Number needed to harm-Major or Non-major clinically relevant bleeding



Benefit/Risk

- Evidence of efficacy of Rivaroxaban for anticoagulation prophylaxis
 - In terms of Total VTE
- No evidence of superiority of Rivaroxaban compared to Enoxaparin
 - For “Symptomatic VTE or Death”
- Consistent evidence of increased risk of bleeding for Rivaroxaban compared to Enoxaparin

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Protecting and Promoting Public Health www.fda.gov

Ongoing Evaluation of Potential Severe Liver Injury Signal in Rivaroxaban Clinical Trials

FDA / CDER Regulatory Briefing
May 1, 2009

Kate Gelperin, M.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Epidemiology

1

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Severe Liver Injury

- Defined in this review as ALT >3xULN and TBL >2xULN
- Rationale:
 - ALT (alanine aminotransferase) is a sensitive test for severe liver injury but poorly specific
 - Evaluating concurrent TBL (total bilirubin) improves specificity and increases positive predictive value for serious outcomes

2

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"Hy's Law" – severe liver injury

- Instances (even very few of them) of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present) have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant)*
- Estimated mortality at least 10%
- Explanation: hepatocellular injury great enough to interfere with bilirubin excretion (in the absence of biliary obstruction) involves a large fraction of the liver cell mass

* Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver. Appleton-Century-Crofts, New York, 1978, 1999.

3

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Graphic Display of Lab Data for a Hypothetical Drug

Distribution of Peak Values

Slide and graphic concept courtesy Dr. John Senior

4

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Evaluation of Drug-Induced Serious Hepatotoxicity

Lab Data RECORD 1-4: rivaroxaban (N=6183) vs. enoxaparin (N=6200)

Lab Data RECORD 1-4: rivaroxaban (N=6183) vs. enoxaparin (N=6200)

Slide courtesy Dr. Ted Guo

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Enoxaparin Labeling

- Approved: March 29, 1993
- Labeled liver events: Asymptomatic increases in ALT greater than 3 times upper limit of normal have been reported in 5.9% of patients
- Elevations reversible and rarely associated with bilirubin increases*

* LOVENOX (enoxaparin sodium injection) prescribing information (May 2008, sanofi-aventis)

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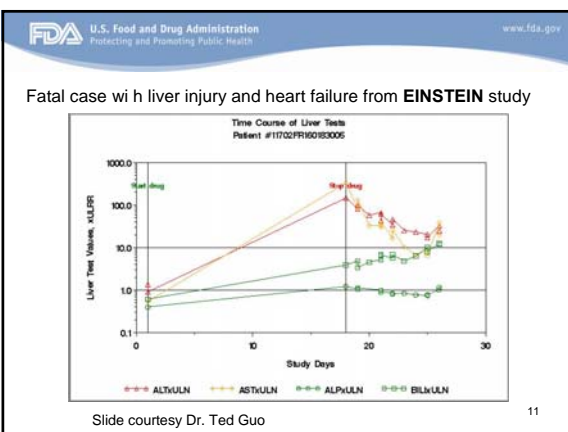
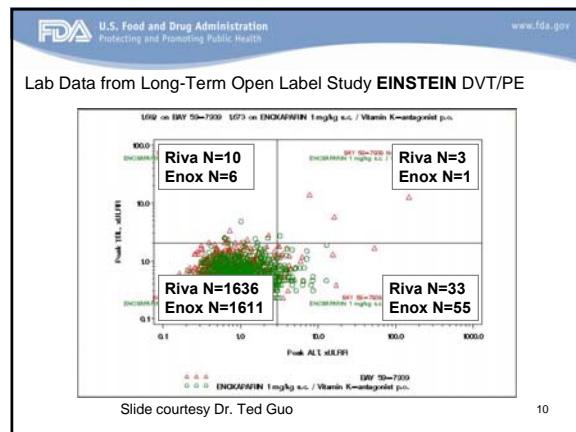
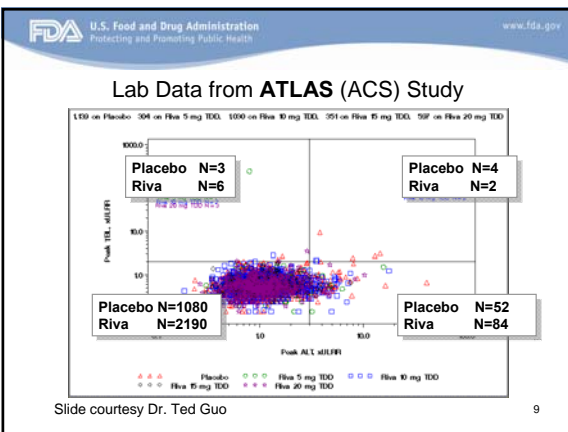
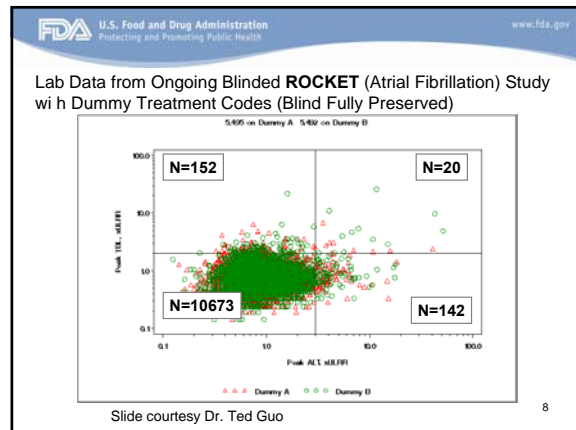
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LAP* Causality Assessments for Potential “Hy’s Law” Cases in RECORD 1-4

- Rivaroxaban
 - Total with concurrent increased ALT >3xULN and TBL >2xULN = 9 cases
 - Possibly related to drug (LAP) = 7 cases
- Enoxaparin
 - Total with concurrent increased ALT >3xULN and TBL >2xULN = 7 cases
 - Possibly related to drug (LAP) = 3 cases

* LAP (Liver Advisory Panel) is the Sponsor’s expert hepatology panel

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FDA Experience with Hepatotoxins “Hy’s Law” with Troglitazone

In the Troglitazone NDA database (n=2510):

- No cases of liver failure
- 1.9% of patients had ALT >3x ULN
- 0.2% (5 patients) had ALT >30x ULN (two with jaundice) » “Hy’s Law” cases in retrospect

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FDA Experience with Hepatotoxins “Hy’s Law” with Troglitazone

- Drug was withdrawn from US market in March 2000
 - FDA reviewed 94 cases of drug-induced liver failure received postmarketing *
 - Progression to irreversible liver injury occurred within less than one month interval in 19 of these patients
- Casts doubt on the value of monthly monitoring in setting of rapid liver injury

* Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. Am J Med 2003; 114: 299-306.

13

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

FDA Experience with Hepatotoxins “Hy’s Law” with Ximelagatran

- Anticoagulant (direct thrombin inh bitor) developed for similar indications as rivaroxaban
- Severe liver injury in long-term trials:
 - Ximelagatran 37/6948 (0.5%)
 - Warfarin 5/6230 (0.08%)
 - Relative risk 6.6
- No signal for severe liver injury seen in short-term trials but strong signal in long-term trials for stroke prevention in atrial fibrillation patients

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FDA Experience with Hepatotoxins “Hy’s Law” with Ximelagatran

- Initial signs of liver injury within first 30 days for six study subjects in LT trials who went on to develop severe liver injury
- Drug not approved in the US
- Later, sponsor decided to withdraw drug from worldwide marketing

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OSE Conclusion and Recommendation

- A potential signal for severe liver injury with rivaroxaban has not been fully characterized at this time.
- Complete assessment, fully evaluating pertinent safety data from long term clinical trials, should be undertaken.

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Acknowledgments

- DMIHP colleagues
- John Senior, MD
- Ted Guo, PhD
- Mark Avigan, MD, CM
- Allen Brinker, MD, MS
- Solomon Iyasu, MD, MPH
- Kathryn O’Connell, MD, PhD
- Gerald Dal Pan, MD, MHS

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/s/

Kathy Robie-Suh
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Andrea F. Kollath DVM Director, Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 00869-0602

Dear Ms. Kollath:

Please refer to your new drug application (NDA) dated August 13, 2008, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for XARELTO.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and found the Drug Master Files 21580, 21581, and 21592 rivaroxaban to be inadequate to support the NDA. Communications detailing the deficiencies have been issued to the designated agents.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope
5/1/2009 10:21:03 AM

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE: April 29, 2009

APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Andrea F. Kollath, DVM,
Director, Regulatory Affairs
e-mail: AKollath@its.jnj.com
Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: Pharmacology/Toxicology information

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, April 29, 2009 8:08 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following Pharmacology/Toxicology information on or before April 30, 2009.

Please provide the primary study sources of these dose multiples:

"Reproduction studies have been performed in rats and rabbits at exposure levels up to 40 (rat) and 94 (rabbit) times the therapeutic exposure levels based on unbound AUC in humans at a rivaroxaban dose of 10 mg/day."

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato
4/30/2009 04:01:46 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2009. The purpose of the meeting was to discuss some discrepancies noted in the pooled statistical analysis.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 24, 2009
TIME: 10:00 AM - 11:00 AM EST
LOCATION: CDER WO conf Rm 1311, Bldg 22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type C, Guidance, Statistics
MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader
Aloka G Chakravarty, Ph.D., Director

OFFICE OF BIOSTATISTICS

Ram Tiwari, Ph.D., Associate Director

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Gary Peters, MD Franchise Medical Leader
Lloyd Haskell, MD, Compound Development Team leader
Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs

BAYER

Martin Homering Statistical Sciences

Torsten Westermeier PhD Therapeutic Area Expert Statistician

Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology

BACKGROUND:

The appropriateness of the pooled statistical analysis of the four RECORD studies was discussed at the March 19, 2009 Advisory Committee (AC) meeting. The sponsor and FDA agreed to meet to discuss some discrepancies in the pooled statistical analyses in greater detail.

MEETING OBJECTIVES:

To discuss the discrepancies observed in the pooled statistical analyses between the sponsor and FDA.

DISCUSSION POINTS:

J&J presented slides (see attached).

Slides 1-8

J&J expressed concern regarding the FDA AC presentations and stated that it does not regard the FDA derived hazard ratio of 3.92 for the RECORD 2 major or non-major clinically relevant bleeding events adjusting duration of treatment as an accurate representation. J&J does not believe that adjusting for treatment duration provides the best representation as treatment duration confounds the treatment effect.

FDA emphasized that the impact of these types of analyses on labeling may be moot because whether using the sponsor's hazard ratio of 1.2 or using the FDA ratio of 3.92 both are statistically significant and point to a concern for bleeding. FDA does not expect to have comparative safety and/or efficacy claims in the label (ie., direct claims of comparative effects between rivaroxaban and enoxaparin). FDA further emphasized that point estimates from any modeling are not anticipated for the labeling.

Slides 9-17

J&J expressed similar concern regarding the FDA AC presentations on the pooled symptomatic venous thromboembolism (VTE) or death analyses.

FDA stated that the sponsor submitted statistical analysis plan was submitted prior to unblinding RECORD 4 but after RECORD 1-3 had been unblinded. FDA emphasized the exploratory nature of this pooled analysis, as stated in the plan. J&J stated that, based on the statement of objective, the plan for hypothesis testing was implied. FDA advised that when the results of 3 studies were available (prior to finalization of the analytical plan) it is difficult to then say that the final pooled analysis was a confirmatory analysis. FDA continues to regard the pooled (symptomatic VTE) analysis as exploratory as it lacked a clearly stated hypothesis. FDA

emphasized that it does not disapprove of J&J examining the data in subsequent pooling analysis, in an exploratory manner to help understand the totality of the data. However, drawing conclusions to propose certain claims is inappropriate, based on exploratory analyses. J&J reminded the agency that it is not seeking a superiority claim (compared to enoxaparin).

DECISIONS (AGREEMENTS) REACHED:

- FDA continues to regard the pooled analyses of "symptomatic VTE" as exploratory in nature. FDA acknowledges multiple approaches to summarizing the bleeding data. Considerations for labeling will depend upon multiple factors, including the clinical importance of analytical findings, the analytical methods and the best approach to describing important clinical information.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None

ACTION ITEMS:

- None

ATTACHMENTS/HANDOUTS:

- J&J submitted slides

NDA 22-406

Rivaroxaban

April 24, 2009
Biostatistics Meeting
J&J/Bayer

Purpose of Meeting

1. Reconcile currently identified differences
 - AdCom bleeding results
 - AdCom symptomatic VTE or death results
 - Pooling strategy
2. Identify any new differences
3. Identify any new requests

Agenda

Reconcile Differences

- Pooled bleeding analysis (Question 2c ii)
- Pooled symptomatic VTE or death analysis (Questions 1c, 1d and 1e)
- Validity of Sponsor's pooling strategy (Questions 1a and 1b)
- FDA BD multiple bleeds (Question 2c i)
- Other differences (Question 2a)

New requests (Question 2b)

Pooled bleeding analysis (Question 2c ii)

- Take major or non major clinically relevant bleeding events as an example
- RECORD 2
- Pooled RECORD 1-4

Treatment Emergent Major or Non Major Clinically Relevant Bleeding Events Safety Population

STUDY	Rivaroxaban	Enoxaparin	Absolute risk difference [†] (95% CI)	Hazard ratio (95% CI)
RECORD 1 (THR)	3.17% (70/2209)	2.52% (56/2224)	0.63% (-0.35, 1.61) p = 0.206	1.25 (0.88, 1.78)
RECORD 2 [‡] (THR)	3.34% (41/1228)	2.77% (34/1229)	0.59% (-0.77, 1.95) p = 0.394	1.20 (0.76, 1.89)
RECORD 3 (TKR)	3.28% (40/1220)	2.74% (34/1239)	0.53% (-0.81, 1.87) p = 0.439	1.19 (0.76, 1.88)
RECORD 4 (TKR)	3.01% (46/1526)	2.25% (34/1508)	0.78% (-0.36, 1.92) p = 0.179	1.34 (0.86, 2.09)

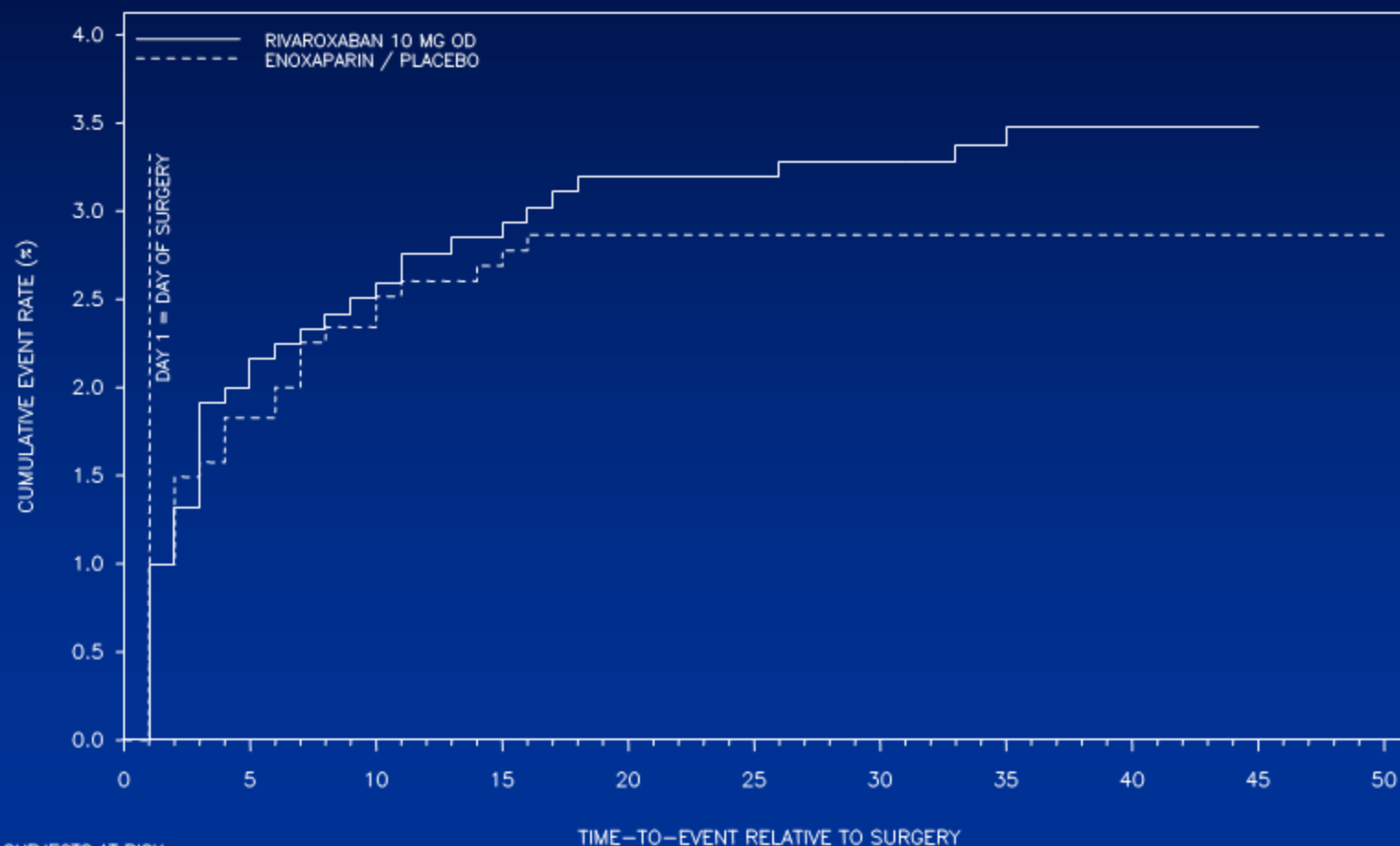
[†]primary analysis

[‡] Active comparator included a placebo control period after day 12

RECORD 2: Major or Non-Major Clin. Relevant Bleeding Events - Safety Population

	Riva	Enox		p-
Pooled Analyses	K/N (%)	K/N (%)	HR (95% CI)	Value
FDA AdCom			3.92 (2.03,7.58)	0.000
Bayer/J&J				
Treatment emergent	41/1228 (3.34)	34/1229 (2.77)	1.20 (0.76, 1.89)	0.432
Adj for Age	41/1228 (3.34)	34/1229 (2.77)	1.20 (0.76, 1.89)	0.429
Until Day 12 \pm 2:	34/1228 (2.77)	32/1229 (2.60)	1.06 (0.65, 1.71)	0.821

Treatment Emergent Major or Non-Major Clinically Relevant Bleeding RECORD 2 Safety Population



NUMBER OF SUBJECTS AT RISK

	N=1228	N=1162	N=1134	N=1118	N=1104	N=1099	N=1092	N=963	N=149	N=1	N=0
RIVAROXABAN											
ENOXAPARIN	N=1229	N=1156	N=1126	N=1111	N=1095	N=1083	N=1074	N=949	N=157	N=3	N=1

FDA Analysis Results for Bleeding

Proportional Hazard Regression Model

Adjusted for Covariates

Type of Bleeding	P-value	HR	95% CI
Major or Non-Major Clinically Relevant Bleeding (sponsor's results)	<0.0001 (0.039)	1.56 (1.3)	(1.2, 1.9) (1.0, 1.5)
Major Bleeding (sponsor's results)	0.0037 (0.078)	3.0 (1.8)	(1.4, 6.2) (0.94, 3.6)
Major Bleeding Incl Surgical Site (sponsor's results)	0.0035 (0.063)	1.6 (1.3)	(1.1, 2.1) (1.0, 1.7)
Any Bleeding (sponsor's results)	0.0226 (0.26)	1.17 (1.1)	(1.0, 1.4) (0.9, 1.2)

Pooled symptomatic VTE or death analysis (Question 1c)

- RECORD 2
- Pooled RECORD 1-4

Symptomatic VTE or Death Treatment Phase By Study and Pooled Safety Population

Symptomatic VTE or death			Hazard Ratio	
Study	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Pt Estimate	(95% CI)
RECORD 1	10/2209 (0.45)	15/2224 (0.67)	0.67	(0.30, 1.48)
RECORD 2	5/1228 (0.41)	20/1229 (1.63)	0.25	(0.09, 0.66)
RECORD 3	8/1220 (0.66)	26/1239 (2.1)	0.31	(0.14, 0.68)
RECORD 4	12/1526 (0.79)	21/1508 (1.39)	0.56	(0.28, 1.15)
Pooled RECORD 1-2	15/3437 (0.44)	35/3453 (1.01)	0.43	(0.23, 0.78)
Pooled RECORD 3-4	20/2746 (0.73)	47/2747 (1.71)	0.42	(0.25, 0.72)
Pooled RECORD 1-4	35/6183 (0.57)	82/6200 (1.32)	0.42	(0.29, 0.63)

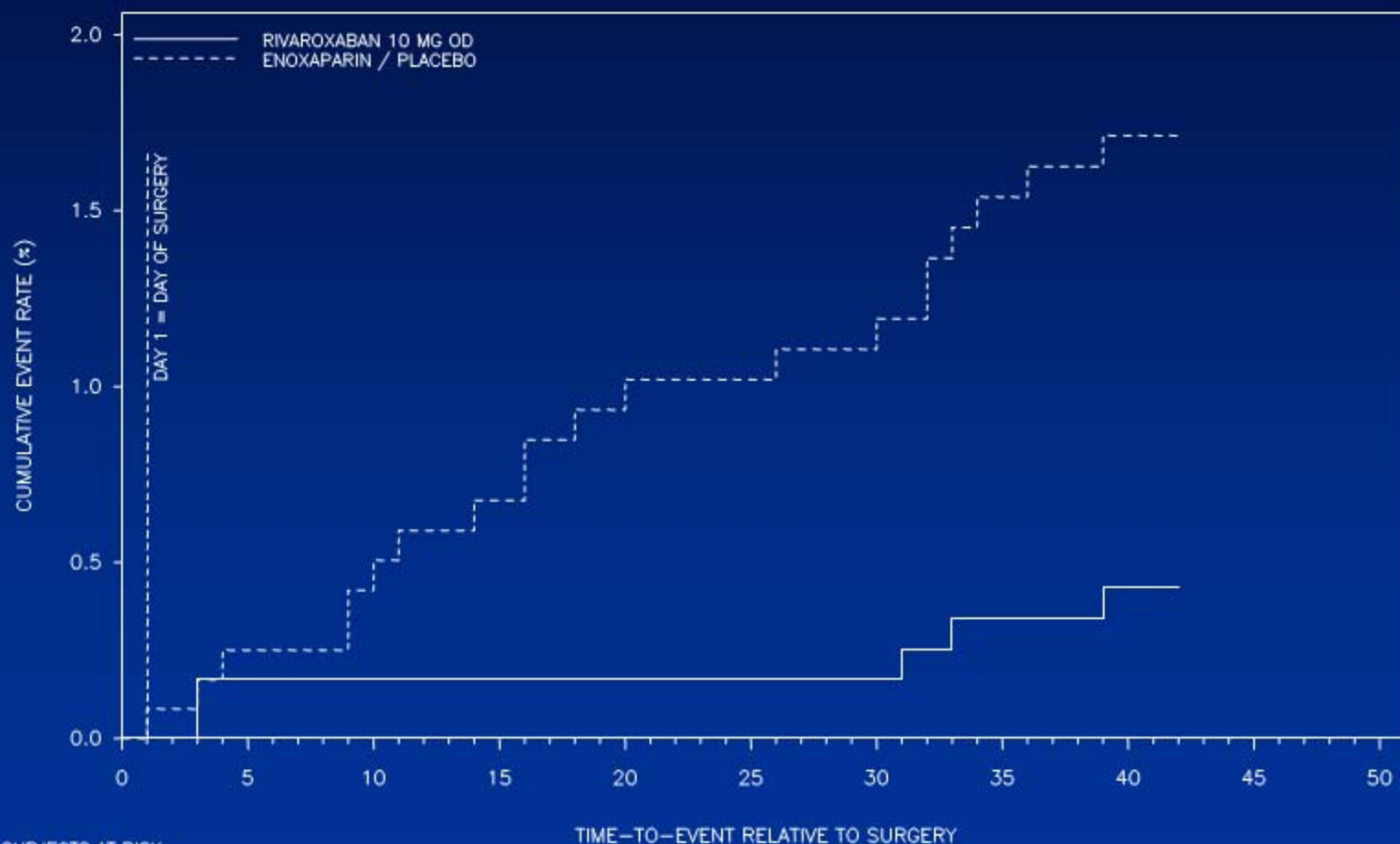
RECORD 2: Symptomatic VTE or death

Safety Population

	Riva	Enox	
Pooled Analyses	K/N (%)	K/N (%)	HR (95% CI)
FDA AdCom			2.14 (0.77, 5.94)
Bayer/J&J			
RECORD: 2	5/1228 (0.41)	20/1229 (1.63)	0.25 (0.09, 0.66)
RECORD: 2 until Day 12 \pm 2	2/1228 (0.16)	5/1229 (0.41)	0.40 (0.08, 2.05)

Symptomatic VTE or Death

RECORD 2 Safety Population



NUMBER OF SUBJECTS AT RISK

	N=1228	N=1191	N=1180	N=1172	N=1166	N=1162	N=1160	N=1140	N=1116	N=0	N=0
RIVAROXABAN											
ENOXAPARIN	N=1229	N=1184	N=1172	N=1158	N=1152	N=1147	N=1145	N=1133	N=1110	N=0	N=0

Pooled RECORD 1-4: Symptomatic VTE or death Safety Population

	Riva	Enox		p-Value
Pooled Analyses	K/N (%)	K/N (%)	HR (95% CI)	Treat/Inter
FDA AdCom Slide 14			0.65 (0.30,1.44)	0.291
FDA AdCom Slide 15			0.69 (0.46,1.04)	0.07
Bayer/J&J				
Study as covariate	35/6183 (0.57)	82/6200 (1.32)	0.42 (0.29,0.63)	<0.001
Study as strata	35/6183 (0.57)	82/6200 (1.32)	0.43 (0.29,0.63)	<0.001
Until Day 12 \pm 2	29/6183 (0.47)	60/6200 (0.97)	0.48 (0.31,0.75)	0.001

Validity of Sponsor's pooling strategy (Question 1a) Pre-specified

Objectives and Rationale for the integrated SAP

- Pre-planned in SAP
- Assessment of clinically relevant, infrequent outcomes
- Components of primary composite endpoints-total VTE
- Consistent with draft "Guidance for Industry: Integrated Summary of Effectiveness, Aug 2008"

Efficacy Endpoints

- Symptomatic VTE or death

Safety Endpoints

- Adjudicated bleeding events
- Liver function lab tests

Validity of Sponsor's pooling strategy (Question 1b) Multiplicity Adjustment

- Symptomatic VTE/Death: low incidence (component of composite of total VTE) and low power within individual studies
- For the integrated analysis, only one primary endpoint: composite endpoint of symptomatic VTE or death.
- Pre-specified primary statistical analysis
- No adjustment of type I error was needed

Time to Event Analyses of Multiple TE Bleeds

Pooled RECORD 1-4 Safety Population

(Question 2c i)

	Riva	Enox	Abs Diff %	Hazard Ratio	
	(N=6183)	(N=6200)	Riva-Enox	Riva vs. Enox	p-Value
	K (%)	K (%)		(95% CI)	
TE Major bleeds					
FDA					0.05
Bayer/J&J				1.84 (0.94,3.62)	0.076
Only One	24 (0.39)	13 (0.21)	0.18		
> One	0 (0.00)	0 (0.00)	0.00		
TE Major bleeding including surgical site					
FDA					0.05
Bayer/J&J				1.35 (1.02,1.79)	0.036
Any	111 (1.80)	85 (1.37)	0.43		
Only One	107 (1.73)	85 (1.37)	0.36		
> One	4 (0.06)	0 (0.00)	0.06		
TE Major or non-major clinically relevant bleeds					
FDA					0.02
Bayer/J&J				1.21 (0.98,1.49)	0.083
Any	197 (3.19)	158 (2.55)	0.64		
Only One	191 (3.09)	151 (2.44)	0.65		
> One	6 (0.10)	7 (0.11)	-0.02		

Other differences (Question 2a)

New requests (Question 2b)

- ?

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/s/

Marcus Cato
4/30/2009 03:23:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 21, 2009. The purpose of the meeting was to provide clarification regarding the April 17, 2009, chemistry, manufacturing and controls (CMC) information request.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: April 21, 2009
TIME: 10:00 AM - 10:30 AM EST
LOCATION: CDER WO 3560 conf Rm, Bldg21
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type C, Guidance, CMC

MEETING CHAIR: Dr. Sarah Pope

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF PHARMACEUTICAL SCIENCE / OFFICE OF NEW DRUG QUALITY ASSESSMENT/
DIVISION OF PRE-MARKETING ASSESSMENT AND MANUFACTURING SCIENCE BRANCH V

Patrick Marroum, Ph.D., Quality Reviewer
Sarah Pope, Ph.D., Branch Chief

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION
OF CLINICAL PHARMACOLOGY 3

Tapash Ghosh, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Nancy Micalizzi, J&J CMC RA
Donald Doyle, J&J CMC
Sanjay Jalota, J&J RA
Andrea Kollath, J&J RA

BAYER

Larry Winick, Bayer RA
Robert Kelly, Bayer CMC RA
Stephan Bartel, Bayer CMC RA
Kerstin Pauli, Bayer

BACKGROUND:

On April 17, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a CMC information request. The sponsor and FDA agreed to meet to allow for clarification and discuss this request in greater detail.

MEETING OBJECTIVES:

To clarify the April 17, 2009 information request and discuss in greater detail.

DISCUSSION POINTS:

FDA acknowledged that the information requested could be located in the sponsor submitted drug master files (DMFs) however the agency is requesting that J&J submit the information to the NDA. FDA clarified that it was requesting all dissolution profile data along with whatever the sponsor believes necessary to support the dissolution method selection. FDA would not require electronic data sets and the information does not necessary have to be included in module 3 of the application. FDA also requested any available information regarding f2 and data used to calculate and validate f2.

DECISIONS (AGREEMENTS) REACHED:

- J&J would submit the information to the NDA.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- J&J to submit the information to the NDA

ATTACHMENTS/HANDOUTS:

- None

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Marcus Cato
4/30/2009 03:13:36 PM

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE: April 17, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Andrea F. Kollath, DVM
Director, Regulatory Affairs
e-mail: AKollath@its.jnj.com
Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: CMC information

Cato, Marcus

From: Cato, Marcus
Sent: Friday, April 17, 2009 4:03 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following CMC information on or before April 24, 2009.

Provide the following information in the original NDA submission:

- Full development (justifying the choice of method parameters and discriminatory power) and a validation report for the in-vitro dissolution method.
- Full validation of the analytical method.
- The full in-vitro dissolution data set (preferably in electronic format) used to generate the in-vitro dissolution profiles.
- A full report of the calculations involved (f2 etc.) with generating the proposed specification.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato
4/30/2009 04:59:37 PM
CSO

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE: April 16, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Andrea F. Kollath, DVM,
Director, Regulatory Affairs
e-mail: AKollath@its.jnj.com
Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: 30 count HDPE bottle marketing

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, April 16, 2009 5:20 PM
To: Cato, Marcus
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406
Attachments: emfalert.txt

Hi Marcus

No, we will not withdraw the 30 count HDPE bottle from the application because the 30 count bottle will be used for the SNF/TLC setting.

We will be filing an amendment to the Gurabo Drug product DMF 21592 for the marketed blister packs. (the blister included in the original DMF was a (b) (4) blister)

In the retail setting we will only be marketing a trade blister, with specific packs which would be used as a means to limit off label use for the product.

If you have any questions please let me know.

Kind regards

Andrea

-----Original Message-----

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, April 16, 2009 5:12 PM
To: Kollath, Andrea [PRDUS]
Subject: FW: NDA 22-406

Hi Andrea,

I just remembered to ask about the below e-mail.

Thanks

~Marcus

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From: Cato, Marcus
Sent: Thursday, April 09, 2009 9:02 AM
To: 'Jalota, Sanjay [PRDUS]'

4/17/2009

Cc: Kollath, Andrea [PRDUS]

Subject: NDA 22-406

Dear Sanjay,

Do you all plan to withdraw the HDPE bottle and market in blister packs? If so, please provide (to the application) written confirmation that you will not be marketing the bottle presentation of rivaroxaban.

Kindly,

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato
4/17/2009 03:26:01 PM
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MEMORANDUM OF TELEPHONE CONVERSATION

DATE: April 16, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Andrea F. Kollath, DVM,
Director, Regulatory Affairs
Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: NDA 22-406 application questions

Dr. Kollath.

Called to discuss a number of questions she had outlined in an e-mail. We discuss the question and I responded as outlined below.

1 Stats Meeting April 24th- Have you received any feedback on the stats questions we had sent? Who will be attending this meeting from FDA? Is Dr. Rieves attending?

FDA response: There is no Update at this time our team plans to address all questions in the April 24th Meeting.

2. Peds meeting April 28th- Will there be PERC members attending or not?

FDA response: The PeRC is a congressionally mandated committee with required members. It does not meet with industry.

3. Clin PK feedback- any updates from the reviewers?

FDA response: There is no Update at this time.

4. Trade name status? Have you been able to obtain any feedback?

FDA response: There is no Update at this time

5. I need to request a meeting date for " Major Surgery" indication for sometime in June. I'm sure this will be hard to schedule but we are looking for potentially June 15, 16, or 19th.

FDA response: We will review the Meeting Request internally and if Granted we will work to schedule a mutually agreeable date.

6. Safety Surveillance Plan: Do we need to submit an updated SSP ? Any feedback from OSE/Division on next steps?

FDA response: I will follow up with the team and get back to you.

7. You may have already sent me this but who were the attendees at the April 1st Telecon?

FDA response: I will look into it and get back to you.

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/s/

Marcus Cato
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 1, 2009. The purpose of the meeting was to discuss the FDA perspective on the dose and exposure response relationship in certain populations.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: April 1, 2009
TIME: 11:30 AM - 12:30 PM EST
LOCATION: CDER WO 2327 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type C, Guidance, Clinical Pharmacology

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Ping Zhao, Ph.D., Clinical Pharmacology Reviewer
Nam Atiqur Rahman, Ph.D., Director

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ PHARMACOMETRICS DIVISION

Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters, MD Franchise Medical Leader
Mehul Desai MD, Clinical

Leonard Oppenheimer, PhD. Statistical Sciences
Donald L. Heald, Ph.D., Global Head of Clinical PK
Achiel Van Peer, Ph.D. Global Senior Scientific Leader Clinical Pharmacology
An Thyssen, PhD, Clinpharm Leader Rivaroxaban
An M. Vermeulen PhD Senior Director Advanced PK/PD Modeling & Simulation
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead
Andrea Kollath, DVM, Regulatory Affairs,

BAYER

Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis and Hemostasis CV and Coagulation
Andrea Derix, PhD, Sen. Global Regulatory Strategist
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitz, PhD Global Clinical Pharmacology Project Leader, BSP
Wolfgang M. Mueck, Dr. rer. nat. Director Clinical Pharmacokinetics

BACKGROUND:

On February 5, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a Clinical Pharmacology discipline review letter requesting that the sponsor develop a lower strength or scored 10 mg tablet in order to match exposure in patients with renal and/or hepatic dysfunction. Whether or not a lower dose should be available to patients with renal and/or hepatic dysfunction was discussed at the March 19, 2009 Advisory Committee (AC) meeting. The sponsor and FDA agreed to meet to discuss the dose and exposure response relationship in certain populations in greater detail. On March 31, 2009, J&J submitted background information (see attached).

MEETING OBJECTIVES:

To discuss the dose and exposure response relationship in certain populations in greater detail.

DISCUSSION POINTS:

J&J presented the slides submitted March 31, 2009.

Slides 2-3

J&J stated it appeared from the FDA AC presentations that FDA regarded a two-fold increase in exposure as clinically relevant. FDA emphasized that to draw a line in the sand at a particular exposure is not a favorable approach and it is advisable to examine each population. FDA does not agree that a two-fold or greater increase in exposure is the level for clinical relevance. FDA further emphasized that the two-fold exposure increase would be the calculated mean. If the sponsor selected 2.0 as the level for clinical relevance, in a patient population with a mean of 1.8

there would be patients with a two-fold or greater increases in exposure. J&J inquired if FDA considered a two-fold increase in exposure problematic. FDA agreed that a two-fold increase was a problem however it is uncertain if exposure increases less than two-fold higher than normal are problematic as well. FDA stated its goal would be to match exposure.

FDA maintains its position regarding dose titration, however, it is planning to take action based on the 10 mg dose of rivaroxaban. FDA's view of the labeling will reflect the 10 mg use and as a consequence rivaroxaban would not be recommended in certain populations.

J&J and FDA discussed slides 4-12. FDA informed the sponsor that it is still considering all the information submitted to the application, how the drug will be used in practice and having internal discussions. The Sponsor and FDA agreed to continue discussions at a later date.

DECISIONS (AGREEMENTS) REACHED:

- FDA is planning to take action based on the 10 mg dose of rivaroxaban.
- The Sponsor and FDA agreed to continue discussions at a later date.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- FDA and J&J to continue discussions at a later date.

ATTACHMENTS/HANDOUTS:

- J&J submitted background information

**Rivaroxaban (JNJ-39039039, BAY 59-7939)
10mg Immediate Release Tablets
NDA 22-406**

Meeting Date: April 01, 2009

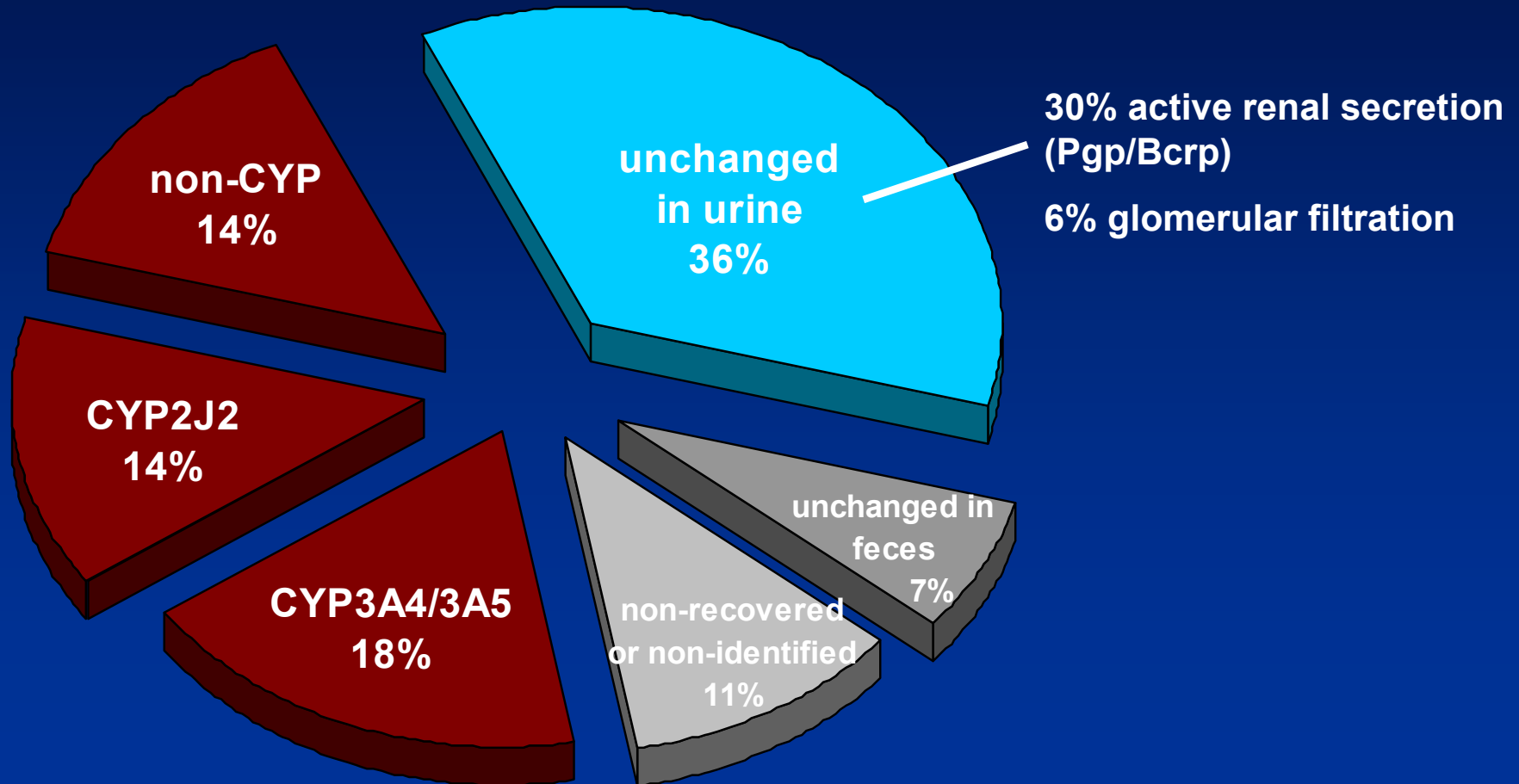
Key Questions (as defined by FDA)

- Is there evidence of dose-exposure-response for efficacy and safety?
 - Shallow dose-response for efficacy
 - Increased major bleeding risk with increasing rivaroxaban dose/exposure
- **Which special populations are at risk for clinically relevant increases in exposure?**
 - Moderate-severe hepatic patients
 - Use of strong CYP3A4/Pgp inhibitors
 - Mild-moderate renal impairment + moderate CYP3A4/Pgp inhibitors
- What are the strategies to address increased exposure and risk of bleeding in special populations ?

Bleeding Dose Response - Sponsor's View

- Dose and exposure response relationships similar
- 30-50% increase in bleeding events with rivaroxaban dose increase from 10 mg to 20 mg
- Limit exposures above 2X increase

Multiple Elimination Pathways



Hepatic Impairment

Moderate hepatic impairment (Child Pugh B):

- Pronounced effect on both PK and PD
- Prolonged PT at baseline (approx. 3 seconds) → underlying coagulopathy → inherent bleeding risk
- Increased slope for PT/rivaroxaban plasma concentration relationship by more than 2-fold: 3.1 seconds/(100 µg/L) for healthy subjects vs 7.8 seconds/(100 µg/L) for Child Pugh Grade B patients) → reflects underlying disease

Severe hepatic impairment (Child Pugh C): not studied

Table 3-10: Effect of Hepatic Impairment - Mean Ratios (Stratum 2/Stratum 1) of Pharmacokinetic and Pharmacodynamic Parameters and Associated 90% Confidence Intervals (Phase 1)

Stratum 1	Stratum 2	AUC	C _{max} or E _{max}
PK parameters AUC and C_{max}			
Normal Hepatic Function	Child-Pugh A	1.15 (0.85 - 1.57)	0.97 (0.75 - 1.25)
	Child-Pugh B	2.27 (1.68 - 3.07)	1.27 (0.99 - 1.63)
Percent Inhibition of FXa activity			
Normal Hepatic Function	Child-Pugh A	1.08 (0.70 - 1.68)	0.98 (0.86 - 1.13)
	Child-Pugh B	2.59 (1.69 - 3.98)	1.24 (1.09 - 1.42)
Relative Prolongation of PT			
Normal Hepatic Function	Child-Pugh A	1.06 (0.79 - 1.42)	1.02 (0.93 - 1.12)
	Child-Pugh B	2.14 (1.61 - 2.84)	1.41 (1.28 - 1.54)

n=8/Child-Pugh class; n=16 for subjects with normal hepatic function

Hepatic Impairment - Sponsor's View

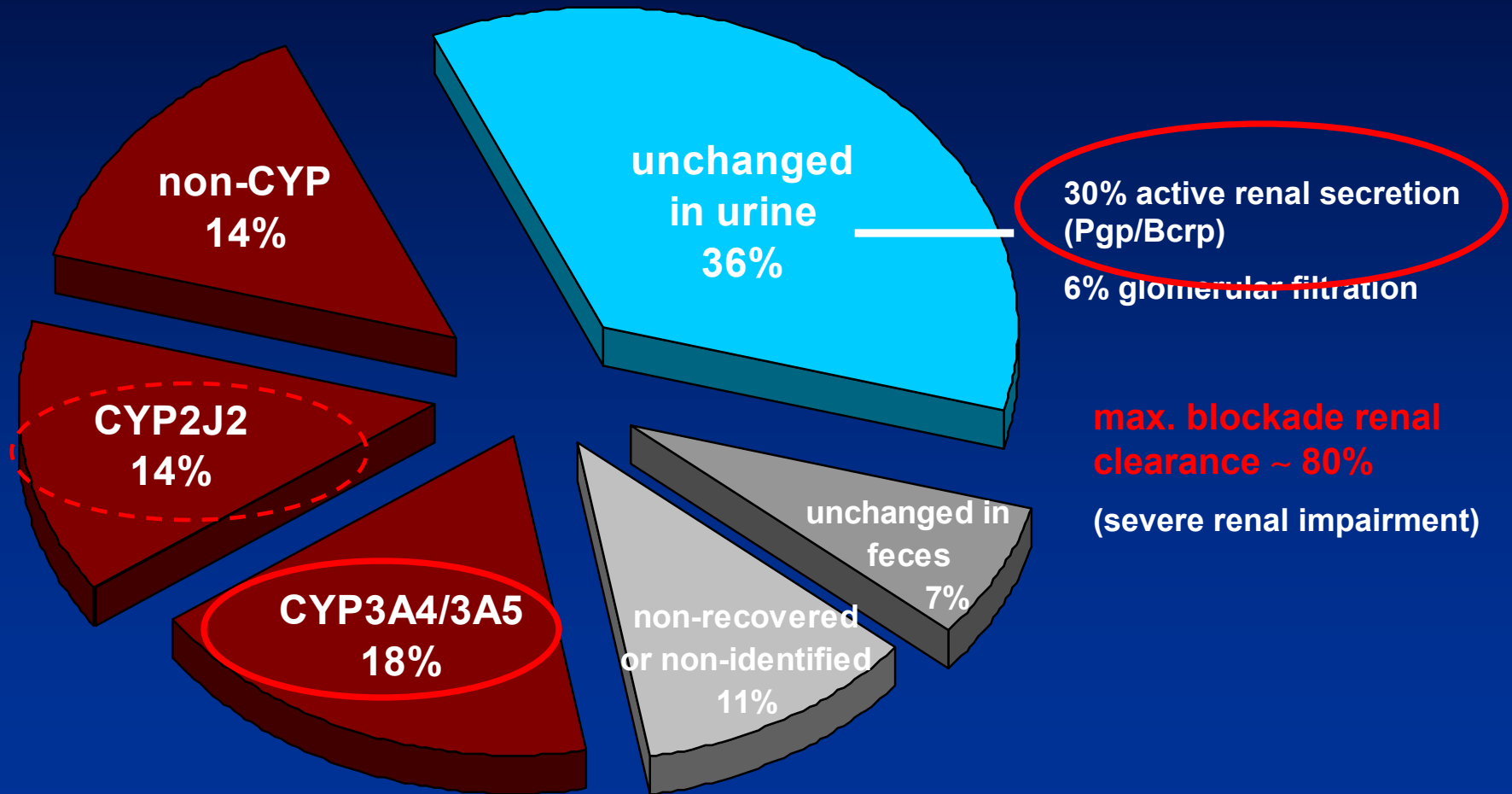
- Intent is to contraindicate hepatic disease with any prolongation of PT
 - Not many of these patients have elective joint replacement surgery
 - Broader than just moderate or severe Child –Pugh score
 - Increased risk for bleeding even with a lower dose due to underlying liver disease and increased PD sensitivity

Pharmacokinetic Interactions

CYP3A4/Pgp Inhibitors

Influence of		AUC ratio [90%CI]		C _{max} ratio [90%CI]	
Strong inhibitor of <u>both</u> CYP 3A4 and P-gp					
ketoconazole	200 mg qd	1.82	[1.59 - 2.08]	1.53	[1.27 - 1.85]
ketoconazole	400 mg qd	2.58	[2.36 - 2.82]	1.72	[1.61 - 1.83]
ritonavir	600 mg bid	2.53	[2.34 - 2.74]	1.55	[1.41 - 1.69]
Strong CYP3A4 inhibitor & weak-to-moderate P-gp inhibitor					
clarithromycin	500 mg bid	1.54	[1.44 – 1.64]	1.40	[1.30 - 1.52]
Moderate CYP 3A4 & P-gp inhibitor					
erythromycin	500 mg tid	1.34	[1.23 - 1.46]	1.34	[1.21 - 1.48]

Impact of Renal Impairment and CYP3A4 Inhibition



max. blockade hepatic clearance ~ 90%
(strong CYP3A4 Pgp inhibitor - ketoconazole)

Phase 1 Estimations: Impact of Renal Impairment and Concomitant Use of CYP3A4 Inhibitor

x-fold Increase in AUC (vs Normal Renal Function)

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
	> 80 mL/min	50-80 mL/min	30-50 mL/min	<30 mL/min
No CYP3A4 inh	1.00	1.49	1.66	1.79
30% CYP3A4 inh	1.09	1.64	1.84	1.99
50% CYP3A4 inh ^a	1.15	1.75	1.98	2.15
90% CYP3A4 inh ^b	1.32	2.04	2.35	2.57

^a Erythromycin reflects moderate CYP3A4 inhibitor ^b clarithromycin reflects strong CYP3A4 inhibitor

Ketoconazole & Ritonavir (strong inhibitors of both CYP3A4 and Pgp) increases AUC 2.6/2.5 fold

CYP3A4 clearance: 23% of total clearance

38% of hepatic clearance

Frequency of Combined Renal Impairment and Concomitant Use of CYP3A4 Inhibitor

Pooled RECORD 1-4 Safety Population

Total N=12268	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
	> 80 mL/min	50-80 mL/min	30-50 mL/min	<30 mL/min
No CYP3A4 inh	54.9% (6739)	31.6% (3878)	5.8% (717)	0.4% (52)
Weak CYP3A4 inh (30%)	1.7% (208)	0.9% (107)	0.2% (20)	<0.1% (1)
Moderate CYP3A4 inh (50%)	2.0% (252)	1.7% (209)	0.4% (50)	<0.1% (4)
Strong CYP3A4 inh (90%)	0.1% (16)	0.1% (13)	<0.1% (2)	<0.1% (0)

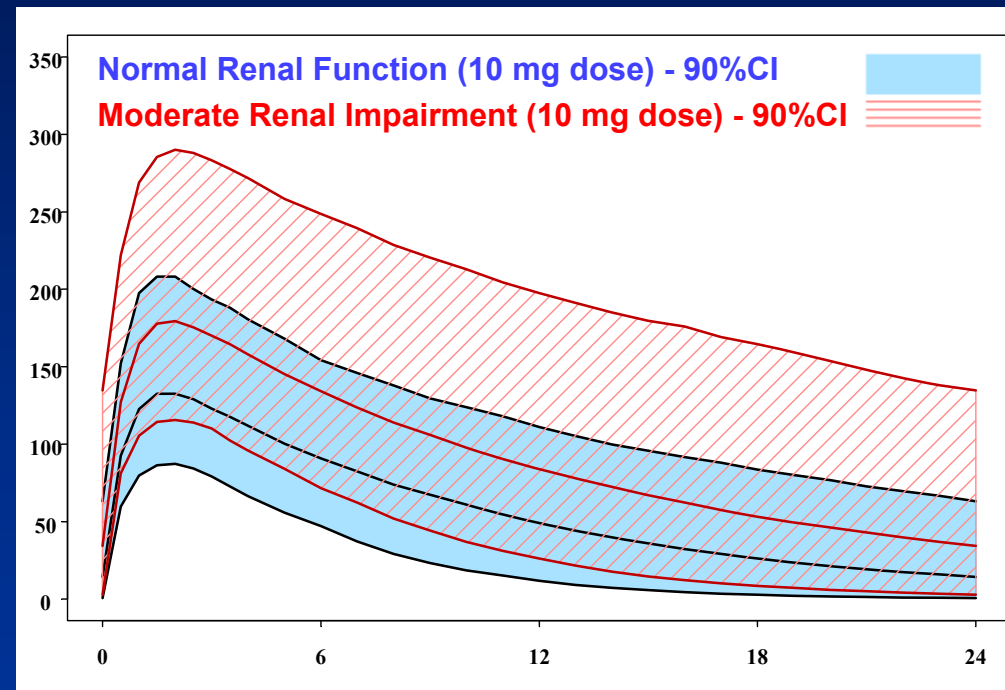
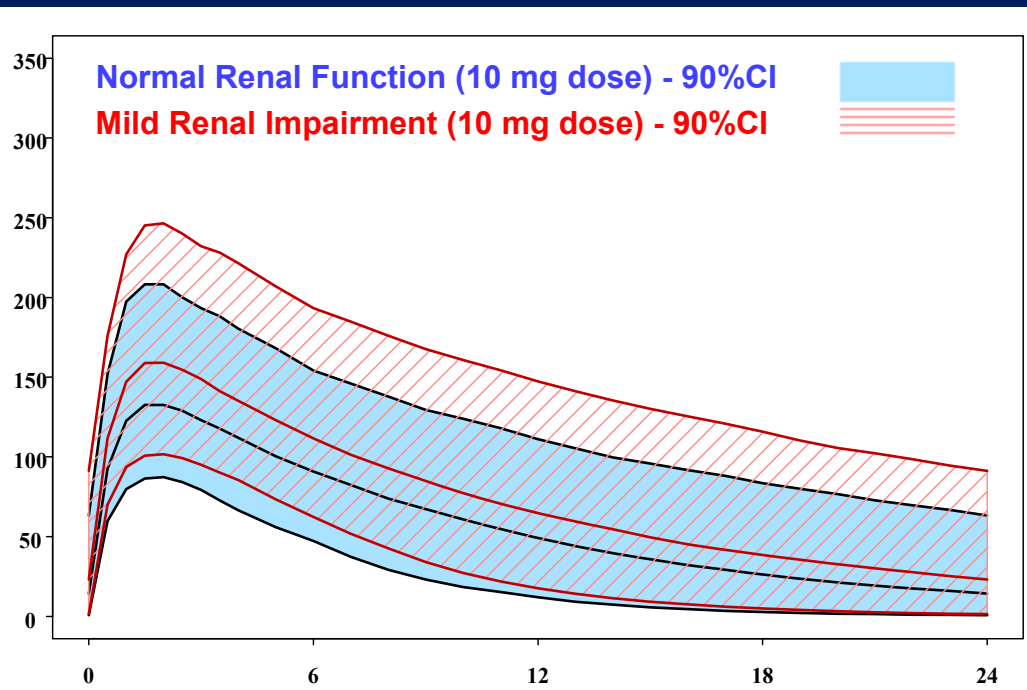
Frequency of Combined Renal Impairment and Concomitant Use of CYP3A4 Inhibitor

US Pooled RECORD 1-4 Safety Population

Total N=1709	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
	> 80 mL/min	50-80 mL/min	30-50 mL/min	<30 mL/min
No CYP3A4 inh	62.4% (1067)	22.8% (389)	4.7% (80)	0.2% (3)
Weak CYP3A4 inh (30%)	2.0% (35)	0.6% (10)	0.1% (2)	<0.1% (0)
Moderate CYP3A4 inh (50%)	5.0% (86)	1.7% (29)	0.3% (5)	<0.1% (0)
Strong CYP3A4 inh (90%)	0.1% (2)	<0.1% (1)	<0.1% (0)	<0.1% (0)

Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

Normal Renal Function vs Mild and Moderate Renal Impairment



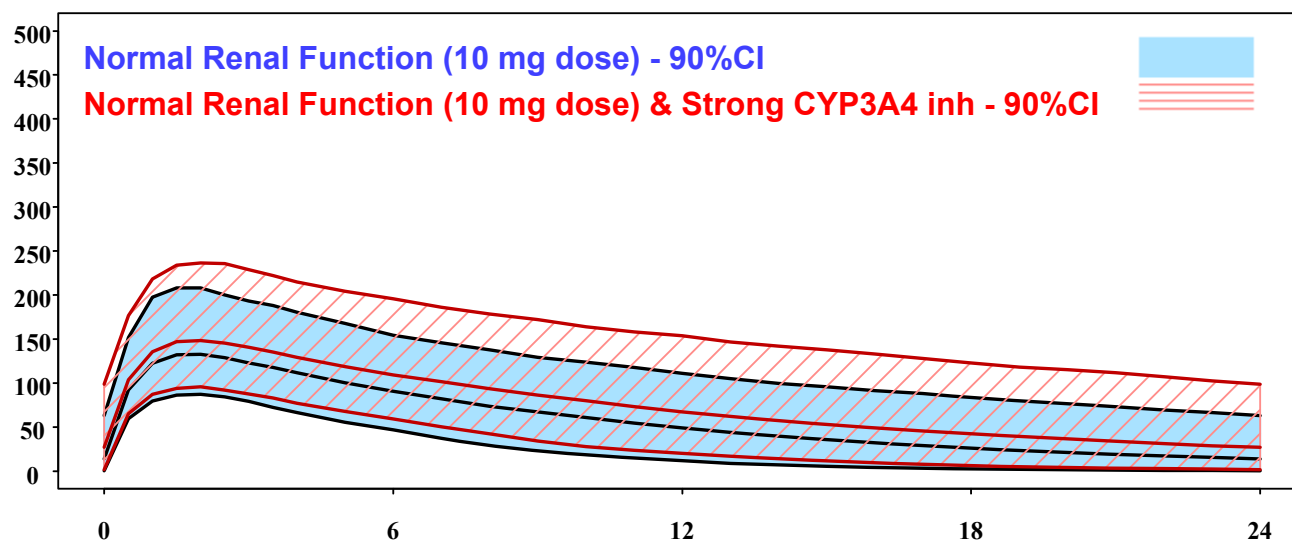
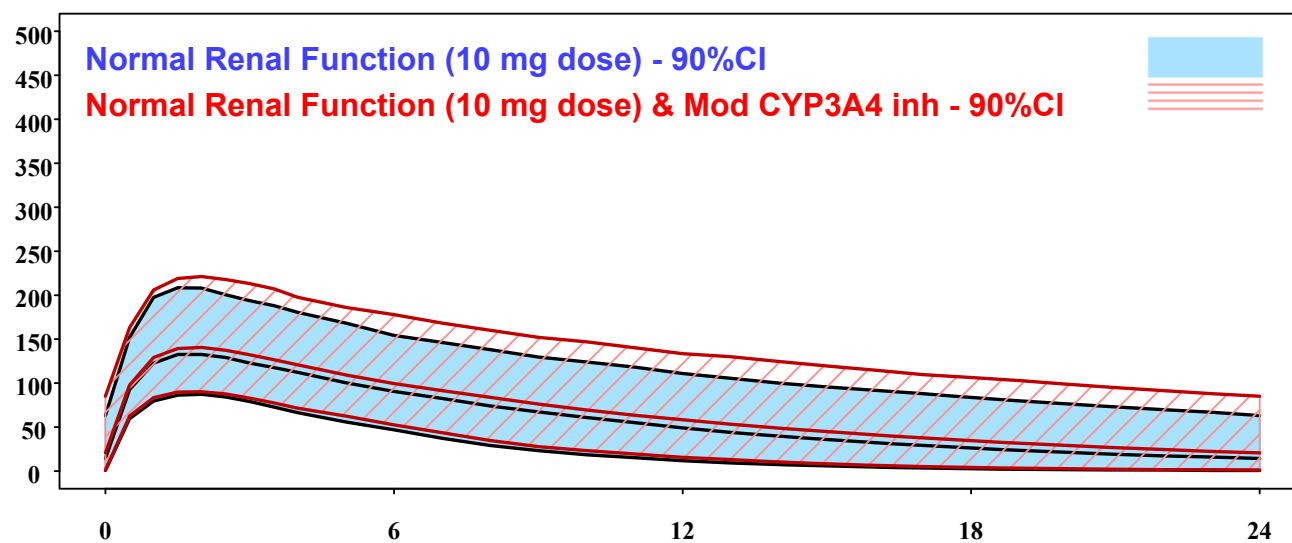
Renal Impairment - Sponsor's View

- All levels of renal impairment (including severe) less than 2x increase in exposures (AUC)
- Sufficient Phase 3 data in moderate renal impairment to support use of 10 mg dose
- Use 10 mg dose with caution in severe renal impairment due to limited data (exclusion due to enoxaparin in Phase 3)
- Use not recommended in renal failure (dialysis)
 - No data
 - Very uncommon to have joint replacement and marked increase in complication rates

Predicted Steady State Plasma Concentration Window

10 mg qd in Phase 2 Target Population

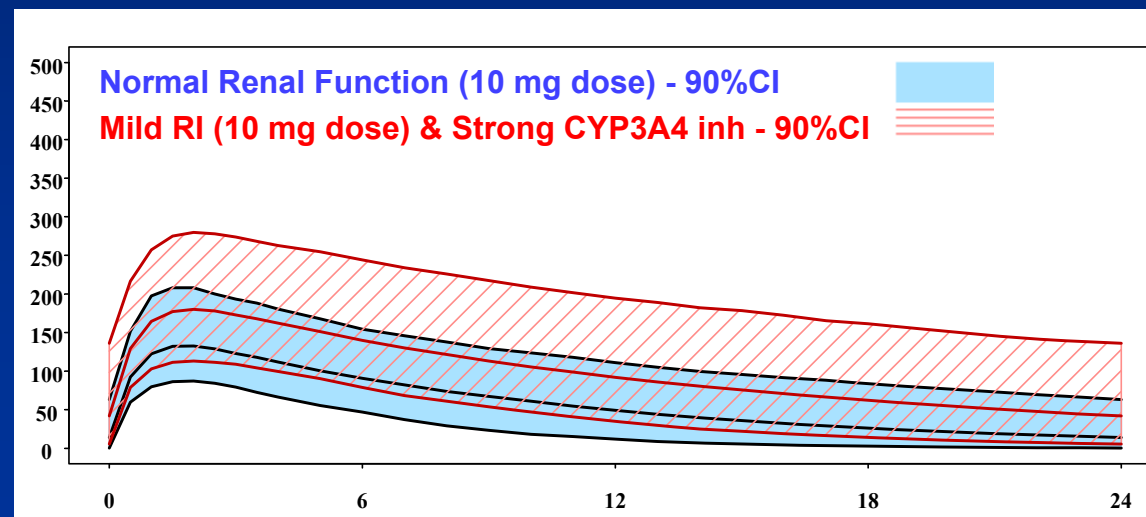
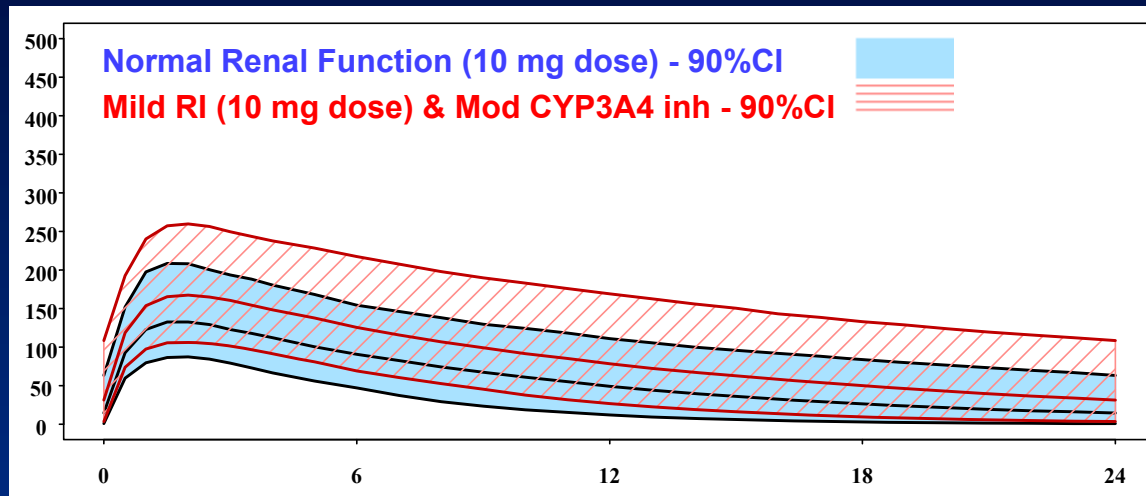
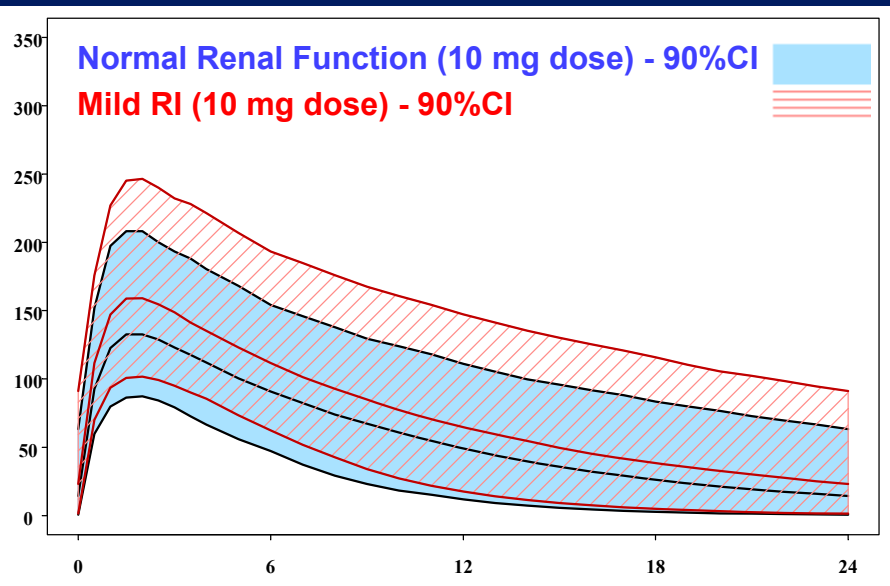
Normal Renal Function and Moderate or Strong CYP 3A4 Inhibition



Predicted Steady State Plasma Concentration Window

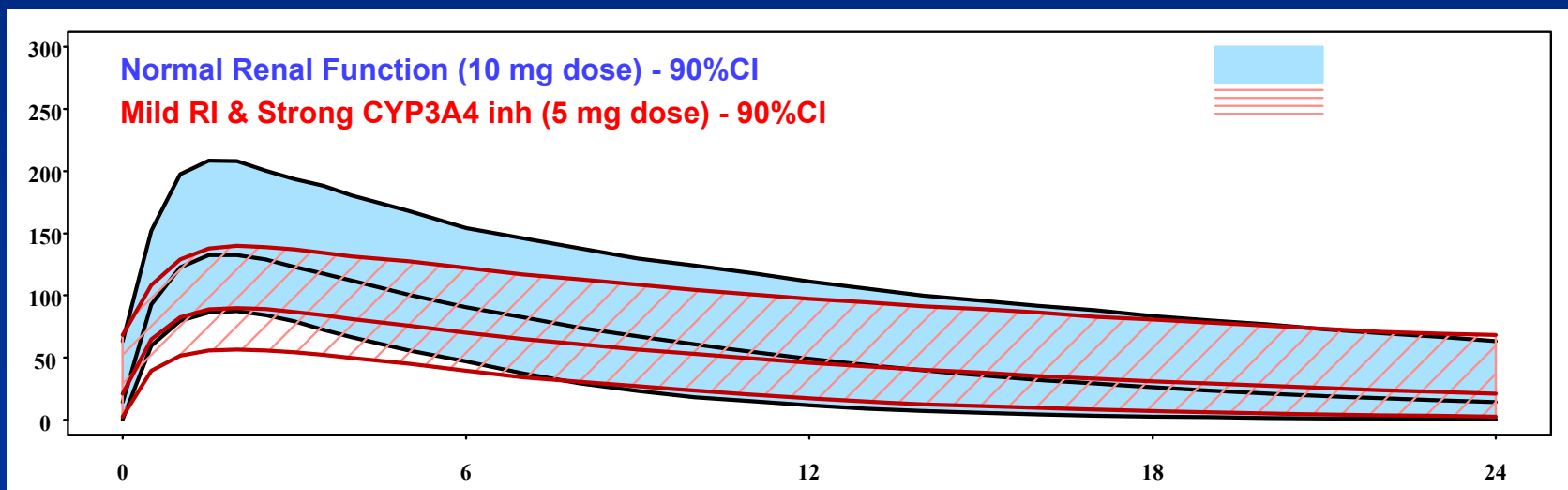
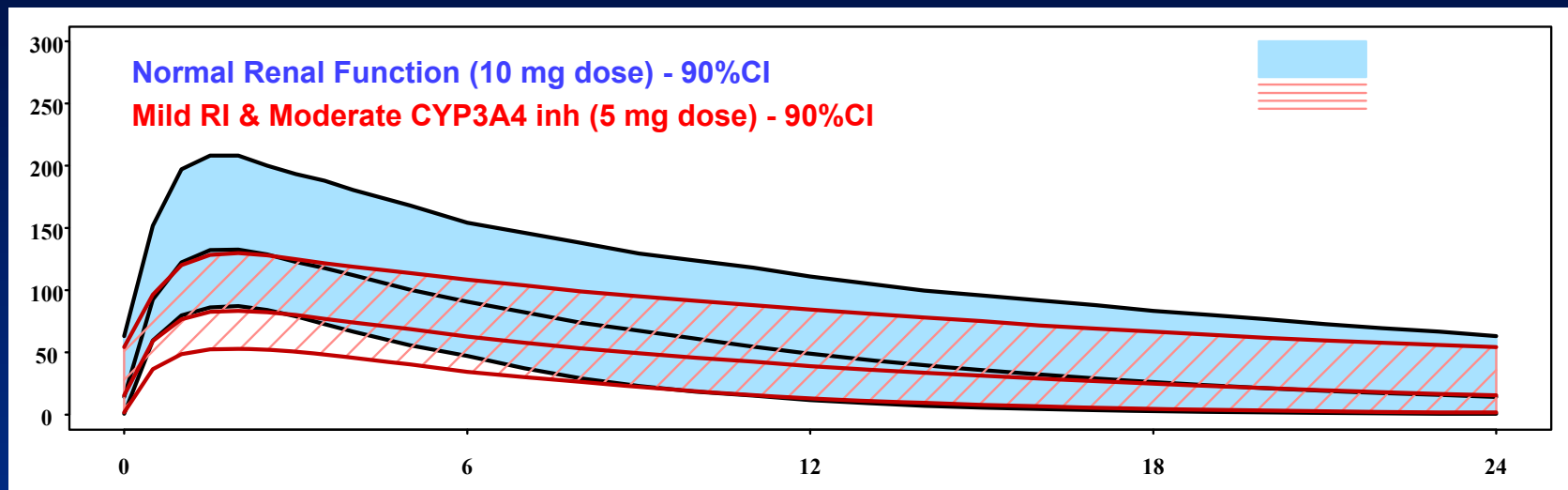
10 mg qd in Phase 2 Target Population

Mild Renal Impairment and Moderate or Strong CYP 3A4 Inhibition



Predicted Steady State Plasma Concentration Window 5 mg qd in Phase 2 Target Population

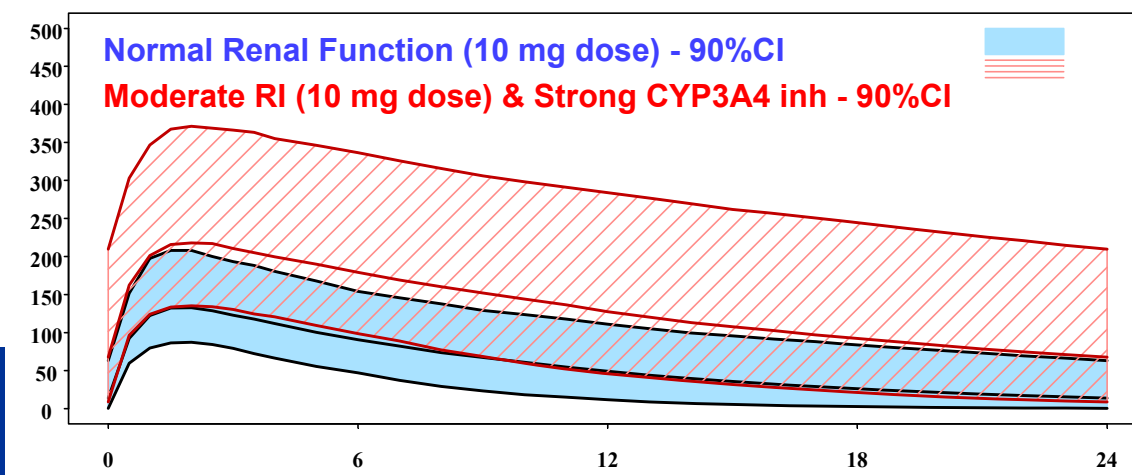
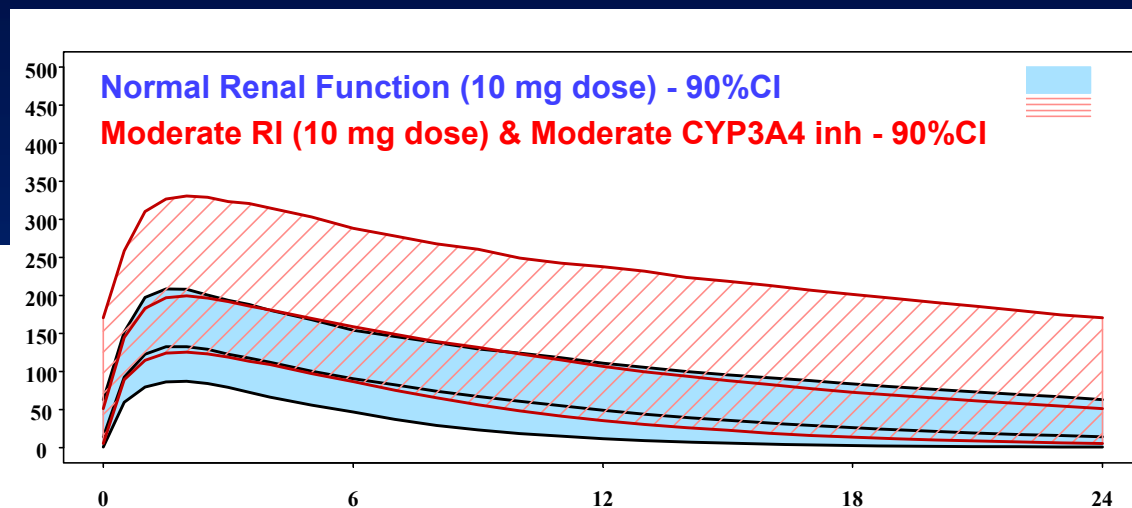
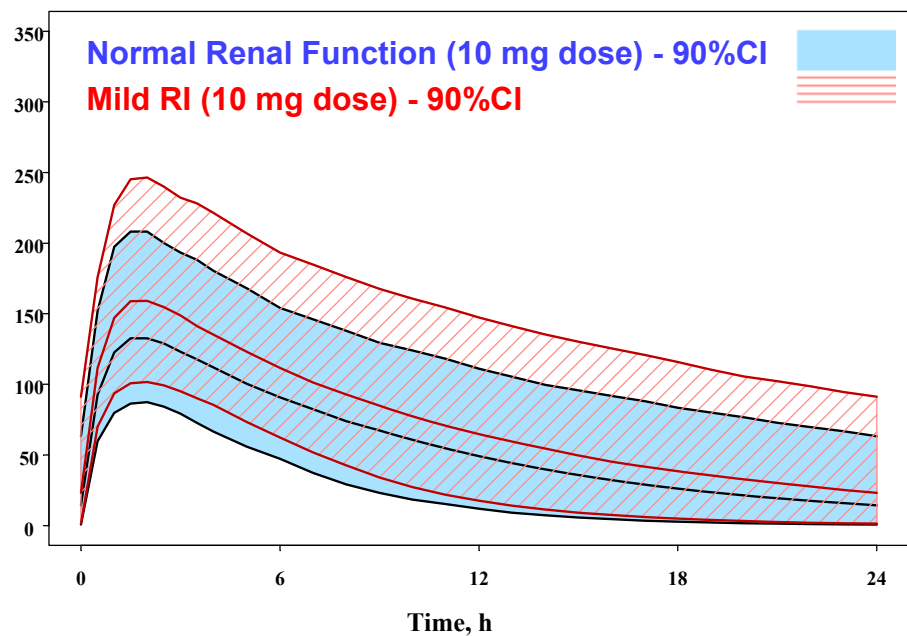
Mild Renal Impairment and Moderate or Strong CYP 3A4 Inhibition



Predicted Steady State Plasma Concentration Window

10 mg qd in Phase 2 Target Population

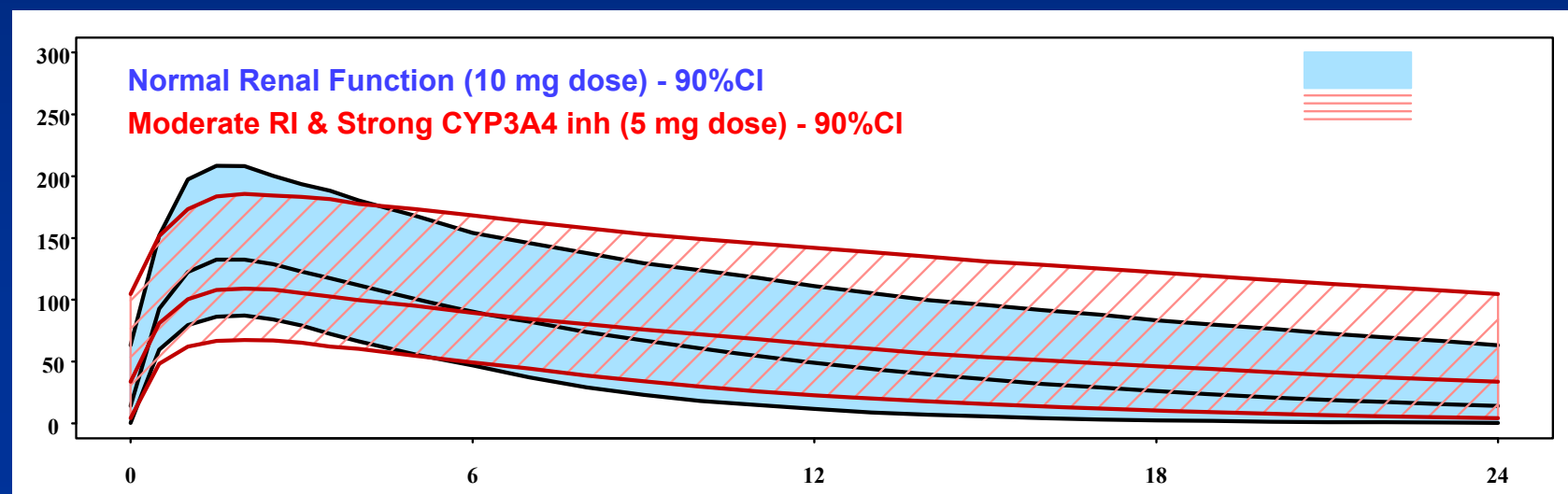
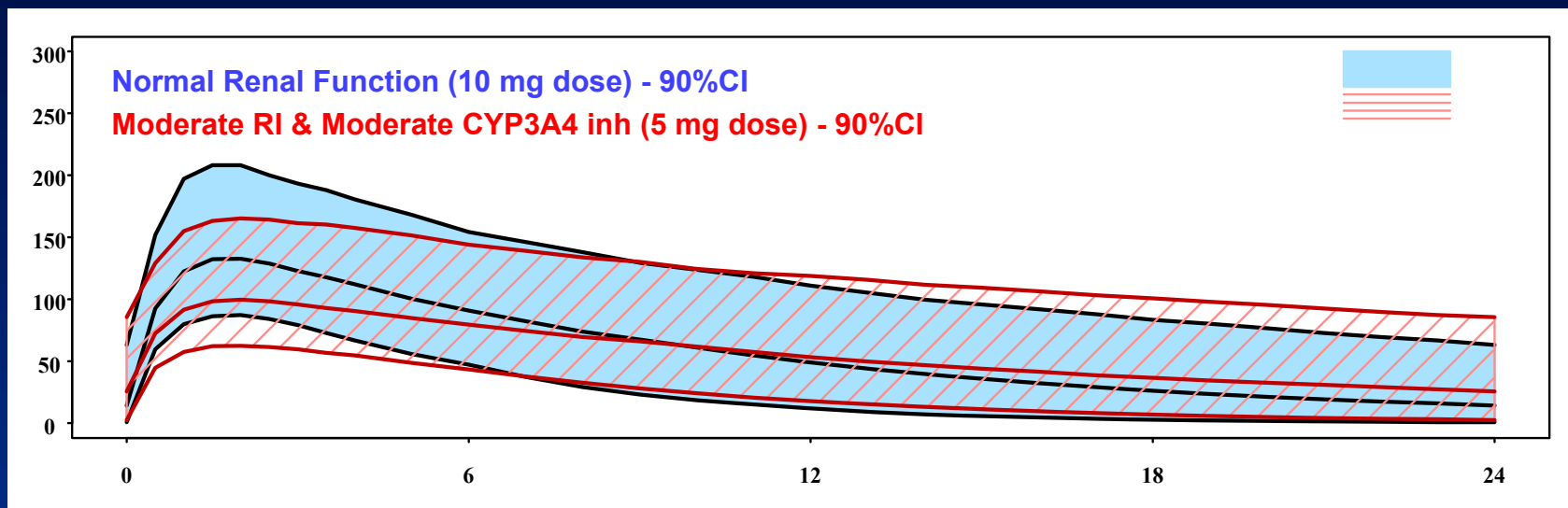
Moderate Renal Impairment and Moderate or Strong CYP 3A4 Inhibition



Predicted Steady State Plasma Concentration Window

5 mg qd in Phase 2 Target Population

Moderate Renal Impairment and Moderate or Strong CYP 3A4 Inhibition



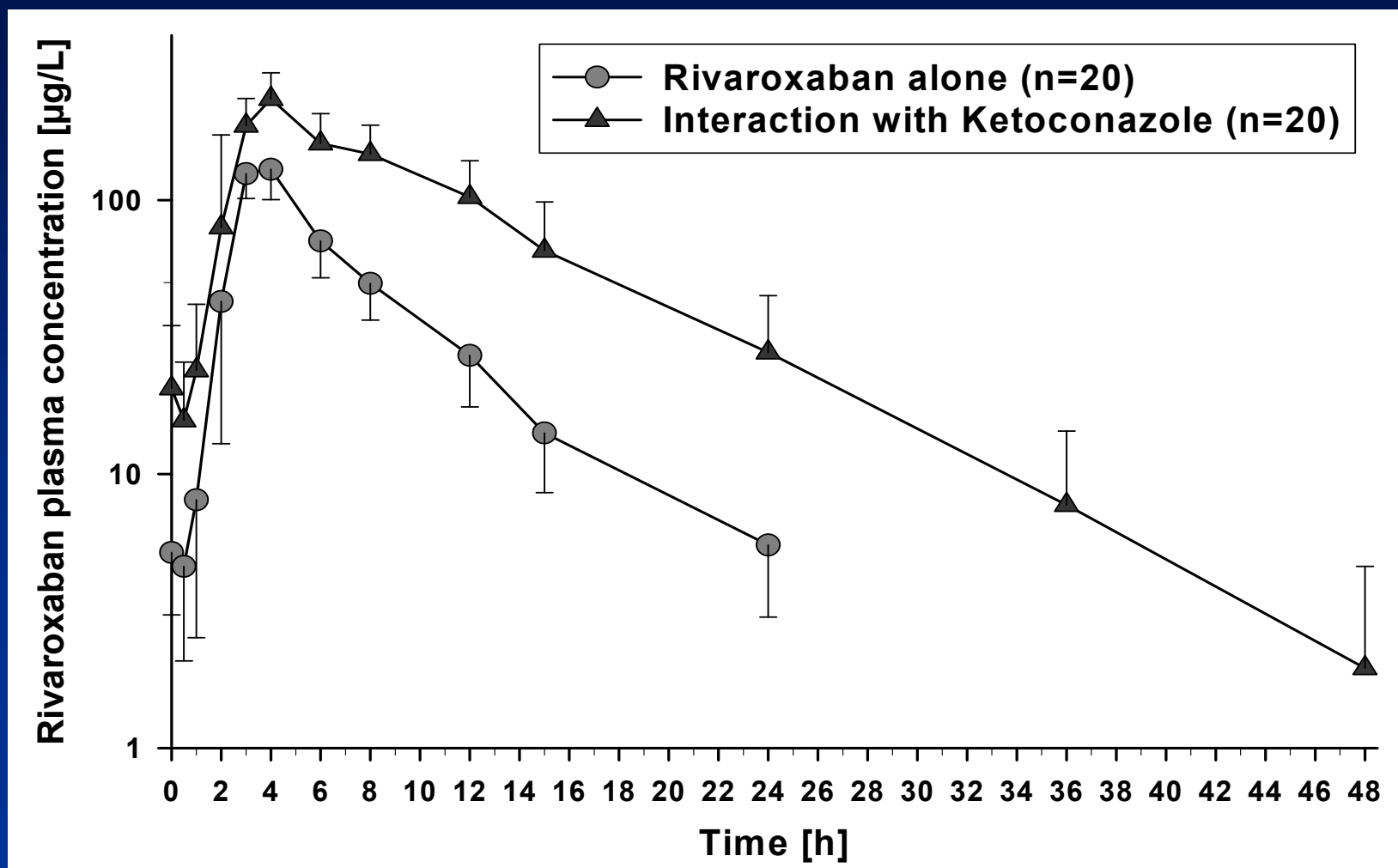
Renal Impairment and CYP Inhibition - Sponsor's View

- No special instructions necessary for normal renal function or mild renal impairment + CYP3A4 inhibitor
- Caution for use with moderate CYP inhibition and either moderate or severe renal impairment
 - Exposures about 2x increase
 - Not a common situation
 - Not contraindicated since overall benefit risk may be favourable
- Ketoconazole and ritonavir represent situations with strong inhibition of CYP and severe renal impairment (i.e. lower right quadrant)
 - Use not recommended due to exposures >2x increase
 - Not a common situation
 - Not contraindicated since overall benefit risk may be favourable

Background

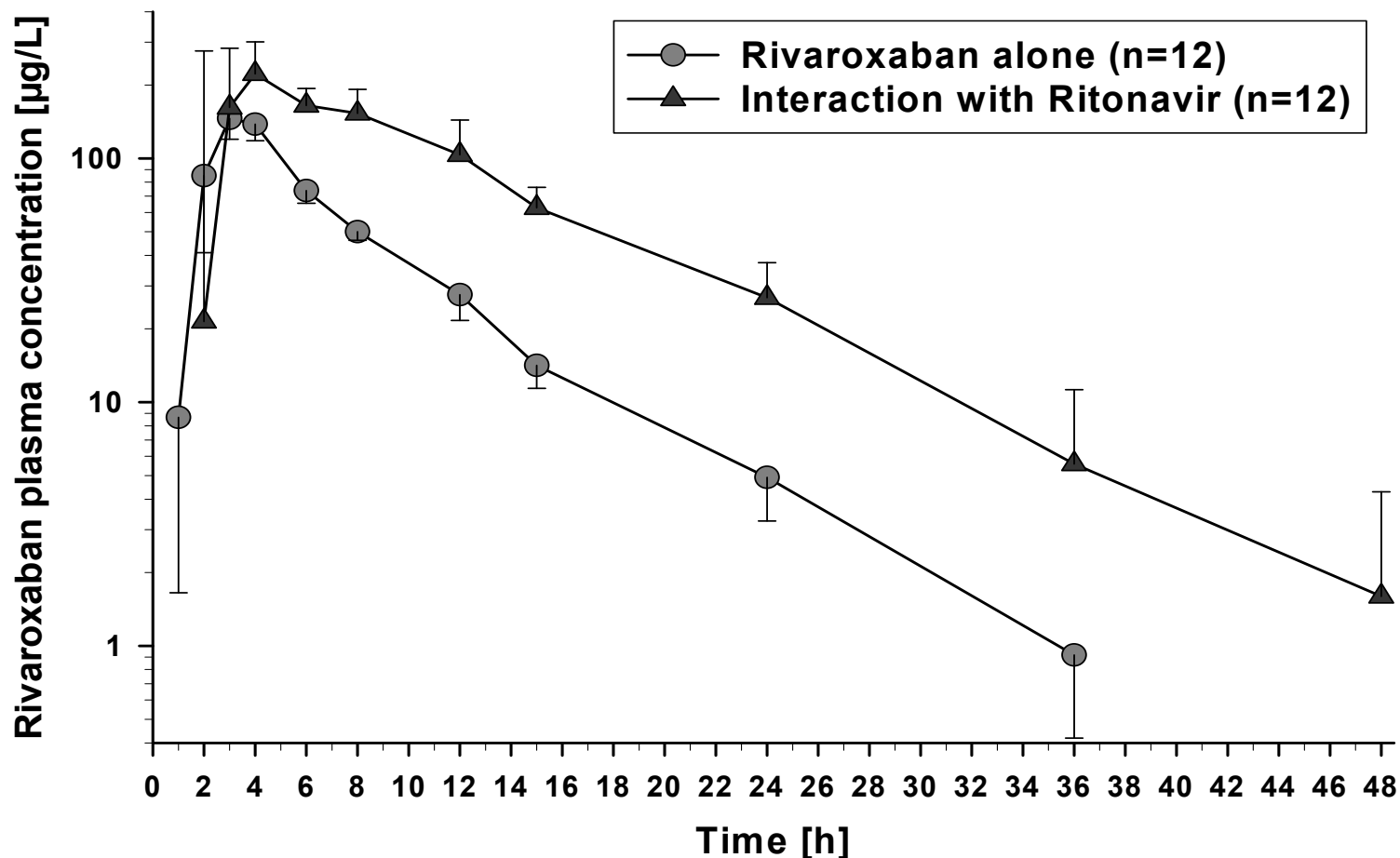
Ketoconazole 400 mg qd - Rivaroxaban 10 mg Interaction

Steady-State Plasma Concentrations of Rivaroxaban



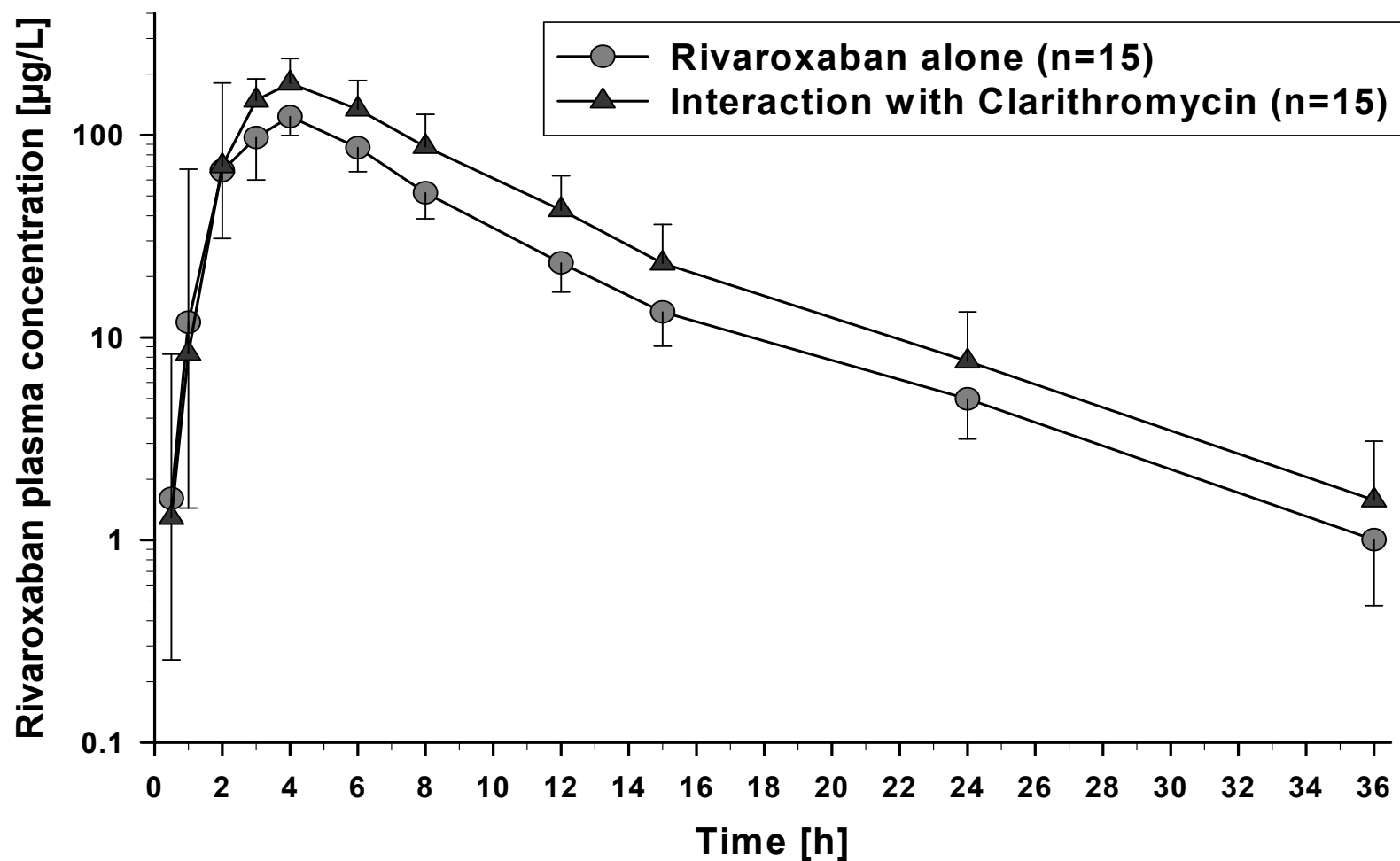
Ritonavir 600 mg bid - Rivaroxaban 10 mg Interaction

Plasma Concentrations of Rivaroxaban

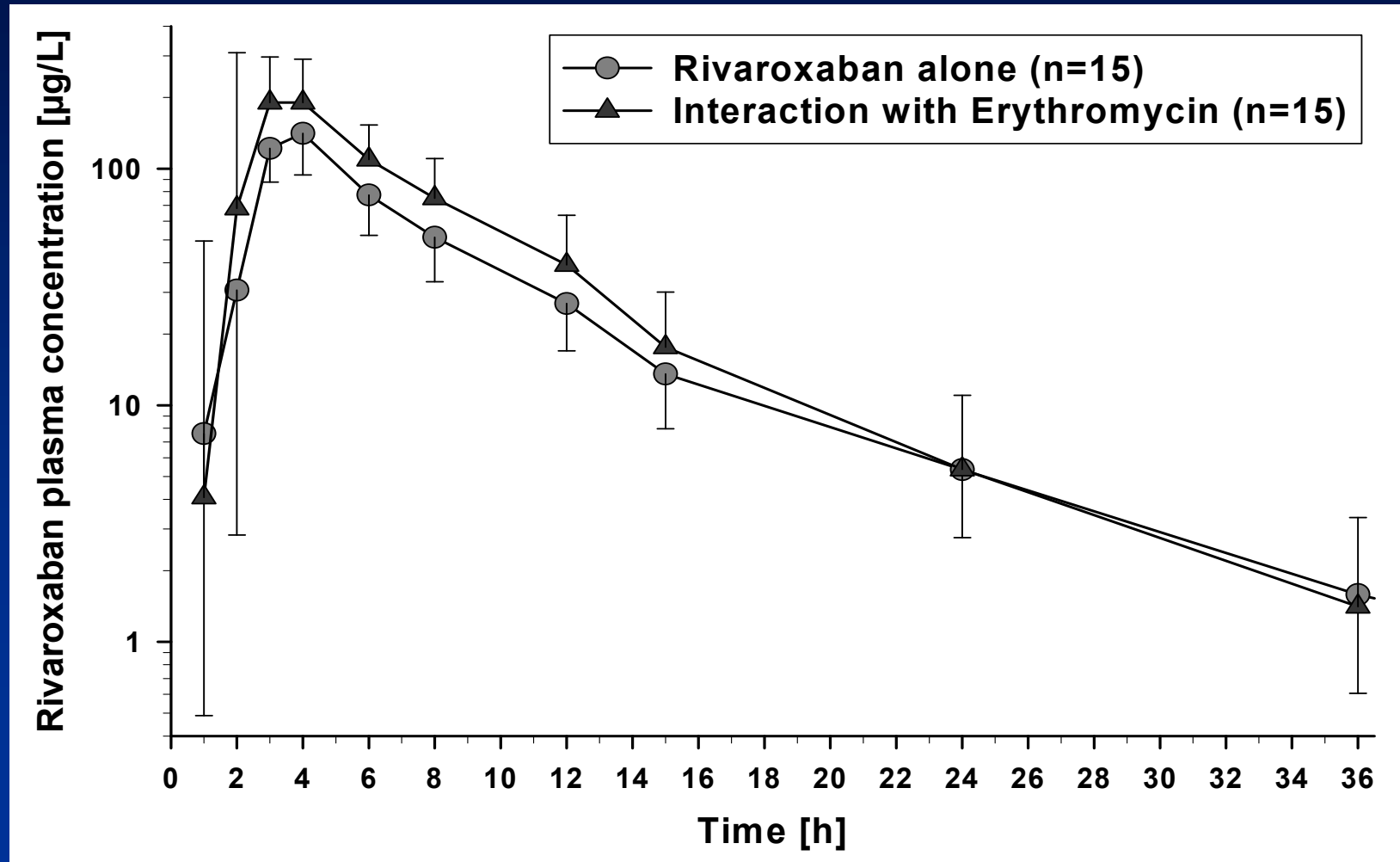


Clarithromycin 500 mg bid - Rivaroxaban 10 mg Interaction

Plasma Concentrations of rivaroxaban



Erythromycin 500 mg tid - Rivaroxaban 10 mg Interaction Plasma Concentrations of Rivaroxaban



In vivo Effect of Inhibitors of CYP3A4 and Pgp on Plasma Exposure and Clearance

Treatment	Parameter	Estimate (90% CI)
Rivaroxaban + Erythromycin 500 mg tid	AUC	1.34 (1.23 – 1.46)
	C _{max}	1.38 (1.21 – 1.48)
	CL/f	0.75 (0.69 – 0.81)
	CL _{RS}	1.07 (0.90 – 1.27)
Rivaroxaban + Clarithromycin 500 mg bid	AUC	1.54 (1.44 – 1.64)
	C _{max}	1.40 (1.30 – 1.52)
	CL/f	0.65 (0.61 – 0.69)
	CL _{RS}	0.90 (0.80 – 1.01)
Rivaroxaban + Ketoconazole 200 mg od	AUC	1.82 (1.59 – 2.08)
	C _{max}	1.53 (1.27 – 1.85)
	CL/f	0.55 (0.48 – 0.63)
Rivaroxaban + Ketoconazole 400 mg od	AUC	2.58 (2.36 – 2.82)
	C _{max}	1.72 (1.61 – 1.83)
	CL/f	0.39 (0.35 – 0.42)
	CL _{RS}	0.56 (0.47 – 0.68)
Rivaroxaban + Ritonavir 600 mg bid	AUC	2.52 (2.34 – 2.74)
	C _{max}	1.55 (1.41 – 1.69)
	CL/f	0.40 (0.37 – 0.43)
	CL _{RS}	0.18 (0.14 – 0.24)

In Vitro DDI in Human Liver Microsomes - Inhibition of Rivaroxaban Oxidative Metabolism

- 82 compounds at 6 concentrations tested
- Inhibition of M2 formation
(CYP3A4/3A5 and 2J2 mediated)
- Inhibition of M9 formation
(CYP3A4/3A5 mediated)
- HIV protease inhibitors and antifungal azoles inhibited both M2 and M9 formation
- Some CYP3A4 substrates inhibited M9 formation more than M2 formation (e.g., erythromycin), some inhibited M2 formation more than M9 formation (e.g., verapamil)

In vitro Inhibition of Oxidative Metabolism and Renal Secretion

Inhibitor	C _{max} [μM]	M-2 form. CYP3A4/ CYP2J2 IC ₅₀ [μM]	M-9 form. CYP3A4 IC ₅₀ [μM]	P-gp Transp. IC ₅₀ [μM]	Bcrp Transp. IC ₅₀ [μM]	In vivo x- fold increase exposure
Ketoconazole 400 mg qd	10	0.28	0.28	9.0	5.8	AUC: 2.6 C _{max} :1.7
Ritonavir 600 mg bid	15	0.54	0.42	27.9	11.0	AUC: 2.5 C _{max} :1.6
Clarithromycin 500 mg bid	3.1	189	44	- NS at 10	- NS at 10	AUC: 2.5 C _{max} :1.4
Erythromycin 500 mg tid	4.2	>200	37	- NS at 10	- [NS at 10	AUC and C _{max} :1.3

In Vitro DDI - HIV Protease Inhibitors

Inhibitor	Cmax [μM]	M2 form. CYP3A4/ CYP2J2 IC50 [μM]	M9 form. CYP3A4 IC50 [μM]	P-gp transp. IC50 [μM]	Bcrp transp. IC50 [μM]
Ritonavir 600 mg bid	15	0.54	0.42	27.9	11.0
Atazanavir 400 mg od	5.4	2.4	1.2	-	-
Indinavir 800 mg tid	12.9	4.3	1.7	-	-
Saquinavir 1200 mg tid	1.6	11	10	-	-

In Vitro DDI - Azole Antifungals

Inhibitor	C _{max} [μM]	M2 form. CYP3A4/ CYP2J2 IC ₅₀ [μM]	M9 form. CYP3A4 IC ₅₀ [μM]	P-gp transp. IC ₅₀ [μM]	Bcrp transp. IC ₅₀ [μM]
Ketoconazole 400 mg od	10	0.28	0.28	9.0	5.8
Itraconazole 200 mg bid	2.8	5.6	4.0	0.16	-
Clotrimazole (non-systemic)	< 0.03	10	0.25	13.6	-
Miconazole (non-systemic)	< 0.96	3.6	2.2	15.1	-
Fluconazole 400 mg od	60	179	20	not known	not known

In Vitro DDI – P-gp Inhibitors

Inhibitor	C _{max} [μM]	M2 form. CYP3A4/ CYP2J2 IC ₅₀ [μM]	M9 form. CYP3A4 IC ₅₀ [μM]	P-gp transp. IC ₅₀ [μM]	Bcrp transp. IC ₅₀ [μM]
Ivermectin 12 mg	0.11	not known	not known	0.25	not known
Cyclosporin 1.8 mg/kg/day	0.88	9.7	3.6	2.3	-
Quinidine	8.9	not known	not known	4.3	not known
Amiodarone 400 mg qd	3.5	> 200	> 200	14.1	not known
Diltiazem 240 mg qd	0.5	84	33	78 (for digoxin)	not known
Verapamil 240 mg qd	0.56	21	52	4.3	-

Summary of Efficacy by CYP3A4 or Pgp Inhibitor Use

RECORD 1-4 Pooled Studies

Subgroup	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Odds/Hazard ratio (95%CI)
Total VTE			
CYP or Pgp no	156/3918 (3.98)	356/3942 (9.03)	0.42 (0.34, 0.51)
CYP or Pgp yes	25/330 (7.58)	46/322 (14.29)	0.49 (0.28,0.85)
Major VTE			
CYP or Pgp no	26/4317 (0.60)	109/4330 (2.52)	0.23 (0.15, 0.36)
CYP or Pgp yes	6/360 (1.67)	19/347 (5.48)	0.28 (0.09, 0.75)
Symptomatic VTE/death			
CYP or Pgp no	32/5682 (0.56)	70/5705 (1.23)	0.46 (0.30, 0.69)
CYP or Pgp yes	3/501 (0.60)	12/495 (2.42)	0.24 (0.07, 0.86)

Summary of Bleeding Events by CYP3A4 or Pgp Inhibitor Use RECORD 1-4 Pooled Studies

Subgroup	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Hazard ratio (95%CI)
Major or non-major clinically relevant bleeding event			
CYP or Pgp no	175/5682 (3.08)	149/5705 (2.61)	1.18 (0.95, 1.46)
CYP or Pgp yes	22/501 (4.39)	9/495 (1.82)	2.37 (1.09, 5.16)
Any bleeding event			
CYP or Pgp no	381/5682 (6.71)	372/5705 (6.52)	1.03 (0.89, 1.18)
CYP or Pgp yes	53/501 (10.58)	29/495 (5.86)	1.81 (1.15, 2.85)

CYP3A4 or Pgp Inhibitors in Phase 3

Pooled Phase 3 - PT Analysis Population

Drug	Rivaroxaban (N=6093)	Drug	Rivaroxaban (N=6093)
Any CYP3A4 or Pgp inhibitors	460		
Amiodarone	47	Fluconazole	9
Aprepitant	6	Fluoxetine	52
Cyclosporin	8	Fluvoxamine	8
Cimetidine	119	Itraconazole	1
Clarithromycin	9	Ketoconazole	3
Diltiazem	101	Quinidine	1
Erythromycin	8	Verapamil	109

weak CYP3A4 inhibitor

moderate CYP3A4 inhibitor

strong CYP3A4 inhibitor

CYP3A4 Inhibitors in Phase 3

Pooled Phase 3 - PT Analysis Population

Drug	Rivaroxaban (N=6093)	Drug	Rivaroxaban (N=6093)
Any CYP3A4 inhibitors	451	Diltiazem	101
Weak inhibitors		Erythromycin	8
Cimetidine	119	Fluconazole	9
Fluoxetine	52	Verapamil	109
Fluvoxamine	8	Strong inhibitors	
Moderate inhibitors		Clarithromycin	9
Aprepitant	6	Itraconazole	1
Amiodarone	47	Ketoconazole	3
weak inhibitor	moderate inhibitor	strong inhibitor	

Pgp Inhibitors in Phase 3

Pooled Phase 3 - PT Analysis Population

Drug	Rivaroxaban 10 mg qd (N=6093)
Any Pgp inhibitor	130
Cyclosporin	8
Erythromycin	8
Itraconazole	1
Ketoconazole	3
Quinidine	1
Verapamil	109

Phase 2 Simulations: **Effect of Renal Impairment and Concomitant Use of CYP3A4 Inhibitors: Number of Subjects**

Number of subjects	Normal Renal Function CLCR ≥80 mL/min	Mild Renal Impairment CLCR 50-79 mL/min	Moderate Renal Impairment CLCR 30-49 mL/min	All
5 mg dose group	62	48	13	123
10 mg dose group	76	58	6	140
20 mg dose group	66	52	13	131
All doses (5-10-20 mg)	204	158	32	394

Demographics Phase 2 comparable to Phase 3

- mean age 64.0-65.0 years (for 5-10-20 mg dose groups) vs. 64.1 years (pooled RECORD 1-4)

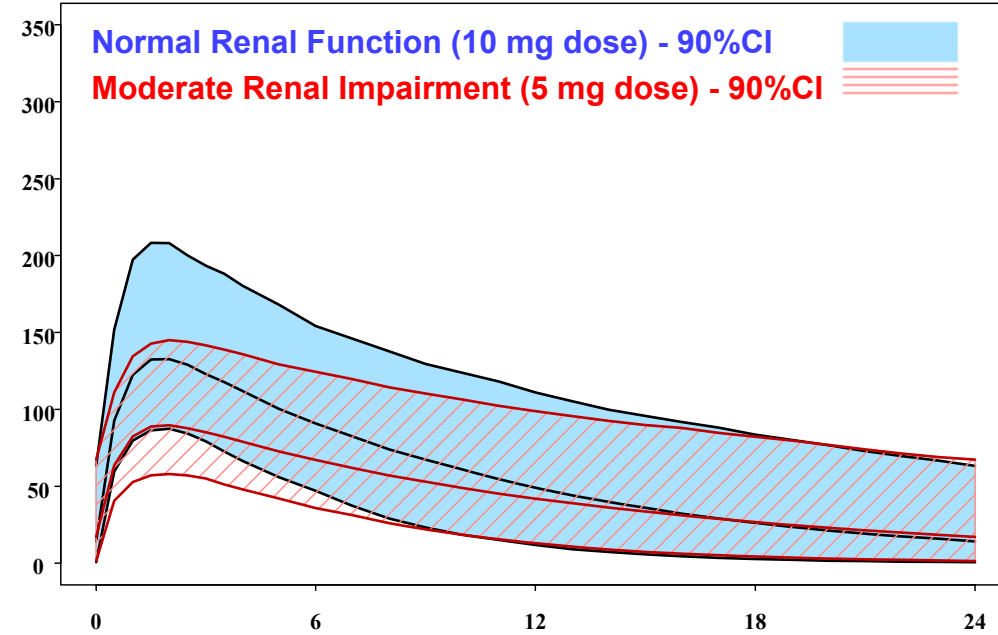
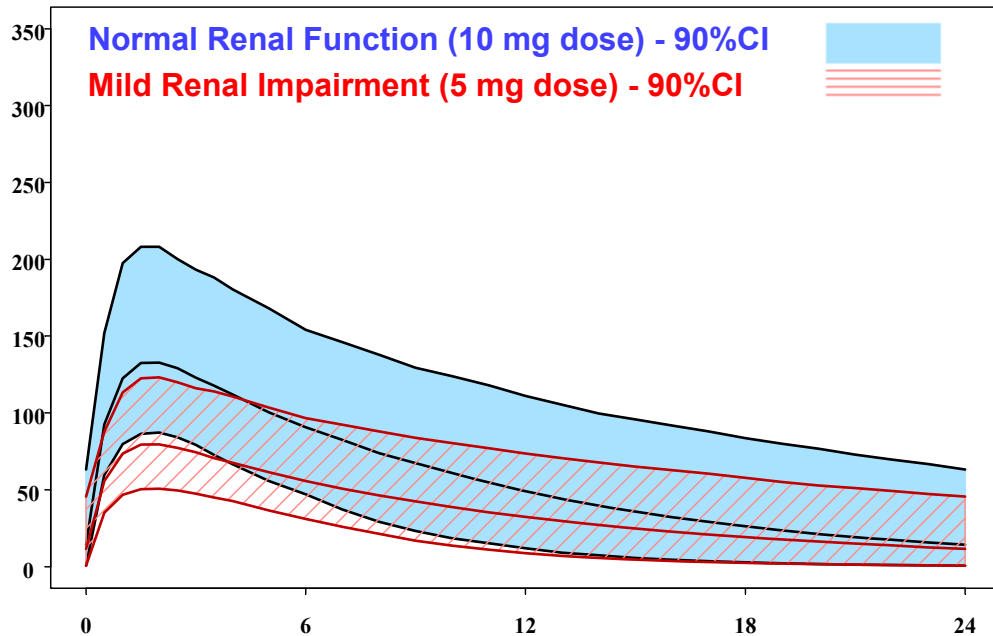
Phase 2 Simulations: **Effect of Renal Impairment and Concomitant Use of CYP3A4 Inhibitors**

- Patients from Phase 2 qd study (5-20 mg dose groups)
 - Categorized according to their CLCR values into: normal renal function (CLCR > 80 mL/min), mild (CLCR 50-79 mL/min) & moderate reduced renal function (CLCR 30-49 mL/min)
- Patient's total clearance derived from POP PK analysis
- Fraction CYP3A4 clearance vs. total clearance in patient population estimated based on ratio derived from renal impairment study
 - Assuming CYP 3A4 clearance = 23% of total clearance or 38% of hepatic clearance
 - fraction (11%) non-recovered & non-identified structures equally divided over CYP3A4 - CYP2J2 & non-CYP metabolism
- Simulations for different strengths of inhibition of CYP3A4
 - 30% - 50% en 86% (each with 20% variability)
- 1000 simulations for each of renal functions groups
 - re-sampling from 'real pool' of subjects

Predicted Steady State Plasma Concentration Window

5 mg qd in Phase 2 Target Population

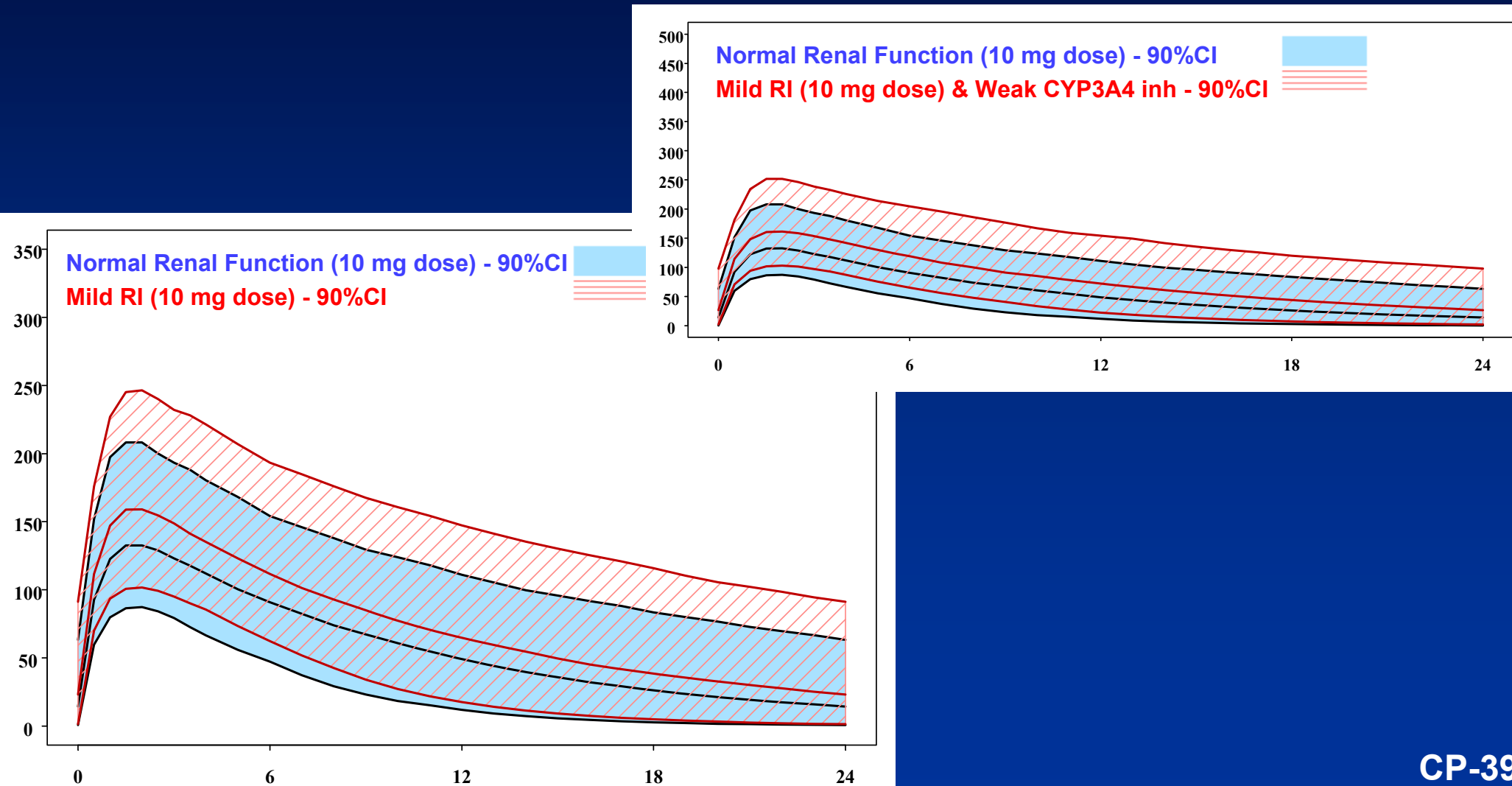
Normal Renal Function vs Mild and Moderate Renal Impairment



Predicted Steady State Plasma Concentration Window

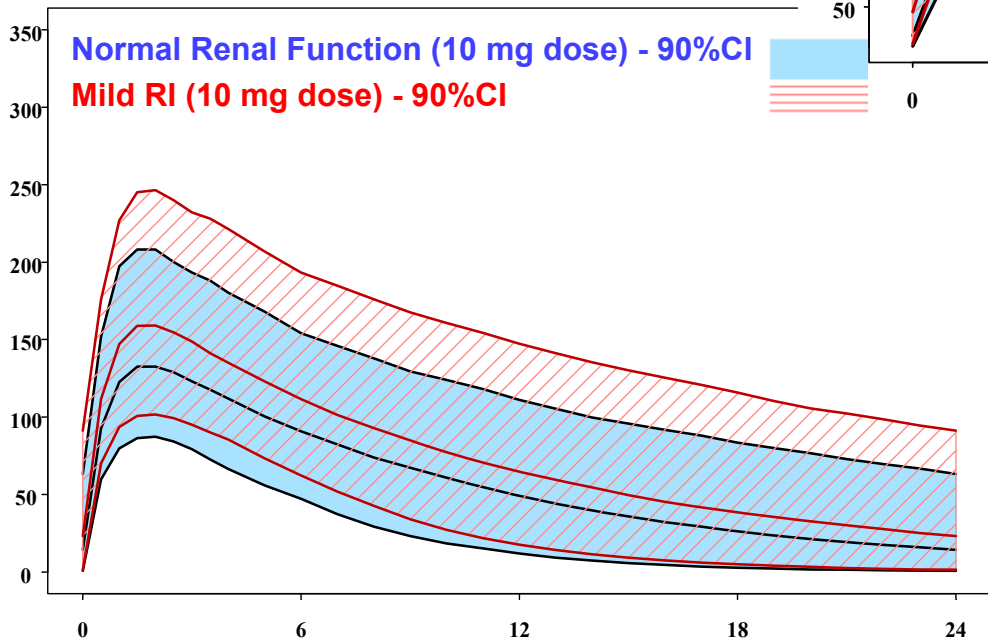
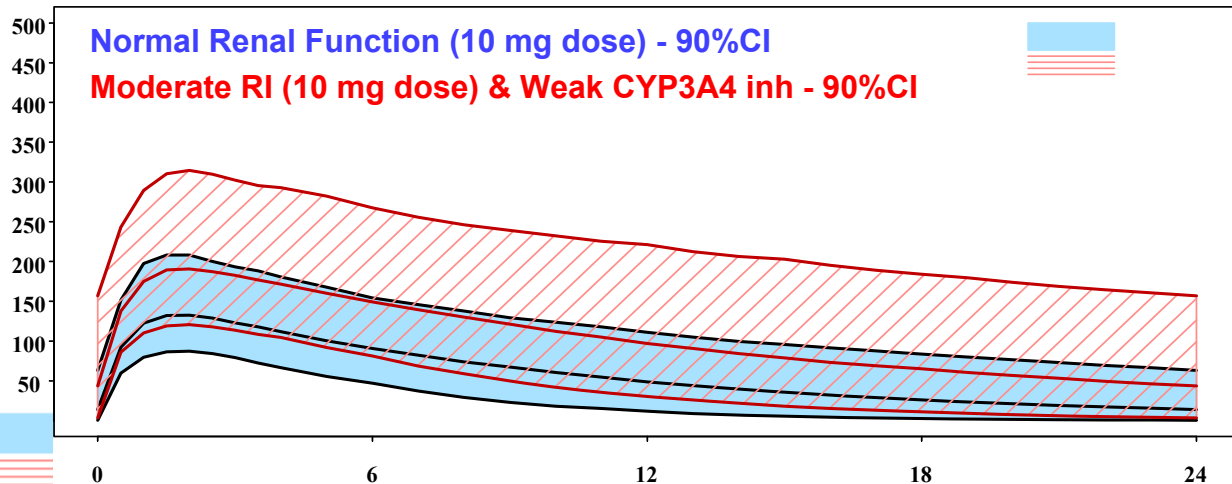
10 mg qd in Phase 2 Target Population

Mild Renal Impairment and Weak CYP 3A4 Inhibition



Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

Moderate Renal Impairment and Weak CYP 3A4 Inhibition



Phase 2 - Target Population -10 mg qd Simulations

Impact Renal Impairment and Concomitant CYP3A4 Inhibitor x-fold Increase in AUC & C_{max}

	Normal Renal Function > 80 mL/min	Mild Renal Impairment 50-80 mL/min	Moderate Renal Impairment 30-50 mL/min
AUC			
No CYP3A4 inh	1.00	1.28	1.59
30% CYP3A4 inh	1.07	1.38	1.80
50% CYP3A4 inh	1.14	1.48	1.95
90% CYP3A4 inh	1.29	1.70	2.28
C_{max}			
No CYP3A4 inh	1.00	1.20	1.35
30% CYP3A4 inh	1.03	1.22	1.44
50% CYP3A4 inh	1.06	1.26	1.50
90% CYP3A4 inh	1.12	1.36	1.65

Phase 2 - Target Population

Impact Renal Impairment and Concomitant CYP3A4 Inhibitor x-fold Increase in AUC & C_{max}

5 mg rivaroxaban qd vs. 10 mg qd in subjects with normal renal function

	Normal Renal Function > 80 mL/min	Mild Renal Impairment 50-80 mL/min	Moderate Renal Impairment 30-50 mL/min
AUC			
No CYP3A4 inh	1.00	0.64	0.79
30% CYP3A4 inh	0.54	0.69	0.90
50% CYP3A4 inh	0.57	0.74	0.98
90% CYP3A4 inh	0.64	0.85	1.14
C_{max}			
No CYP3A4 inh	1.00	0.60	0.68
30% CYP3A4 inh	0.52	0.61	0.72
50% CYP3A4 inh	0.53	0.63	0.75
90% CYP3A4 inh	0.56	0.68	0.82

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/s/

Marcus Cato
4/27/2009 11:35:01 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>		
TO (Office/Division): Office of Surveillance and Epidemiology/through Janet Anderson		FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Medical Imaging and Hematology Products		
DATE April 2, 2009	IND NO.	NDA NO. 22-406	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT July 22, 2008
NAME OF DRUG Xarelto (rivaroxaban) tablets	PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Anti-Xa	DESIRED COMPLETION DATE April 15, 2009	
NAME OF FIRM: Johnson and Johnson Pharmaceutical Research & Development, LLC				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <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): Trade name review </div> </div>				
II. BIOMETRICS				
<div style="display: flex;"> <div style="width: 50%;"> <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): </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>				
III. BIOPHARMACEUTICS				
<div style="display: flex;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div> </div>				
IV. DRUG SAFETY				
<div style="display: flex;"> <div style="width: 50%;"> <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 </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </div> </div>				
V. SCIENTIFIC INVESTIGATIONS				
<div style="display: flex;"> <div style="width: 50%;"> <input checked="" type="checkbox"/> CLINICAL </div> <div style="width: 50%;"> <input type="checkbox"/> NONCLINICAL </div> </div>				
COMMENTS / SPECIAL INSTRUCTIONS: <p>Please review the tradename Xarelto (rivaroxaban) tablets. Please find enclosed the proposed package insert and the proposed immediate container and carton labeling. (Note that the name was submitted to IND 64,892 on August 23, 2007 and to NDA 22-406 on August 26, 2008).</p> <p>PDUFA DATE: ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND/NDA HFD-160/Division File, HFD-160/RPM, HFD-160/Reviewers and Team Leaders</p>				
SIGNATURE OF REQUESTOR Marcus Cato		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

Marcus Cato

4/2/2009 10:20:32 AM

Newman, Tyree

From: Greeley, George
Sent: Wednesday, March 25, 2009 3:39 PM
To: Cato, Marcus
Cc: Mathis, Lisa; Leaman, Diane V
Subject: NDA 22-406 Xarelto

Importance: High

Hi Marcus,

The Xarelto (rivaroxaban) full waiver was reviewed by the PeRC PREA Subcommittee on March 25, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because there are too few children with disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.

It is also recommended that the Division request a consult with PMHS (Pediatrics and Maternal Health Staff) to determine if a Written Request for this product is feasible.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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/s/

TYREE L NEWMAN
07/01/2011

RECORD OF TELEPHONE CONVERSATION

NDA: 22-406/Rivaroxaban

Today's date: March 25, 2009

Speakers: Dwaine Rieves for FDA (prepped record)
Michael Kronig for J and J

Dr. Kronig had called and left a voice mail for me. I returned the telephone call and make the following notes:

-Dr. Kronig stated they looked forward to labeling discussions.

-I stated that reviews are on-going and I inquired about the status of the ATLAS 46 study report.

-Dr. Kronig stated they anticipated the Atlas study report "within a few weeks." Without questioning, Dr. Kronig stated that the company preferred lengthening the review cycle to receipt of a complete response letter. I stated that this aspect was a component of the review.

-Dr. Kronig stated that the sponsor would particularly like to discuss the clinical pharmacology and statistical aspects of the review with the review team. He noted that the sponsor preferred to have detailed discussions in which their statisticians talked with FDA statisticians. I stated we would look into the possibility but emphasized the challenges of schedules.

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/s/

Marcus Cato
3/30/2009 12:00:45 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 13, 2009. The purpose of the meeting was to discuss the upcoming advisory committee (AC) meeting.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: March 13, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer
Diane Leaman, Safety Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS VII

Chava Zibman, Ph.D., Statistical Reviewer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ PHARMACOMETRICS DIVISION

Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Peter DiBattiste	M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters	M.D. Franchise Medical Leader
Lloyd Haskell	M.D. VP, CDTL
Leonard Oppenheimer	Ph.D. Statistical Sciences
Mehul Desai	M.D. Clinical
Jesse A. Berlin	ScD, VP, Epidemiology
G.K. (Dina) Anand	M.D., Post-Marketing Safety Franchise Leader
Michael Kronig	M.D. , VP Cardiovascular Regulatory Affairs
Sanjay Jalota	MRPharmS, Regulatory Global Regulatory Lead
Donald L. Heald	Ph.D. VP and Global Head of Clinical PK
Achiel Van Peer	Ph.D. Global Sr. Scientific Leader Clinical Pharmacology
An Thyssen	Ph.D. Clinpharm Leader Rivaroxaban
Harry Flanagan	DO, Post-Marketing Safety Expert, Benefit Risk Management
Sigmond Johnson	MS, MBA Program Coordinator
John Zhang	Ph.D. Statistical Sciences

BAYER

Frank Misselwitz	M.D. , Ph.d., VP Head Therapeutic Area CV & Coagulation
Scott D. Berkowitz	M.D. FACP, FACC, VP, Head, Thrombosis & Hemostasis CV and Coagulation
Gerhard Schlueter	Regulatory Head of General Medicine/Cardiology
Alice Benson	Principal Statistician, Global Clinical Statistics
Patricia Hagerty	Statistical Analyst –Global Statistical Programming
Larry Winick	MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitza	Ph.D. Global Clinical Pharmacology Project Leader
Torsten Westermeier	Ph.D. Therapeutic Area Expert Statistician CC
Aasia Bhatti	M.D. Deputy Director for Int'l Drug Safety Division
Bernard Glombitza	M.D. Global Project Leader Wuppertal, Germany
Harald Kallabis	
Wolfgang Muerk	

BACKGROUND:

N/A

MEETING OBJECTIVES:

To provide clarifications regarding FDA presentations and discuss expectations for the March 19, 2009, advisory committee meeting (AC).

DISCUSSION POINTS:

FDA provided an overview of their expectations for the AC. FDA emphasized that all its comments are subject to change. In general FDA expects:

- Introductory Comments- Dr. Rieves (5 minutes)
- Sponsor Speakers (1.5 hours)
- Questions to Sponsor
- Break
- FDA Presentations
 - Overview of Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Treatment in Patients Undergoing Hip or Knee Replacement Therapy (10 min).
 - Safety and Efficacy of Xarelto for prophylaxis in patients undergoing hip or knee replacement surgery— (30 minutes)
 - Statistical Analysis Considerations (10 min)
 - Hepatotoxicity Concerns (15 min)
 - Dose Adjustment Considerations (10 min)

FDA does not anticipate an emphasis upon efficacy in the FDA presentation. The main FDA presentation will predominantly relate to safety. FDA questions to the AC will likely be about the utility of a lower dose for special populations, if the data identify a risk for liver toxicity, the importance of ongoing data in the characterization of safety and the overall risk/benefit assessment.

J&J discussed its plans and mentioned their comments are subject to change as their process is fluid also. At the moment J&J plans to present:

- The current state of prophylaxis of DVT in orthopedic surgery in the context of the US and the rest of the world,
- The trial data with emphasis on efficacy, and safety
- A substantial liver presentation
- The overall risk/benefit assessment.

DECISIONS (AGREEMENTS) REACHED:

- N/A

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- N/A

ATTACHMENTS/HANDOUTS:

- N/A

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/s/

Marcus Cato
3/18/2009 12:16:02 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Office/Division): PEDIATRIC AND MATERNAL HEALTH STAFF (CDER/OND/PMHS)/ through George Greeley			FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Medical Imaging and Hematology Products	
DATE March 13, 2009	IND NO. N/A	NDA NO. 22-406	TYPE OF DOCUMENT background info for the PeRC meeting	DATE OF DOCUMENT N/A
NAME OF DRUG Xarelto™ (Rivaroxaban) Tablets		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Factor Xa inhibitor	DESIRED COMPLETION DATE March 25, 2009
NAME OF FIRM: Johnson and Johnson (J&J)				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <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 </div> <div style="width: 30%;"> <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 </div> <div style="width: 30%;"> <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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): background info for the PeRC meeting </div> </div>				
II. BIOMETRICS				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <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): </div> <div style="width: 45%;"> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>				
III. BIOPHARMACEUTICS				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES </div> <div style="width: 45%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div> </div>				
IV. DRUG SAFETY				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <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 </div> <div style="width: 45%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </div> </div>				
V. SCIENTIFIC INVESTIGATIONS				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> CLINICAL </div> <div style="width: 45%;"> <input type="checkbox"/> NONCLINICAL </div> </div>				
COMMENTS / SPECIAL INSTRUCTIONS: DMIHHP requests PMHS to review the background materials and attend the PeRC meeting for Xarelto NDA 22-406 scheduled 3/25/09.				
SIGNATURE OF REQUESTOR Marcus Cato, RPM, Division of Medical Imaging and Hematology Products			METHOD OF DELIVERY (Check one) <input checked="" 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	

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-406

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: DMIHP

PDUFA Goal Date: 5/28/09

Stamp Date: 7/28/2008

Proprietary Name: Xarelto

Established/Generic Name: rivaroxaban

Dosage Form: tablets

Applicant/Sponsor: Johnson and Johnson Pharmaceutical Research & Development, LLC

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery

Q1: Is this application in response to a PREA PMR?

Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

☒ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☒ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification [†]
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

[†] Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.

If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
☒ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
☐ No: Please check all that apply:
☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
☐ Completed for some or all pediatric subpopulations (Complete Sections D)
☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
☐ Disease/condition does not exist in children
☒ Too few children with disease/condition to study
☐ Other (e.g., patients geographically dispersed): _____
☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☒ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): ____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: ____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.

If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE **PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

Pediatric Research and Equity Act Waivers

NDA #:22-406 Supplement Type: N/A Supplement Number: N/A

Product name and active ingredient/dosage form: Xarelto (Rivaroxaban) Tablets

Sponsor: Johnson & Johnson

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to age 16 years.
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

3. Pediatric age group(s) to be waived. Birth to age 16 years.
4. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration

Alzheimer's disease

Amyotrophic lateral sclerosis

Atherosclerotic cardiovascular disease

Benign prostatic hypertrophy

Chronic Obstructive Pulmonary Disease

Erectile Dysfunction

Infertility

Menopausal and perimenopausal disorders

Organic amnesic syndrome

(not caused by alcohol or other psychoactive substances)

Osteoarthritis

Parkinson's disease

Postmenopausal Osteoporosis

Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:

Basal cell

Bladder

Breast

Cervical

Colorectal

Endometrial

Gastric

Hairy cell leukemia

Lung (small & non-small cell)

Multiple myeloma

Oropharynx (squamous cell)

Ovarian (non-germ cell)

Pancreatic

Prostate

Renal cell

Uterine

1.9.1 Request for Waiver of Pediatric Studies

The sponsor is requesting a waiver for the conduct of a clinical program with rivaroxaban for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in pediatric patients (<18 years of age) undergoing total hip or knee replacement surgery. The rationale for the waiver for the conduct of such a clinical program in this indication is the rarity of joint replacement surgery in the pediatric population and the lower risk of DVT and PE (collectively referred to as venous thromboembolism [VTE]), which does not necessarily require routine prophylaxis.

Patients over 40 years old have a clearly increased risk for the development of VTE across multiple clinical settings compared with younger patients. The incidence of VTE in children is considered rare and usually happens only in the presence of a strong predisposing risk factor (Anderson 2003). However, even with a strong predisposing factor like major trauma, the incidence of clinically-detected VTE is lower in patients 17 years old or less compared with those over 17 years, based on a Level 1 trauma center registry (Azu 2005). VTE events were experienced in:

- 0 of 2320 (0.0%) trauma patients under the age of 13 years
- 2 of 1025 (0.2%) trauma patients between the ages of 13 to 17 years
- 57 of 10549 (0.5%) trauma patients older than 17 years

Based on these data, the authors concluded that VTE prophylaxis after trauma is unnecessary in children since the risk of clinically significant VTE is negligible. In adults, routine VTE prophylaxis after major trauma is a Grade 1A recommendation (Geerts 2008). Similarly, a review of all patients 17 years old or less hospitalized for at least 72 hours and having 2 or more risk factors for VTE, found only 1 case with symptomatic DVT (Rohrer 1996). Since this patient had at least 3 risk factors for VTE (i.e., head trauma, neurologic deficit, and multiple surgeries), the authors conclude that VTE prophylaxis is not required for patients with only 1 or 2 risk factors.

Total joint replacements are performed in the pediatric population primarily for the joint deformities and disabilities associated with juvenile rheumatoid arthritis (and similar conditions) (Kim 2008, Kitsoulis 2006). Since these procedures are technically challenging and will eventually lead to revision surgery due to the finite functional lifespan of the artificial joint, they are performed infrequently and only after medical therapy has failed. Joint replacement surgery is also occasionally performed in pediatric patients for malignant bone disease (e.g., with proximal femoral resection) (van Kampen 2008). Reflecting the low number of surgeries, the largest case series reported in the literature has been 47 patients from the Mayo Clinic (Klassen 1979). There does not appear to be any data in the literature on the occurrence of VTE following joint replacement surgery in pediatric patients, but based on the above data in other settings, the VTE risk would be expected to be substantially lower than for adults.

Since pediatric subjects were excluded from all rivaroxaban clinical studies and the risk of VTE is likely different from that in adults, the safety and effectiveness of rivaroxaban have not been established in children and adolescents <18 years of age and therefore, rivaroxaban is not recommended for use in this population in the proposed product labeling.

The conduct of a clinical program to establish the safety and effectiveness of rivaroxaban in the pediatric population after joint replacement surgery is not feasible due to the limited number of procedures performed and the low expected incidence of symptomatic VTE events in this population. Therefore, the sponsor requests a waiver for the conduct of such a clinical program.

References

- Anderson FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107;I-9-I-16. 5.4-1
- Azu MC, McCormack JE, Scriven RJ, Brebbia J, Shapiro MJ, Lee TK. Venous thromboembolic events in pediatric trauma patients: is prophylaxis necessary? *J Trauma Inj Infect Crit Care* 2005;59:1345-1349. 5.4-1
- Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:381S-453S. 5.4-1
- Kim HJ, Kahn B, Figgie MP. Total joint replacement in childhood arthritis. *Curr Rheumatol Rep* 2008;10(2):135-41. 5.4-1
- Kitsoulis PB, Stafilas KS, Siamopoulou A, Soucacos PN, Xenakis TA. Total hip arthroplasty in children with juvenile chronic arthritis: long-term results. *J Pediatr Orthop* 2006;26(1):8-12. 5.4-1
- Klassen RA, Parlasca RJ, Bainco AJ. Total joint arthroplasty. Applications in children and adolescents. *Mayo Clin Proc* 1979;54(9):579-82. 5.4-1
- Rohrer MJ, Cutler BS, MacDougall E, Herrmann JB, Anderson FA, Wheeler HB. A prospective study of the incidence of deep venous thrombosis in hospitalized children. *J Vascular Surg* 1996;24(1)46-9. 5.4-1
- van Kampen M, Grimer RJ, Carter SR, Tillman RM, Abudu A. Replacement of the hip in children with a tumor in the proximal part of the femur. *J Bone Joint Surg (American)* 2008;90(4):785-95. 5.4-1

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.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable. The conduct of a clinical program to establish the safety and effectiveness of Rivaroxaban in the pediatric population after joint replacement surgery is not feasible due to the limited number of procedures performed and the low expected incidence of symptomatic VTE events in this population.

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Marcus Cato
3/13/2009 08:44:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Office/Division): PEDIATRIC AND MATERNAL HEALTH STAFF (CDER/OND/PMHS)/ through Tammie Brent Howard,			FROM (Name, Office/Division, and Phone Number of Requestor): Marcus Cato, RPM, Division of Medical Imaging and Hematology Products	
DATE March 10, 2009	IND NO. N/A	NDA NO. 22-406	TYPE OF DOCUMENT Xarelto PI/Review	DATE OF DOCUMENT N/A
NAME OF DRUG Xarelto™ (Rivaroxaban) Tablets		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG Factor Xa inhibitor	DESIRED COMPLETION DATE March 25, 2009
NAME OF FIRM: Johnson and Johnson (J&J)				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <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 </div> <div style="width: 30%;"> <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 </div> <div style="width: 30%;"> <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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <p style="margin-left: 20px;">pregnancy portion of the PI (labeling)</p> </div> </div>				
II. BIOMETRICS				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <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): </div> <div style="width: 45%;"> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>				
III. BIOPHARMACEUTICS				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES </div> <div style="width: 45%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div> </div>				
IV. DRUG SAFETY				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <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 </div> <div style="width: 45%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS </div> </div>				
V. SCIENTIFIC INVESTIGATIONS				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> CLINICAL </div> <div style="width: 45%;"> <input type="checkbox"/> NONCLINICAL </div> </div>				
COMMENTS / SPECIAL INSTRUCTIONS: DMIHP request PMHS to review and comment on the pregnancy portion of the proposed (labeling).				
SIGNATURE OF REQUESTOR Marcus Cato, RPM, Division of Medical Imaging and Hematology Products			METHOD OF DELIVERY (Check one) <input checked="" 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	

6. Reproductive and Developmental Toxicity

6.1 Study of Fertility and Early Embryonic Development in Rats after Oral Administration (Study Number: T2062789)

Key findings: BAY-59-7939 at oral doses of 12.5 to 200 mg/kg/day in male and female rats during the fertility and reproductive performance period produced a reduction in number of dams (90.5%) with viable fetuses and a slight increase in post implantation loss. A dose related reduction in ovarian weight by 8.8% in the dams of the high dose group also occurred. The NOAEL was 50 mg/kg/day which provided 41 times the safety margin for the clinical dose.

Study no.: T2062789/AT01125/PH-33273

Conducting laboratory and location: The Department of Experimental Toxicology of BHC-PH-PD-T, 42096-Wuppertal, Germany.

Date of study initiation and completion: August 19, 2002 and April 7, 2004

GLP compliance: A statement of compliance was attached.

QA reports: yes (X) no ()

Drug, lot #, and % purity: J20020528, 9.5 % BAY 59-7939 coprecipitate; batch #F033082 and 99.3% pure, suspension made using 20 % Solution HS 15 and 80 % demineralized water in addition with PEG 6000 according to the maximum PEG 6000 content of the high dose group formulation.

Methods

Doses: Male and female animals (12 week old; 24/sex/dose group) were randomly assigned to 4 groups using a randomization list by a computer program. BAY 59-7939 was administered by oral gavage, the intended route in humans in 10 ml/kg volume. Male rats were treated for 4 weeks prior to mating and during the subsequent mating period up to necropsy. Female rats were treated for 2 weeks prior to mating, during the mating period and to gestation day 7. The dose selection was based on a subacute toxicity study in rats (T7070622) and two kinetic studies with doses of 300 mg/kg and 400 mg/kg (T5068560 and T4062790). No meaningful higher exposure was achieved. The doses and the concentrations of the compound in each dose group are shown in sponsor's Table 7-2 of the submission:

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Table 7-2	
	Dose (mg/kg bw/day)
Group 1 (Control)	0
Group 2	12.5
Group 3	50
Group 4	200
	Test compound concentration (mg/ml)
	0 (vehicle only)
	1.25
	5
	20

Species/strain: SPF-bred Wistar rats (strain: Hsd Cpb:WU),

(b) (4)

Route, formulation, volume: Oral, suspension made using 20 % Solution HS 15 and 80 % demineralized water in addition with PEG 6000; 10 ml/kg.

Groups used for toxicokinetics: TK was not done

Parameters and endpoints evaluated: The general observations, appearance, behavior, excretion (feces and urine) and mortality were monitored twice daily during the pretreatment period (estrus determination days -6 to 0) in the female animals, during the entire treatment period in male and female animals. Females were observed up to the time of cesarean section (days 14 to 16 p.c.).

Body weight/Food Consumption: Body weights were taken twice a week during the entire treatment period in the male and female animals up to (and on) the day of necropsy. In inseminated females, daily body weight was monitored till the day of cesarean section. The food consumption changes were recorded during treatment up to the start of the mating period (weekly evaluation in males and females) as well as for inseminated females on day 0-7, and 7-14 p.c. The water consumption was estimated daily by visual examination of the water bottles.

Gross pathological examination: The animals were killed using deep carbon dioxide anesthesia and males were necropsied between study days 45 to 51 and, females on days 14 to 16 p.c. The gross examination of live and dead fetuses was done and, number of corpora lutea, implantation sites, resorptions, live and dead fetuses was counted and, placenta of each of the live and dead fetus was examined for gross changes. The reproductive organs (testes, epididymides, prostate, seminal vesicles, uterus, vagina, ovaries and pituitary gland) from all animals were separated, preserved in Davidson' solution (testes and epididymides) or in 10 % neutral buffered formalin solution. The implantation sites in non-pregnant animals without visible implantations were counted after staining with a solution of 10 % ammonium sulfide.

Results

Mortality: Four animals died and these were 2 males (1 of 50 and 200 mg/kg/day groups) were sacrificed in moribund condition on day 29 and day 18, respectively. Two females in 200 mg/kg/day treatment group died on pre-mating day 10 and on gestation day 6. These animals showed sunken flanks, respiratory sounds, piloerection, and increased salivation after administration, and decreased water consumption. One male of control group also died on day 3. This animal showed hypoactivity, respiratory sounds, gasping breathing, reduced amount of feces, and salivation. The deaths were due to dosing errors.

Clinical signs: Increased incidence and duration of salivation in males of 50 and 200 mg/kg/day groups were noted.

Body weight changes: A reduction of 17.1% in the body weight gain was observed in females of 200 mg/kg/day group during treatment period and, 15.8% reduction was seen during gestation period. It was related to the reduction of food intake. The initial and final body weight of control females was 259 and 423 g.

Food and water consumptions: The food consumption of the 200 mg/kg/day treatment group males and females was significantly ($p < 0.01$) less than the control from pre-mating to mating and gestation periods. The food consumption in different study groups are shown in the sponsors table 8-1 and scanned below:

Table 8-1: Mean feed consumption (g/day) in the male animals during the pre-mating period:

Dose (mg/kg bw/day)	week 1	week 2	week 3	week 4
0	29.14	28.12	27.03	27.08
12.5	28.98	26.95	26.70	27.55
50	28.04	27.61	27.43	27.67
200	24.99**	26.99	27.34	27.29

** significantly different from control, $p < 0.01$

Table 8-2: Mean feed consumption (g/day) in the female animals during the pre-mating period and during gestation:

Dose (mg/kg bw/day)	week 1	week 2	days 0 – 7 p.c.	days 7 – 14 p.c.
0	17.11	17.67	21.41	23.55
12.5	16.89	16.95	21.18	25.10
50	16.33	17.20	20.39	22.97
200	14.90**	17.66	20.46	22.93

** significantly different from control, $p < 0.01$

There was no treatment related effects on water intake and excretory products in any animal of study dose groups among both genders.

Toxicokinetics: Not done

Necropsy:

One male of the 200 mg/kg/day group showed a treatment related black-brownish hematoma between testis and epididymides. No notable pathology was observed during necropsy in study dams included in the study.

Insemination Index, Fertility Index, Gestation Index

The insemination index, females with implantations, and with embryonic viability was similar in treated groups compared to controls. One of 21 females of high dose group was sacrificed because of moribund condition and another female showed reduced viable embryos. These females were excluded. The females with live embryos were 100, 100, 100 and 90.5% among 0, 12.5, 50 and 200 mg/kg/day groups, respectively, with viable embryos significantly less in the 200 mg/kg/day group. The data is shown in the following sponsor's table:

Table 8-6: Insemination index, fertility index and gestation index:

Dose (mg/kg bw/day)	used	inseminated		with implantations		with viable embryos	
		n	% of those paired	n	% of those inseminated	n	% of those with implantations
0	23	22	95.7	19	86.4	19	100.0
12.5	24	24	100.0	20	83.3	20	100.0
50	24	24	100.0	21	87.5	21	100.0
200	23	23	100.0	21	91.3	19 ⁺	90.5

+ one female with sacrifice in moribund condition on day 6 p.c. was excluded

The mean number of estruses/female during 14 days of pre-mating period were 2.9, 3.2, 3.5 and 3.3 in 0, 12.5, 50 and 200 mg/kg/day groups, respectively, therefore, treatment did not affect the number of estruses.

Cesarean Section Observations:

The number of corpora lutea, preimplantation and post implantation sites are shown in sponsor's table 8-9 and scanned here:

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Table 8-9: Results obtained at cesarean section (mean values per female):

Dose (mg/kg bw/day)	0	12.5	50	200
Number of females	19	20	21	20
Corpora lutea	13.9	14.3	14.2	13.8
Implantations	11.5	13.0	12.4	11.9
Preimplantation loss	2.5	1.3	1.8	2.0
Postimplantation loss	0.2	0.4	0.7	0.8
Viable embryos	11.3	12.6	11.7	11.1

The mean number of corpora lutea was similar in treated animals compared to the control group animals.

Pre- and Post- implantation losses:

A dose related decrease in the mean number of post-implantation losses per female was observed in treated animals, i.e., number of late resorptions were 0.2, 0.4, 0.7 and 0.8 per female in study group animals. The number of matings, fertility index and number of corpora lutea were similar in treated groups compared to control group females.

Weight of the Testes and Ovaries

The mean testicular and mean combined weights of the ovaries are given in the following table of sponsor and scanned below:

Table 8-5: Mean absolute combined testes and ovaries weights (g):

Dose (mg/kg bw/day)	0	12.5	50	200
Testes	3.693	3.701	3.647	3.710
Ovaries	0.114	0.106	0.106	0.104

BAY 59-7939 treatment up to 200 mg/kg/day produced a reduction in the mean ovarian weight (in comparison to control) of 5.3, 7.0 and 8.8% in females belonging to 0, 12.5, 50 and 200 mg/kg/day groups. The testes weight was not affected in males of the study.

In summary, BAY-59-7939 from the oral doses of 12.5 to 200 mg/kg/day in male and female rats during the fertility and reproductive performance period produced a reduction in number of dams (90.5%) with viable fetuses and a slight increase in post implantation loss and a dose related reduction in ovarian weight by 8.8% in the dams of the high dose group. The NOAEL was 50 mg/kg/day provides 41 times the safety ratio for the clinical dose.

B. Study title: Developmental Toxicity Study in Rats after Oral Administration (Study #T3063590/PH-33582)

Key findings: BAY 59-7939 when administered in pregnant rats from 0, 10, 35 and 120 mg/kg/day doses from day 6 to 17 postcoitum produced dose related increase in plasma concentrations and vaginal bleeding, piloerection, hypo-activity and reduced feed intake. A severe body weight loss,

uterine bleeding, pale liver, kidneys and enlarged adrenal glands was reported in these animals. Dose related adverse effects of necrotic placental borders, necrotic, engorged and/or pale placentas were observed in fetuses of dams treated from 10 mg/kg/day or greater dose. BAY 59-7939 was not teratogenic in pregnant rats. Based on body surface exposure (mg/mm³), it provides 97 times greater exposure than the proposed clinical dose.

Study no.: Study Number: T3063590/PH-33582

Conducting laboratory and location: Bayer HealthCare AG, PH-PD Toxicology International, Wuppertal (Germany)

Date of study initiation and completion: July 09, 2002 and November 18, 2004

GLP compliance: A statement of compliance with the OECD Principles of Good Laboratory Practice and with the revised German Principles of Good Laboratory Practice (German Chemicals Act (Bundesgesetzblatt Part I, No. 40, issued June 27, 2002) was attached.

QA reports: yes (X) no ()

Drug, lot #, and % purity: J20020528 – Coprecipitate 10%, 101

Methods

Doses Used: 0, 10, 35 and 120 mg/kg/day (vol = 10 ml/kg) once daily beginning from days 6 to 17 p.c.

Species/strain: The SPF-bred Wistar rats (strain – Hsd Cpb:WU, (b) (4))

Number/sex/group: 22 pregnant females/group

Route, formulation, volume, and infusion rate: Oral gavage suspension (prepared in demineralized water blended with PEG (polyethylene glycol) 6000, 10 ml/kg and the suspension made every two weeks.

Satellite groups used for toxicokinetics: 5 females/treated group treated and blood samples collected under light ether anesthesia on day 18 p.c. 1, 3, 7, and 24 hours after administration. The animals were killed on day 18 p.c. and plasma samples stored deep frozen (< - 15°C) till sent for plasma concentrations.

Study design: Selected females were assigned to 4 treatment groups as shown below.

Table 5-1		
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	mg/kg body weight/day	concentration in mg/ml
Group 1 (Control)	0	0.0
Group 2 (Low dose)	10	1.0
Group 3 (Medium dose)	35	3.5
Group 4 (High dose)	120	12.0

On day 20 p.c., the general observations were recorded and the animals were c-sectioned and fetal intrauterine development was observed.

Clinical observations: All females of main study were examined twice/day excepting on weekends and holidays when examined once/day. The satellite groups were also examined twice/day and killed on days 18 p.c. (TK groups) and 20 p.c. (main groups). All findings related to changes in the general conditions of the rats and changes in feces and urine excretion were noted.

Body Weight & Feed and Water Intake of Females: Dams were weighed on day 0 p.c. and then daily from days 6 to 18 p.c. (satellite groups) or from days 6 to 20 p.c. (main groups). The corrected body weight gain calculated by subtracting the weight of the uterus on day 20 p.c. from the body weight gain over the period from day 0 to day 20 p.c. The food consumption was estimated for gestation days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, and 18-20 (in main groups). Water consumption was determined once daily by visual examination of remaining quantities of water in the bottles.

Toxicokinetic Investigations:

Venous blood samples were collected from study females of 10, 35 and 120 mg/kg/day satellite groups under light ether anesthesia on day 17 p.c. 1, 3, 7, and 24 hours after administration. The plasma from the blood samples and the samples were deep frozen (<-15°C) and sent for analysis and the toxicokinetic evaluations estimated.

Necropsy of Females:

On day 18 and 20 p.c., the satellite and main study group animals, respectively were subjected to cesarean section. The main study group uterine contents of females were examined for number of implantations (in females without visible implantation sites after staining of the uterus with a solution of 10 % ammonium sulfide). The uterus and placenta were weighed (individual weight and appearance), number of early resorptions (only implantation site visible) and late resorptions (fetal or placental remnant visible), and dead fetuses (fetuses without signs of life, but without maceration), number of live fetuses, fetal sex and their weights were taken.

External, visceral malformations and minor adverse abdominal, pelvic and thoracic organs abnormalities were evaluated in about half of the fetuses. The remaining half fetuses were used for skeletal abnormalities/ malformations after staining by the modified Dawson technique.

Results

Maternal observations:

Mortality: One female of 120 mg/kg/day dose group was sacrificed as it showed severe body weight loss, reddish vaginal discharge, piloerection, sunken flanks and hypoactivity. A reddish-brown fluid (blood) in the uterus and, pale liver, kidneys and enlarged pale adrenal glands was seen.

Clinical signs: Bloody vaginal discharge and piloerection were seen in 1 and all females belonging to 10 and 120 mg/kg/day groups, respectively. The bleeding in the 10 mg/kg/day group was claimed incidental since it was not present in 35/kg/day group dams. The treatment related effects in 120 mg/kg/day group were reduced food intake during treatment period (10.2, 16.0 and 24.8% on study days 9-12, 12-16 and 15-18 p.c, respectively), and water intake and reduced fecal contents. On necropsy of these animals, an enlarged spleen and pale liver were seen in 1 female of 120 mg/kg/day group.

Toxicokinetics: Rat plasma concentrations of blood samples collected after 1, 3, 7 and 24 h of the dosing were determined on day 17 post coitum (p.c.). AUC (0-24) was increased in a treatment

related manner. The peak concentration reached in about 1-3 hours. The ratio of the trough to peak concentration increased markedly from 0.7 to 5.7 and 29.2% with increasing doses (saturated and/or protracted absorption) as shown in the table below.

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Dose [mg/kg]	10	35	120
AUC(0-24) [mg·h/L]	18.9	77.7	188
AUC(0-24) _{norm} [kg·h/L]	1.89	2.22	1.57
C _{max} [mg/L]	2.55	6.59	12.9
C _{max, norm} [kg/L]	0.255	0.188	0.108
C(24)/C _{max} [%]	0.713	5.70	29.2
t _{max} [h]	3.00	3.48	2.08

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Embryo-Fetal Survival, Fetal Weight and Gravid Uterine Weight: The mean number of implantations, numbers of corpora lutea, preimplantation losses and implantation sites in the treatment group females were similar to control group animals (shown in sponsor's table 6-3).

Table 6-3

Dose [mg/kg bw/day]	0	10	35	120
inseminated females	22	22	22	22
inseminated females evaluated	22	22	22	22
females with implantations	19	22	20	19 ¹
in % of those inseminated	86.4	100.0	90.9	90.5
mean values per female with implantation sites				
corpora lutea	12.5	13.5	13.1	13.5
preimplantation loss	0.9	1.2	1.6	0.8
implantations	11.6	12.3	11.6	12.7

¹ one female with implantation sites was sacrificed in moribund condition on day 16 p.c.; excluded from calculations

Effect of Test Compound on Intrauterine Development

Gestation Rate

The gestation rate (number of females with viable fetuses as a percentage of the number of females with implantations) was not affected by up to the high dose of 120 mg/kg/day BAY 59-7939 (see Table 6-4 below)

Table 6-4

Dose [mg/kg bw/day]	Females with viable fetuses N	in % of females with implantations	Females with total resorption
0	19	100.0	0
10	22	100.0	0
35	20	100.0	0
120	19	100.0	0

The mean values for the parameters of intrauterine development were unaffected by up to 120 mg/kg/day BAY 59-7939 treatment groups (shown below in sponsor table 6-5).

Table 6-5

Dose [mg/kg bw/day]	0	10	35	120
number of females				
with implantations (a)	19	22	20	19
with viable fetuses (b)	19	22	20	19
means per female				
placental weight in g (b)	0.65	0.62	0.67	0.61
number of live fetuses (b)	11.2	11.3	10.9	12.1
postimplantation loss (a/b)	0.4	1.0	0.7	0.6
% males (b)	56.6	48.7	50.1	43.2
fetal weight in g (b)	3.59	3.57	3.70	3.48

Statistically significant increase in incidences of necrotic placental borders in animals of 10, 35 and 120 mg/kg/day groups were seen. An increased number of engorged placentas and, pale colored and necrotic placentas were found in 120 mg/kg/day group animals. The mean placental weight was not affected in 120 mg/kg/day group.

Postimplantation Loss, Number & sex of Fetuses

One female of 10 mg/kg/day group had reddish vaginal discharge and late resorptions of 5 of 10 implantation sites at the cesarean section time and no postimplantation loss in 120 mg/kg/day group. Mean litter size was in the treated groups were not different from control group. The mean percentage of male fetuses/litter was slightly low (43.2%) in 120 mg/kg/day group.

Fetal Observations:

Mean fetal weights were 3.598, 3.578, 3.70 and 3.48 g and, mean litter size were 11.2, 11.3, 10.9, and 12.1 in the 0, 10, 35 and 120 mg/kg/day groups, respectively. There were no treatment or dose related external, skeletal and visceral malformations among viable fetuses up to 120 mg/kg/day treatment group.

Fetal External and Visceral Deviations

No external and visceral deviations (findings other than malformations) in live fetuses (%) or litters were detected. A treatment-related effect for the occurrence the incidence of hemorrhages at different organs (mandible, thyroid, pericardium, abdominal cavity and liver) was seen. These findings were not dose dependent and were in the range of historical control data of sponsor submitted with the document. BAY 59-7939 administered during the period of organogenesis in pregnant rats caused no developmental abnormalities and was not teratogenic. Based on body surface exposure (mg/mm^3), it provides 97 times greater exposure than the proposed clinical dose.

C. Study title: BAY 59-7939 Developmental Toxicity Study in Rabbits after Oral Administration (Study # TO062930/PH-33380/AT01303)

Key findings: Orally administered BAY 59-7939 produced a linear increase in systemic exposure in 0.5 to 2 h on day 20 p.c. The treatment produced an increased incidence in cold ears at all dose levels. The treatment with BAY 59-7939 produced abortions at all doses and doses of 40 and 160 mg/kg/day were maternally lethal. Treatment related

external and visceral deviations or malformations were not seen up to 160 mg/kg/day. BAY 59-7939 was not teratogenic in rabbits of the study. Systemic maternal NOEL and intrauterine development safe dose was 2.5 mg/kg/day in the study and provides 4 times greater exposure in the study animals.

Study no.: TO062930/PH33380/AT-01303

Conducting laboratory and location: BHC-PH-PD Toxicology International, Bayer HealthCare AG, 42096 Wuppatal, Germany.

Date of study initiation and Completion: June 12, 2002 and July 6, 2004

GLP compliance: A statement that the study was conducted in compliance with ICH guideline "Detection of Toxicity to Reproduction for Medicinal Products" (EU 1993, Japan MHLW 1994, US-FDA 1994).

QA reports: yes (X) no ()

Drug, lot #, and % purity: J20020430, 9.5 % BAY 59-7939

Methods

Animal, Strain: Twenty female Himalayan rabbits/group (between 120 and 274 days old) weights ranged from 2104 to 3361 g on day 0 p.c.

Doses: i. Main study group: 0, 2.5, 10, 40, and 160 mg/kg/day BAY 59-7939 Coprecipitate 10 % 100 in demineralized water.

ii. Toxicokinetics group: 3/sex/group animals

The daily oral dose was administered (gavage) as in addition with PEG 6000 from days 6 to 20 p.c. as shown following table (sponsor's table):

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Table 7-1		
	mg/kg body weight/day	concentration in mg/ml
Group 1 (Control)	0	0
Group 2 (Additional low dose)	2.5	0.5
Group 3 (Low dose)	10	2
Group 4 (Medium dose)	40	8
Group 5 (High dose)	160	32

The dose selection was based on a pilot developmental toxicity study in pregnant rabbits (study #T1071003) with 0, 10, 30, 100 and 200 mg/kg/day (dose volume 5 ml/kg) BAY 59-7939 Coprecipitate 10 % 100 from day 6 to day 20 p.c. One animal of 200 mg/kg/day had reduced gestation rate and aborted on day 20 p.c. Body weight loss was seen in all treatment group animals and necropsy showed an enlarged caecum. The dose of 100 mg/kg/day produced post implantation loss and decreased fetal weights. The dose between 100 and 200 mg/kg/day was identified as the high dose for the present study and sponsor selected 160 mg/kg/day as the high dose in the present study.

Parameters Evaluated:

Clinical observations: All females of main study were examined twice/day from days 0-29 p.c. and satellite group from days 0-21. All findings related to changes in the general conditions of the rabbits (appearance, behavior) and changes in amounts of feces and urine excretion were noted.

Body Weight & Feed and Water Intake of Females: The animals were weighed on day 0 p.c. and daily from days 6 to 21 p.c. (satellite groups) or from days 6 to 29 p.c. (main groups). The food consumption was estimated for gestation Days 0-3, 3 - 6, 6 -9, 9-12, 12-15, 15-18, 18-20, 20-21, 21-24, 24-27, and 27-29 p.c. for the main groups, and days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 20 -21 p.c. for the satellite groups. Water consumption was determined once daily by visual examination of remaining quantities of water in the bottles.

Toxicokinetic Investigations:

Venous blood samples were collected from study females of 2.5, 10 and 40 mg/kg/day satellite groups under light ether anesthesia on day 6 and 20 p.c. at 0.5, 1, 2, 4, 6 and 24 hours after administration. Venous blood samples (extremity veins) were collected from three females of the 160 mg/kg/day main group on day 20 p.c. at 30 minutes as well as 1, 2, 4, 6, and 24 h after administration, because three females were replaced in satellite group. The plasma samples were deep frozen (< - 15°C) and sent for analysis and the toxicokinetic evaluations.

Necropsy of Females:

The females of main and satellite group were dissected on day 29 and 21 p.c., respectively, and uterine contents examined for number of implantations (in females without visible implantation sites after staining of the uterus with a solution of 10 % ammonium sulfide). The uterus and placenta were weighed (individual weight and appearance), number of early (only implantation site visible) and late resorptions (fetal or placental remnant visible), and dead fetuses (fetuses without signs of life, but without maceration), number of live fetuses, fetal sex and their weights were determined. External, visceral malformations and minor adverse abdominal, pelvic and thoracic organs abnormalities were evaluated in about half of the fetuses. The remaining half fetuses were used for skeletal abnormalities/ malformations after staining by the modified Dawson technique.

Results:

A. Maternal Dam Data:

The treatment related incidences of cold ears were increased in 11, 23, 15, and 23 animals in the 0, 2.5, 10, 40 and 160 mg/kg/day groups, respectively, from day 6 p.c. Daily water intake and urine excretion were decreased in animals of 40 and 160 mg/kg/day treatment groups

Mortality: Two of 24 females in each of 40 and 160 mg/kg/day groups were found dead.

Body Weight and Food consumption Changes:

A severe reduction in the body weight gain in animals of 10, 40 and 160 mg/kg/day groups was seen from days 6-20 p.c. as shown below in the Table 8-2.

Table 8-2

Dose (mg/kg b.w./day)	0	2.5	10	40	160
absolute body weight gain (g) days 6 - 20 p.c.	46.5	102.1	29.1	9.9	11.8
absolute body weight gain (g) days 0 - 29 p.c.	206.6	316.6	151.6	157.2	144.2
corrected body weight gain (g) days 0 - 29 p.c.	- 146.0	- 62.3	- 197.7	- 168.3	- 119.7

Fetal Observations & Evaluation:

A marginal reduction was seen in the gestation rate in the 2.5 mg/kg/day group and, total resorption was seen in 1, 1, 2 and 2 females of the 2.5, 10, 40 and 160 mg/kg/day groups, respectively, on days 18 to 26 p.c. One, 2 and 2 females in each of 10, 40 and 160 mg/kg/day groups, respectively, aborted between day 18 and 26 p.c. The females that aborted or all females in these groups showed decrease in feed intakes and body weight loss since beginning of treatment on day 6 p.c. The females which had total resorptions showed slight to marked body weight loss during treatment (-40 g to -194 g), cold ears, and reddish excretion.

Gross Pathology Changes:

Enlarged and gaseous contents in caecum was observed in 4 and 1 females of the 40 and 160 mg/kg/day groups, respectively and only enlarged caecum was in females of the 2.5 and 10 mg/kg/day groups. Pale liver, enlarged gall bladder, hardened fatty tissue, mottled and smaller in size spleen, and pale kidneys were the other observation in the 160 mg/kg/day group.

General Reproduction Data:

The fertility data including mated females and, number of implantations, corpora lutea and preimplantation losses were similar in treatment group animals compared to the control group animals (as shown in the following table scanned from sponsor's submission). Three and 2 females of 40 and 160 mg/kg/day groups, respectively, were withdrawn and excluded from the study.

Table 8-3

Dose (mg/kg b.w./day)	0	2.5	10	40	160
mated females	20	20	20	20	12
mated females evaluated	20	20	20	18 ⁺	9 ⁺⁺
females with implantations	20	20	20	18	9
in % of those mated	100.0	100.0	100.0	100.0	100.0
mean values (without females displaying abortions) per female with implantation sites					
corpora lutea	8.0	8.3	7.5	8.0	8.9
preimplantation loss	1.4	0.9	0.5	1.0	1.1
implantations	6.7	7.3	7.0	7.0	7.7

+ two females with death were excluded

++ two females with death were excluded, and one female was excluded due to withdrawal of this dose group

The total resorption was observed in each dose group animals of 2.5, 10, 40 and 160 mg/kg/day and, 1, 2 and 2 females of 10, 40 and 160 mg/kg/day groups aborted. Thus, BAY 59-7939 treatment produced abortions in rabbits from 10 mg/kg/day dose. This should be described in the label. Additionally, increased incidences of coarse grained placentas were noted at 10 mg/kg/day and above study doses.

Table 8-4

Dose mg/kg b.w./day	Females with			
	viaible fetuses on day 29 p.c. n	in % of females with implantations	abortion n	total resorption n
0	20	100.0	0	0
2.5	19	95.0	0	1
10	18	90.0	1	1
40	15	83.3	2	1
160	6	66.7	2	1

Appearance and Weight of Placentas

The increased incidences of course/rough grained placentas were from the 10 mg/kg/day and higher dose treatment groups. Significant increased number of necrotic placentas was reported in 40 and 160 mg/kg/day group animals. The placental weights were decreased in females of 40 and 160 mg/kg/day groups. Therefore, the low dose 10 mg/kg/day produced the changes in external appearance of placentas and increased incidence of coarse grained placentas.

Postimplantation Loss, Number of Fetuses

There was an increase in the mean postimplantation loss in females with viable fetuses at cesarean section in 10, 40 and 160 mg/kg/day treated groups but a statistical significant increase was found in 160 mg/kg/day group animals. The numbers of late resorptions were the consequence of the increased postimplantation loss. The mean number of fetuses was slightly decreased in the 160 mg/kg/day group.

Sex/Weight of Fetuses:

BAY 59-7939 treatment affected the fetal growth and the fetuses from 40 and 160 mg/kg/day treatment groups dams weighed significantly lesser than controls (lower range of sponsor's historical control data). Thus, the fetal growth was affected from 40 mg/kg (slightly) group and the NOAEL was 10 mg/kg/day.

Fetal Malformations:

The treatment with the compound during organogenesis did not produce external and visceral deviations up to 160 mg/kg/day. The retardation of the vertebral ossifications and infusion of sternbrae (variation) was reported in 40 and 160 mg/kg/day groups. The total numbers of fetuses or litters with malformations was not increased in a dose related manner up to 40 mg/kg/day group. The incidence of fused caudal certebra bodies at the 40 mg/kg dose were above the historical control data (up to 2.02 %). The incidences of major ventricular septal defect of the heart with/without enlarged pulmonary artery was found in 1 litter of 160 mg/kg/day group, that was 6.6 % and it was greater than the incidences of up to 1.85 % in historical control data.

Toxicokinetics:

Plasma concentrations of BAY 59-7939 were determined after oral administration to pregnant rabbits on day 6 and day 20 p.c. Blood samples were collected at 0.5, 1, 2, 4, 7 and 24 h after administration. The exposure on day 20 (means, n = 3) was as follows:

		Dose [mg/kg]			
		2.5	10	40	160*
AUC(0-24)	[mg·h/L]	0.736	2.78	13.1	23.9
AUC(0-24) _{norm}	[kg·h/L]	0.294	0.278	0.329	0.150
C _{max}	[mg/L]	0.142	0.294	0.881	1.54
C _{max, norm}	[kg/L]	0.0568	0.0294	0.0220	0.00964
C(24)/C _{max}	[%]	5.36	12.3	46.2	59.2
t _{max}	[h]	0.794	2.00	1.00	1.00
R _{A1}	[%]	79.1	66.4	68.7	n.c.
R _{A2}	[%]	n.c.	328	283	n.c.
R _{A3}	[%]	105	128	132	n.c.

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n.c. = not calculated

* = data for this dose group only available from Day 20

R_{A1} = C_{max, Day 20} / C_{max, Day 6}R_{A2} = C_{(24), Day 20} / C_{(24), Day 6}R_{A3} = AUC_{(0-24), Day 20} / AUC_{(0-24), Day 6}

On day 20 p.c., a linear increase in systemic exposure (AUC_{0-24hr}) was seen in study animals. The maximum concentrations were observed around 0.5 to 2 h on day 20 p.c. Data from the 160 mg/kg/day dose group were only available on day 20 p.c.

In summary, BAY 59-7939 administration produced a linear increase in rabbit plasma concentration (AUC_{0-24hr}) in 0.5 to 2 h on day 20 p.c. Increased incidences of abortions were observed at all dose levels. The doses of 40 and 160 mg/kg/day were maternally lethal. Treatment related external and visceral deviations or malformations were not seen up to 160 mg/kg/day. BAY 59-7939 was not teratogenic in rabbits of the study. Systemic maternal NOEL and intrauterine development safe dose was 2.5 mg/kg/day in the study and provides an exposure which was 4 times the exposure of human dose.

D. Study for Effects on Pre- and Postnatal Development in Rats Including Maternal Function after Oral Administration (Study No. : T9062957)

Key study findings: Wistar rats were treated BAY 59-7939 Coprecipitate 10 % 100 at oral gavage doses of 0, 2.5, 10, and 40 mg/kg/day in pregnant females produced overt pharmacologic effect of generalized tissue bleeding in 10 and 40 mg/kg/day treatment group animals and the 40 mg/kg/day dose was maternally lethal. Still birth and empty stomach/intestines were observed in pups born to 10 and 40 mg/kg/day treated groups dams. The postnatal developmental adverse effects observed in pups were hypoactivity, pale skin, cold to touch surface, and not detectable milk spots. The identified NOAEL for maternal effects (F0) and, pre- and postnatal development of the F1 generation was 2.5 mg/kg/day and provides 4 fold safety margin for the proposed human dose).

Study no.: T9062957/PH34608

Conducting laboratory and location:

Date of study initiation & completion: January 14, 2004 & September 27, 2006

GLP compliance: The study was conducted in compliance with ICH guideline "Detection of Toxicity to Reproduction for Medicinal Products" (EU 1993, Japan MHLW 1994, US-FDA 1994).

QA reports: yes (X) no ()

Drug, lot #, and % purity: #030723-100 BAY 59-7939 Coprecipitate 10 % 100

Methods

Doses: 0, 2.5, 10, and 40 mg/kg/day BAY 59-7939 Coprecipitate 10 % 100 formulated in 20 % Solutol HS 15 and 80 % demineralized water in addition with PEG 6000 (volume = 10 ml/kg)

Species/strain: SPF-bred Wistar rats (strain Hsd Cpb:WU)

Number/sex/group: **F0** - 25/inseminated females/group; **F1** - one male and one female per litter/study treatment group to test the fertility of the F1 generation

Route, formulation, volume: Oral gavage

Study design: The dams treated by oral gavage once daily on Day 6 pc through Day 20 pp with an aim to determine the effects of BAY 59-7939 on pregnancy, parturition, lactation and on pre- and postnatal survival and also on neurobehavioral growth and, the development of reproductive parameters of F1 and F2 generations. The females were allowed to deliver and rear their offspring up to day 21 p.p. During, at the end or after the rearing period the physical and functional development of the F1 pups was monitored. One F1 female/litter were reared up to maturity for reproductive and fertility testing.

Postweaning Evaluations

F1 Pups were tested for auditory startle reflex (postnatal day 27 to 31), passive avoidance test for learning/retention once between postnatal Day 40 and 50 using an automated system and, motor activity (postnatal day 54 to 61).

Fertility, Reproductive performance and parturition observations of F1 rats:

The estrous cycle of F1 females was determined from postnatal day 64 to 73 (beginning on postnatal day 73 to 80) until mated. Mated females (F1) were allowed to deliver their F2 litters. The dams were weighed on day 0, 7, 14 and 21 pc and day 1 and 7 pp and, checked frequently between 0800 and 1800 hours to record the date and time of parturition. Number of pups, the day parturition (pp day 0) were noted and pups counted and weighed on day 0, 7, 14 and 21 pc and day 1 and 7 pp. The test to determine 'stillborn'/'born alive' pup was performed. F1 females were euthanized on post natal 23 and uterine contents examined for implantations (stained with ammonium sulfide if apparently not pregnant), resorptions and live and dead fetuses were counted.

F2 pup evaluations and termination: The pups were examined by general observation, number, weights and sex determined. The pups were weighed on postnatal days 1 and post-partum day 7. The cause of death (still born/born dead) of F2 was determined and surviving F2 pups were euthanized by carbon dioxide asphyxiation on Day 7 pp and discarded.

Results:

F0 Dams:

General Observations: The fertility index of study groups F0 dams up to 40 mg/kg/day was comparable to control and in the range of historical control data. But the rearing index of dams treated with 40 mg/kg/day group was decreased. The gross necropsy in one 40 mg/kg/day female revealed a cervix tightly filled with greenish muddy fluid and 14 dead fetuses in the

uterus. An additional female of 40 mg/kg/day group showed a preterm delivery and all pups died. In 40 mg/kg/day group females, treatment related hypoactivity, high stepping gait, piloerection, cold skin, pale eyes, and salivation were noted. Increased incidences of light colored feces during gestation (0-21 p.c.) period were reported. During the lactation period, discolored feces were seen in 10 and 40 mg/kg/day groups.

Mortality: Seven of 25 females of 40 mg/kg/day group were sacrificed in moribund condition. Salivation, hypoactivity, high stepping gait, piloerection, cold skin, reddish vaginal discharge, preterm delivery (female no. 51, only), pale eyes, and salivation were observed. Gross necropsy of the dams showed a pale liver and spleen. All of the pups of these animals died.

Body weight/Food consumption: A 16.8% reduction in the body weight was reported in the females of 40 mg/kg/day treatment group during the treatment period between days 6-20 p.c. The body weight reduction was 20.6% during the gestation period (days 0-20 p.c.). The food consumption was reduced significantly in animals of 40 mg/kg/day group as shown below in the table:

Table 6-1: Mean Feed Intake of the F0 Females

Dose [mg/kg bw/day]	0	2.5	10	40
Mean feed consumption during gestation [g/female/day]				
days 0 - 6 p.c.	21.4	21.0	21.5	21.0
days 6 - 11 p.c.	21.7	21.7	22.1	19.9*
days 11 - 16 p.c.	23.2	23.1	23.2	21.0**
days 16 - 20 p.c.	26.6	25.4	26.1	20.9**
Mean feed consumption during lactation [g/female/day]				
days 0 - 7 p.p.	42.4	40.5	41.6	40.1
days 7 - 14 p.p.	65.5	62.3	61.7	61.6

Statistically significant difference to control * = $p < 0.05$

Statistically significant difference to control ** = $p < 0.01$

C-Section Observations of (F0) rats: Placentas with greenish/yellowish borders were seen and dark red mass (clotted blood) most likely due to an impaired delivery in lung and heart was reported in pups born to 40 mg/kg/day treatment group animals. A treatment related enlarged spleen was noted in two females of the 10 mg/kg/day.

Table 6-3: Fertility, Gestation, and Rearing Indices of the F0 Females

Dose [mg/kg bw/day]	females used		Fertility index females with implantations		Gestation index females which delivered		Rearing index females which reared pups	
	n	n	% of those used	n	% of those with implantations	n	% of those which delivered	
0	25	19	76.0	18	94.7	18	100.0	
2.5	25	21	84.0	21	100.0	21	100.0	
10	25	23	92.0	23	100.0	23	100.0	
40	25	24	96.0	22	91.7	17	77.3	

The gestation index was similar in treated and control group animals but the rearing index was decreased at the 40 mg/kg/day group. Gestation period was unaffected by BAY 59-7939 but impaired delivery was noted in 2 of 24 females of the 40 mg/kg/day group. One of these animals was killed in moribund condition and the other animal had a preterm delivery and all pups died thereafter. The viability index (up to day 4 p.p.) was

statistically significantly decreased in pups of 40 mg/kg doses. The lactation index (up to day 21 p.p.) was unaffected by treatment up to 40 mg/kg.

F1 Generation Physical & Behavioral Development Evaluation:

A statistically significant increase in pup mortality (including pups found dead, missing, sacrificed in moribund condition, and cannibalized) occurred at the 40 mg/kg level from days 0-4 p.p. Increased incidences of hypoactivity, pale skin, cold to touch surface in 40 mg/kg/day group pups was reported. An increased incidence of pale skin was also seen in pups of 10 mg/kg/day group. At necropsy on day 42 p.p. a treatment related pale liver and increased incidences of pups with no milk spots of 40 mg/kg group animals was reported. The reflex and behavioral tests showed adverse toxic effects on sucking reflexes of pups in 40 mg/kg/day group and no effect on sensory functions up to 40 mg/kg/day dose. The necropsy data of F1 pups is shown in the following table (sponsor's table on page 121 of eTCD). On day 42 p.p., an increase in the incidences of pups with empty stomach and intestines at 40 mg/kg/day and, stillborn pups occurred at 10 mg/kg/day or higher dose.

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(F0 GENERATION)

SUMMARY OF PUP NECROPSY OBSERVATIONS

BAY 59-7939

		0 MG/KG	2.5 MG/KG	10 MG/KG	40 MG/KG
Litters Evaluated	N	18	21	23	21
Pups Evaluated	N	167	195	199	168
Live	N	167	195	199	168
Stillborn	N	0	0	0	0
LIVER					
LIVER PALE					
Pup Incidence	N	0 f	0	0	1
	%	0.0	0.0	0.0	0.6
	p-value	0.342			
Litter Incidence	N	0 f	0	0	1
	%	0.0	0.0	0.0	4.8
	p-value	0.393			
Affected Pups/Litter	MEAN%	0.00 k	0.00	0.00	0.68
	S.D.	0.000	0.000	0.000	3.117
	p-value	0.399			
LIVER BLACKISH DISCOLORED					
Pup Incidence	N	0 f	2	4	3
	%	0.0	1.0	2.0	1.8
	p-value	0.313			
Litter Incidence	N	0 f	1	2	1
	%	0.0	4.8	8.7	4.8
	p-value	0.645			
Affected Pups/Litter	MEAN%	0.00 k	0.79	1.93	2.04
	S.D.	0.000	3.637	7.226	9.352
	p-value	0.658			
STOMACH					
STOMACH EMPTY					
Pup Incidence	N	0 f	0	0	16**
	%	0.0	0.0	0.0	9.5
	p-value	0.000			0.000
Litter Incidence	N	0 f	0	0	2
	%	0.0	0.0	0.0	9.5
	p-value	0.109			
Affected Pups/Litter	MEAN%	0.00 k	0.00	0.00	7.01
	S.D.	0.000	0.000	0.000	22.866
	p-value	0.113			

Statistical key: f=Fisher's Exact k=Kruskal-Wallis ** = p<0.01

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The clinical findings of head tilted, respiratory sounds, piloerection, wound, hematoma, blackish discolored or missing tip of tail, tail bent, restricted motility of right forelimb)

were observed in all treated group pups. One pup with tilted neck was also seen in the control group. Increased pup mortality occurred in 40 mg/kg/day treated dams in the study.

F1 Generation Fertility & Reproductive Development Evaluation

The feed and water consumption, excretions, body weights of the F1 generation after weaning, and gross pathological findings showed no treatment related effects in F1 males and females up to 40 mg/kg/day dose. The insemination, fertility, and gestation indices of the F1 generation as well as time to insemination, number of implantation sites, duration of gestation, litter size (number of viable pups) and number of stillborn pups, sex ratio of F2 pups, clinical findings including malformations, and body weights of the F2 pups were also unaffected by treatment with BAY 59-7939 at doses up to and including 40 mg/kg. But an increased incidence of stillborn F2 pups and a slightly increased incidence of pups with pale skin occurred at the 10 and 40 mg/kg/day group. An increased % mortality occurred among F2 of 40 mg/kg/day group from days 0-4 p.p. The other effects of increased incidences of pups with hypoactivity, pale skin, cold to touch surface, and not detectable milk spots were also seen in these pups.

The number of viable pups/litter were similar between the control and was marginally decreased in 10 and 40 mg/kg/day groups due to the increased number of stillborn and deaths of pups in 40 mg/kg/day group. After litter reduction on day 4 p.p. a treatment related effect on litter size was not seen up to 40 mg/kg/day. The litter size of F1 generation is shown below:

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Table 6-8: Mean Litter Sizes of the F1 Generation

Dose [mg/kg bw/day]	0	2.5	10	40
Day p.p.	Number of viable pups (mean values, male and female pups combined)			
0	12.39	11.71	10.91	11.00
4 before reduction	11.83	11.62	10.48	10.59
4 after reduction	7.94	7.67	7.52	7.53
7	7.94	7.67	7.52	7.47
14	7.94	7.57	7.48	7.41
21	7.94	7.52	7.39	7.41

The lactation index (up to day 21 p.p.), sex ratio, mean body weight of F1 Pups during of rearing was similar in treated group animals compared to controls.

Table 6-12: Physical Development of the F1 Pups

Parameter of physical development	0 Days after birth	Dose [mg/kg bw/day]		
		2.5	10	40
Pinnae detachment	2.28	2.44	2.24	2.28
Development of fur	9.49	9.47	9.72	9.50
Incisor eruption	9.48	9.62	9.60	9.50
Eyes opened	16.32	16.40	16.50	16.10
Normal gait	16.61	16.63	16.93	16.37
Balanopreputial separation	46.0	46.0	46.7	46.1
Body weight at balanopreputial separation [g]	219.8	223.5	230.2	215.2
Vaginal opening	32.8	33.2	33.2	33.5
Body weight at vaginal opening [g]	103.5	106.9	107.9	106.5

Reflex and Behavioral Tests on the F1 Pups Reflex Testing

The surface righting reflex, negative geotaxis, hearing test and pupillary reflex tests showed no relevant drug related aberration/change in these tests.

Table 6-13: Reflex Tests of the F1 Pups

	Dose [mg/kg bw/day]			
	0	2.5	10	40
	Tests for reflexes and sensory functions			
Surface righting (days p.p.)	1.03	1.03	1.04	1.02
Negative geotaxis (days p.p.)	5.15	5.13	5.14	5.04
Hearing test (positive in %)	100.00	100.00	100.00	100.00
Pupillary reflex (positive in %)	100.00	100.00	100.00	100.00

Motor Activity & Water-M-Maze Testing

The results of the motor activity testing with the F1 animals showed no treatment related difference between control and treatment group F2 animals. No treatment related adverse development motor effects were seen in F2 pups.

Table 6-13: Reflex Tests of the F1 Pups

	Dose [mg/kg bw/day]			
	0	2.5	10	40
	Tests for reflexes and sensory functions			
Surface righting (days p.p.)	1.03	1.03	1.04	1.02
Negative geotaxis (days p.p.)	5.15	5.13	5.14	5.04
Hearing test (positive in %)	100.00	100.00	100.00	100.00
Pupillary reflex (positive in %)	100.00	100.00	100.00	100.00

Gross Pathological Findings in the F1 Pups up to the End of Rearing

The gross pathological necropsy findings of the F1 pups up to day 42 p.p. were autolytic pups, reduced eye ball size or missing, spleen blackish discolored, liver yellowish or blackish discolored, stomach distended or tightly filled with feed paste, dilation of renal pelvis, contents of intestines blackish discolored, testes missing or reduced in size, abdominal cavity contains dark red to blackish mass, and shortening of skull bones after skeletal staining. A significantly increased incidences of pups with empty stomach and intestines was observed in animals included in the 40 mg/kg/day group.

Pre- and postnatal Development

The gestation duration and index in the treated and control group was unaffected by 40 mg/kg/day BAY 59-7939. The rearing index was slightly decreased at the 40 mg/kg/day dose level. The parturition was affected in two females of the 40 mg/kg group which were sacrificed in moribund condition and these had impaired delivery. One female of 40 mg/kg/day group had a preterm delivery with all pups died. Increased incidences of pups without milk spots and stillborn pups and, an increased incidence of pups with pale skin occurred at the 10 mg/kg/day dose level, for which a treatment related effect cannot be excluded. Increased pup mortality occurred at the 40 mg/kg/day group from days 0-4 p.p. together with increased incidences of pups with hypoactivity, pale skin, cold to touch surface, and not detectable milk spots. The increased pup mortality was in a dose related manner during the study. There was decreased number of viable pups/litter in dams of 10 and 40 mg/kg/day groups. An increased number of stillborn pups were born to 40 mg/kg/day group dams. A treatment related increased incidence of empty stomach and intestines was noted in pups born to 40 mg/kg treated dams and these showed pale liver which suggested possible liver toxicity. Thus, treatment increased the incidences of developmental adverse effect on sucking reflex in pups.

Development of the F1 Generation after Weaning:

Appearance, Behavior, and Mortality:

One female and 1 male of 2.5 and 40 mg/kg/day groups were killed on day 108 p.p. and day 0 after delivery. Treatment related effects on feed and water consumption were not evident in males and females of the F1 generation up to 40 mg/kg/day group. Fecal and urine excretion were not affected by the compound.

Gross Pathological Findings

One F1 male had a left testis lying in a pocket of the abdominal wall, and an additional F1 male of the 40 mg/kg dose group had dilation of the right renal pelvis. The incidence was within the historical data sent by sponsor. Thus, no treatment related gross pathological findings occurred in the F1 males and females. No treatment related change in the mean values for feed consumption during pre-mating and gestation (females, only) period was seen.

Fertility Testing of F1 Generation (Insemination, Fertility, and Gestation Indices):

The insemination index [% = Number of females inseminated x 100 ÷ Number of females paired] were similar in the treated and control group animals and shown below.

Table 6-15: Insemination, Fertility, and Gestation Indices of the F1 Females

Dose [mg/kg bw/day]	Used [n]	Number of F1 Females					
		Inseminated [n]	% of those mated	with I.S. [n]	% of those inseminated	which delivered [n]	% of those with I.S. / used
0	24	23	95.8	19	82.6	19	100.0
2.5	24	24	100.0	23	95.8	22	95.7
10	24	23	95.8	21	91.3	21	100.0
40	24	24	100.0	23	95.8	23	100.0

I.S. = implantation sites

The insemination, fertility and gestation days were not affected in F1 generation rats. The time of insemination in the pups of treated dams showed that the insemination rate and other fertility data in treated and control dams were similar.

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Table 6-17: Mean Values of the Parameters of Intrauterine Development of the F1 Females, Weights and Sex ratio of F2 Pups

Dose [mg/kg bw/day]	0	2.5	10	40
	Mean value per female			
Number of implantation sites	12.05	13.14	13.00	12.48
Duration of gestation [days]	22.06	21.95	22.05	22.05
Number of living pups	11.05	12.57	11.76	11.91
Pups stillborn [% per group]	1.9	1.5	0.8	1.8
Pups found dead [N]	0	0	2 (1)	0
Weight of pups [g]	6.05	5.93	6.07	6.07
Sex ratio [%]	50.83	51.19	53.99	47.25
male pups : total pups				

(1) number of litters affected

The number of implantations, duration of gestation, # of living and dead F2 fetuses (litter size), and sex-ratio of F2 fetuses of the treated groups were not affected by BAY 59-7939 treatment. There were no changes in clinical findings of F2 pups. The body weight/growth of F2 fetuses was similar in control and treated groups. Other intrauterine development parameters are given in table above.

In conclusion, BAY 59-7939 Coprecipitate 10 % 100 treatment in pregnant dams produced maternal preterm delivery and, increased incidences of still birth, empty stomach and intestines in pups of 10 and 40 mg/kg/day groups treated dams. The developmental adverse effects of hypoactivity, pale skin, cold to touch surface, deficient sucking developmental reflex (no detectable milk spots in pups) were reported in F1 pups of dams of 10 and 40 mg/kg/day groups. The identified NOEL for the physical development and reflex and behavioral testing of the F1 generation after weaning was 2.5 mg/kg/day. The NOAEL for maternal effects (FO) and, pre- and postnatal development of the F1 generation was also 2.5 mg/kg/day and based on body surface area it was 2 times greater exposure than the proposed human dose.

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this page is the manifestation of the electronic signature.**

/s/

Marcus Cato
3/10/2009 07:12:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 9, 2009. The purpose of the meeting was to discuss the integrated analyses of symptomatic Venous thromboembolism (VTE) and death in RECORD 1-4.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: March 9, 2009
TIME: 3:30 PM - 4:00 PM EST
LOCATION: CDER WO 2327 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Statistical,

MEETING CHAIR: Dr. Jyoti Zalkikar

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Marcus Cato, M.B.A., Regulatory Health Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS VII

Chava Zibman, Ph.D., Statistical Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer

Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

JOHNSON & JOHNSON

Leonard Oppenheimer, PhD. Statistical Sciences

John Zhang PhD. Statistical Sciences

Juliana Ianus, Ph.D. Statistical Sciences

Yingshan You, Data Programming

BAYER

Torsten Westermeier PhD Therapeutic Area Expert Statistician

Alice Benson PhD, Principal Statistician, Global Clinical Statistics,

Martin Homering PhD, Statistical Sciences

Patricia Hagerty Statistical Analyst - Global Statistical Programming

BACKGROUND:

In a teleconference on March 6, 2009, FDA inquired how J&J accounted for the different treatment durations in their pooled analysis of RECORD studies. The sponsor and FDA statisticians agreed to meet the week starting March 9, 2009, to discuss the pooled analysis in greater detail. On March 9, 2009, J&J submitted background information (see attached).

MEETING OBJECTIVES:

To discuss the integrated analyses of symptomatic VTE and death in RECORD 1-4.

DISCUSSION POINTS:

FDA stated it had reviewed the background information submitted by J&J. FDA stated it was preparing an information request regarding the integrated analysis and would send it soon. FDA has not been able to reproduce the data sets and would like to perform some analyses. J&J offered to perform analyses at FDA request. FDA stated it would like to perform them internally and get back to J&J. FDA requested a quick turn around on the information request.

DECISIONS (AGREEMENTS) REACHED:

- FDA would send an information request regarding the integrated analysis
- J&J would provide a quick turnaround on the information request

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- FDA to send an information request regarding the integrated analysis

ATTACHMENTS/HANDOUTS:

- J&J submitted background information



NDA 22-406 XARELTO™ (rivaroxaban)
Telecon March 9th to discuss Statistical Review

Summary of Rationale and Background of Integrated Analyses of Symptomatic VTE and death in RECORD 1-4

Integrated analyses of the RECORD studies are important for the standard reasons:

- to obtain more precise estimates of treatment differences
- to be able to explore important subgroups
- to be able to assess the effects of lower frequency outcomes

Prior to unblinding any of the RECORD studies both symptomatic VTE/death and bleeding was pre-specified as important endpoints to consider in a pooled analysis because of their clinical relevance in studying an anti-coagulant. Also it was realized that because of their low frequency we might not be able to fully elucidate treatment differences based on individual studies.

Although there were some differences among the four RECORD studies, there were many more similarities including the following:

- similar study designs and randomization processes
- similar rivaroxaban dose of 10 mg QD and start time
- similar CRFs/information collected in a similar manner
- similar inclusion/exclusion criteria
- similar visit schedules
- similar efficacy/safety definitions
- same central labs
- similar ascertainment procedures
- same central and blinded adjudication committees

A SAP for the integrated analysis of RECORD 1, 2 and 3 was prepared and finalized before the unblinding of any of the 4 RECORD studies. The composite of symptomatic

VTE (DVT, PE) or death from all causes was pre-specified as the primary efficacy endpoint for the integrated analysis from RECORD 1, 2 and 3. An updated analysis plan that described the analysis of the pooled RECORD 1-4 studies was finalized before the unblinding of RECORD 4 ([Section 16.1, PH-35415](#) including the original plan).

The primary endpoint for the integrated analysis that included pooled data from the 4 RECORD studies or the separately pooled THR and TKR studies was the composite of symptomatic VTE (DVT, PE) or death from all causes during the double-blind treatment period in subjects valid for safety analysis. This endpoint was the primary objective of the pooled analysis since these events are clinically important and also because the assessment of these events was possible in all subjects regardless of the availability of an adequate venographic assessment. Other supportive endpoints examined included symptomatic VTE, PE, death, and the composite of PE or death. It should be noted that the composite of PE or death was not prespecified in the integrated SAP.

Since symptomatic VTE events could occur at any time during the study, the time to first event analysis was performed for detecting the treatment effect. Studies with different durations could be pooled for time to event analyses when subjects without events were censored at the end of either the treatment phase or the study. A Cox regression model was performed with study and treatment group as covariates to determine the hazard ratio and its 95% CI (rivaroxaban versus enoxaparin). The relative risk reduction was calculated as $100\% \times (1 - \text{hazard ratio})$. To assess study heterogeneity, an interaction test was performed for testing differential treatment effects across the 4 RECORD studies based on an asymptotic 2-sided p value from a Cox regression model with terms for treatment group, study, and a study by treatment interaction. The assumption for proportionality of the Cox model was also assessed. A Kaplan-Meier analysis was also done for accrued events over time for each treatment group. Similar analyses were conducted for individual studies and for components of the primary endpoint. The original RECORD 1-3 analysis for the European Union regulatory filing was to be based on absolute differences but this was changed to an odds ratio approach due to heterogeneity on the risk difference scale. The details of the planned analyses can be found in the Statistical Analysis Plan ([Section 16.1, PH-35415](#)).

The primary analysis for the pooled RECORD studies (1, 2, 3 and 4) was based on the “total duration pool”, which was defined as the double-blind standard-of-care study medication phase (active and placebo control treatment) from all 4 RECORD studies. The “treatment phase” was defined as the time from the day of surgery (Day 1) until Day 42 (Day 36+6) for RECORD 1 and 2 and until Day 17 (Day 13+4) for RECORD 3 and 4. Supportive analyses were also performed for the following:

- “Pool until Day 12±2”, which included events occurring during the double-blind treatment period until Day 12±2 for the pooled RECORD 1-4
- “Active control pool”, which included events occurring during the active treatment periods for each study, excluding the placebo treatment period following enoxaparin treatment in RECORD 2 for the pooled RECORD 1-4
- Entire study period (treatment phase plus follow-up phase) for the pooled RECORD 1-4. The “follow-up phase” was pre-specified in the protocols as 30-35 days after the end of double-blind treatment, i.e. the time period after Day 42 in

RECORD 1 and 2, and after Day 17 in RECORD 3 and 4. All events occurring after Day 42/17 were considered in the Cox model

- Pooled RECORD 1-2 (THR) studies and pooled RECORD 3-4 (TKR) studies separately based on the same duration of the study period.

These results of the symptomatic VTE/death endpoint for the various pools for the pooled RECORD 1-4, which are summarized in the below table, were similar across the 4 analysis pools. The results of the pooled RECORD 1-2 (THR) studies were also similar to the pooled RECORD 3-4 (TKR) studies; these results are included in tabular and graphical format in Section 3.4.11.1 of the ISE.

**Composite of Symptomatic VTE or Death
(Subjects Valid for Safety Analysis in the Pooled RECORD 1-4 Studies)**

Analysis Pool	Rivaroxaban	Enoxaparin	ARD (95% CI)	HR (95% CI)
	n (%) N=6183	n (%) N=6200		
Total Duration – treatment phase	35 (0.57)	82 (1.32)	-0.76% (-1.10, -0.42)	0.42 (0.29, 0.63)
Total Duration – treatment plus follow-up phase	38 (0.61)	79 (1.27)	Not reported	0.48 (0.32, 0.70)
Treatment Phase until Day 12 +-2	29 (0.47)	60 (0.97)	-0.50% (-0.80, -0.20)	0.48 (0.31, 0.75)
Active Control Phase	32 (0.52)	67 (1.08)	-0.56% (-0.88, -0.25)	0.48 (0.31, 0.73)

Abbreviations: ARD=absolute risk difference; CI=confidence interval; DVT=deep vein thrombosis; HR=hazard ratio; PE=pulmonary embolism; VTE=venous thromboembolism

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/s/

Marcus Cato

4/1/2009 09:09:34 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 6, 2009. The purpose of the meeting was to discuss the upcoming advisory committee (AC) meeting.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: March 6, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer
Diane Leaman, Safety Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS VII

Chava Zibman, Ph.D., Statistical Reviewer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

EXTERNAL ATTENDEES:**JOHNSON & JOHNSON**

Peter DiBattiste	M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters	M.D. Franchise Medical Leader
Lloyd Haskell	M.D. VP, CDTL
Paul Burton	M.D. Ph.D. F.A.C.C., Sr. Medical Director, Clinical Leader
Leonard Oppenheimer	Ph.D. Statistical Sciences
Deb Karvois	Project Scientist
Mehul Desai	M.D. Clinical
Jesse A. Berlin	ScD, VP, Epidemiology
G.K. (Dina) Anand	M.D., Post-Marketing Safety Franchise Leader
Yingshan You	Data Programming
Andrea Masciale	FDA Liaison Office, Regulatory Affairs
Steve Miller	VP, Global Regulatory Affairs
Michael Kronig	M.D., VP Cardiovascular Regulatory Affairs
Sanjay Jalota	MRPharmS, Regulatory Global Regulatory Lead
Donald L. Heald	Ph.D. VP and Global Head of Clinical PK
Achiel Van Peer	Ph.D. Global Sr. Scientific Leader Clinical Pharmacology
An Thyssen	Ph.D. Clinpharm Leader Rivaroxaban
Harry Flanagan	DO, Post-Marketing Safety Expert, Benefit Risk Management
Andrea Kollath	DVM, Regulatory Affairs
Sigmond Johnson	MS, MBA Program Coordinator
John Zhang	Ph.D. Statistical Sciences
Juliana Ianus	Ph.D. Statistical Sciences

BAYER

Frank Misselwitz	M.D. , Ph.d., VP Head Therapeutic Area CV & Coagulation
Joseph Scheeren	Pharm.D., SVP Head of Global Regulatory Affairs
Scott D. Berkowitz	M.D. FACP, FACC, VP, Head, Thrombosis & Hemostasis CV and Coagulation
Gerhard Schlueter	Regulatory Head of General Medicine/Cardiology
Alice Benson	Principal Statistician, Global Clinical Statistics
Martin Homering	Statistical Sciences
Patricia Hagerty	Statistical Analyst –Global Statistical Programming
Andrea Derix	Ph.D. Den. Global Regulatory Strategist
Larry Winick	MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitz	Ph.D. Global Clinical Pharmacology Project Leader
Torsten Westermeier	Ph.D. Therapeutic Area Expert Statistician CC
Patricia Hagerty	Statistical Analyst- Global Statistical Programming
Aasia Bhatti	M.D. Deputy Director for Int'l Drug Safety Division
Bernard Glombitza	M.D. Global Project Leader Wuppertal, Germany

BACKGROUND:

N/A

MEETING OBJECTIVES:

To provide clarifications regarding FDA presentations and discuss expectations for the March 19, 2009, advisory committee meeting (AC).

DISCUSSION POINTS:

FDA provided an overview of their expectations for the AC. FDA is in the process of developing its presentations and will have a more solid understanding by the end of the week starting March 9, 2009. FDA has found it to be helpful that AC presentations are clear, simple and focused. FDA emphasized that all its comments are subject to change as the process is in flux and highly dynamic. In general FDA expects to present:

- An Introduction
 - FDA's perspective is that the AC will be part of an ongoing review,
 - An overview of oral anticoagulants
 - Ximelagatran 2004 AC committee review
 - Rivaroxaban introduction highlighting the uniqueness of the regulatory program.
- Regulatory background for prior drugs approved
- Overview of interim safety
- History of hepatotoxicity
- Discussion of the sponsor submitted risk management plan

FDA does not anticipate a focus upon efficacy in the FDA presentation. The FDA presentations will generally focus upon safety. FDA has not determined if clinical pharmacology slides will be presented to address the request for a lower drug dose. The safety questions to the AC are most likely to relate to bleeding and a possible signal for Liver toxicity. FDA also anticipates a question related to the overall risk benefit assessment.

J&J discussed its plans and mentioned their comments are subject to change as their process is fluid also. At the moment J&J has four speakers; two from the company and two consultants. J&J plans to present:

- An introduction,
- The current state of prophylaxis of DVT in orthopedic surgery in the context of the US and the rest of the world,
- The trial data with emphasis on efficacy,
- A safety presentation covering bleeding, cardiovascular concerns and a substantial liver presentation and possibly individual cases,
- A summary to include a safety surveillance plan and risk benefit assessment.

J&J inquired about its response to the February 5, 2009, Clinical Pharmacology discipline review letter. FDA stated it is still considering if it will present at the AC. FDA emphasized that if it does not present at the AC it is not because it does not regard the topic as important but rather the format of the AC may not lend itself to the complexity of the issue. FDA reiterated that increases in exposure in certain populations correspond to an increased risk of bleeding.

J&J asked if FDA viewed the lower dose development as a labeling issue or an approvability issue. FDA stated that it has not settled yet on an answer or if the feedback at the AC would be in the form of a discussion or a vote. J&J expressed that it would be very helpful to get AC input and recommended FDA present the information in a simple format that would allow for discussion.

J&J inquired about presentation topics. FDA reiterated the outline (see above).

FDA inquired how the sponsor accounted for the different treatment durations in their pooled analysis of RECORD studies. The sponsor and FDA statisticians agreed to meet the week starting March 9, 2009, to discuss in greater detail.

DECISIONS (AGREEMENTS) REACHED:

- N/A

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- AC presentations

ACTION ITEMS:

- FDA and J&J to meet the week starting March 9, 2009

ATTACHMENTS/HANDOUTS:

- N/A

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/s/

Marcus Cato
3/18/2009 12:13:32 PM



NDA 22-406

INFORMATION REQUEST LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We are reviewing the Clinical Pharmacology 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.

Clinical Pharmacology

- 1) As discussed in our January 9, 2009, teleconference, an unexplained higher exposure to rivaroxaban in Japanese subjects compared to other tested groups was identified during our preliminary review of your application. It is possible that unmeasured or unreported environmental or demographic factors may have contributed to this difference in exposure to rivaroxaban. Furthermore, differences in genetic background in the disposition pathway of rivaroxaban may contribute. (b) (4)

(b) (4)

Gene	Caucasian	African	Chinese	Japanese
CYP3A4	7	20	5	6
CYP3A5	30	29	29	29
CYP2J2	109	106	109	107
ABCG2	105	101	101	101
ABCB1	287	310	281	274

(b) (4)

(b) (4)

, and 3)

Linkage Disequilibrium (LD) and haplotype structure differ for these genes across the four groups.

Since it is plausible that the PK differences seen in the Japanese population may be explained, at least in part, by genetic differences in any or all of the genes involved in rivaroxaban PK, we recommend that you analyze candidate (b) (4) haplotypes in order to rule out this cause of variability.

- 2) In two studies (Study 11864 and 11279), there appears to be a greater than additive response to clopidogrel-rivaroxaban co-treatment on the bleeding time endpoint. We note that clopidogrel PK samples were not obtained, but Pharmacogenomics (PGx) samples were banked.

It is difficult to rule out a Pharmacokinetic Drug-Drug Interaction (PK DDI) because clopidogrel active metabolite concentrations were not measured. In the absence of these clopidogrel PK samples, we recommend that you consider genotyping patients for variants known to be determinants of clopidogrel response. These include, but are not limited to, CYP2C19 variants (e.g., *2, *3, *4, *5, *6, *8, *9, *10, *17). The *2 reduced function allele is expected to be most common in this Caucasian population. However, any divergence of allele frequencies from the expected frequency could implicate the clopidogrel metabolic pathway in a PK DDI. While the effect of rivaroxaban on various Drug Metabolizing Enzymes (DMEs) has been described, the clopidogrel metabolic pathway is complex and genotyping may offer PK-centric mechanistic hypotheses to the observed effect of co-treatment on bleeding time. This can also be tested by removing the issue of clopidogrel's metabolic complexity (it is a prodrug converted to an active metabolite) by studying a similar drug without the metabolic complexity (e.g., prasugrel).

- 3) We refer to our February 5, 2009, Clinical Pharmacology discipline review letter and our January 9, 2009, teleconference. We request a written response to our request for development of a lower strength tablet or scored 10 mg tablet by February 24, 2009.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, MD
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

2/19/2009 05:20:43 PM



NDA 22-406

INFORMATION REQUEST LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We are reviewing the Clinical and Statistical sections 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.

Clinical

1. Develop a table that summarizes the incidence (number of patients/percentage) of intracranial hemorrhage (using the broad definitions cited in study reports for various terms that refer to any form of bleeding within the skull--e.g., hemorrhage stroke, basal ganglia bleed, subdural hematoma, etc) among all RECORD studies as well as the Magellan and Atlas studies by active versus comparator groups.
2. Develop a table that summarizes the use (number of patients/percentage) of clopidogrel or ticlopidine during the post-treatment initiation period (active treatment period) in the RECORD studies by active vs. comparator groups.
3. Develop a table that summarizes the use of aspirin (number of patients/percentage) during the post-treatment initiation period (active treatment period) in the RECORD studies by active vs. comparator groups.
4. Develop a table that summarizes the use of non-steroidal anti-inflammatory drugs (NSAIDs, exclusive of aspirin) (number of patients/percentage) during the post-treatment initiation period (active treatment period) in the RECORD studies by active vs. comparator groups. NSAIDs are listed at the following web address: <http://www.fda.gov/cder/drug/infopage/cox2/>

5. In the response to the January 21, 2009 FDA requests, you summarize the occurrence of ALT > 3X ULN and TBL > 2X ULN (question 4) by race, for the RECORD studies. Please confirm that the shown table (where the total incidence is 0.15% for rivaroxaban and 0.11% for enoxaparin) includes both the active treatment and follow-up period. We are concerned this table might only include the data from the active treatment period.

Statistical

6. Re-submit bleeding event data (Pooled Study Record 1-4) including study drug variables and other important variables such as:

- Age,
- Gender,
- Venous thromboembolism (VTE) risk factor,
- History of VTE,
- Duration of surgery.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, MD
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

2/11/2009 05:38:47 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 10, 2009
TO: File
FROM: Diane Leaman
SUBJECT: **February 10, 2009 e-mail to Johnson and Johnson regarding Clinical information request.**

NDA 22-406, Xarelto (rivaroxaban) tablets

Andrea,

We would like to request the following information regarding the recently submitted rivaroxaban clinical laboratory datasets:

- Please clarify the data cut-off dates for ongoing studies for which lab datasets were submitted, and provide a brief statement of how the cut-off dates were decided and implemented.
- Please calculate mean duration of blinded study drug exposure at time of data cut-off for three ongoing studies for which laboratory datasets were submitted:
 - J-ROCKET-AF, (12620)
 - EINSTEIN DVT/PE, (11702)
 - ROCKET-AF, (11630)
- A quick evaluation of the data associated with Study 12620jrocket shows that this study includes a total of 1,185 subjects with a single treatment arm labeled BLINDED and coded 9999. Since there was more than one treatment arm in this study, please re-code the treatments using as an example the ROCKET study where the treatment arms are labeled DUMMY_A and DUMMY_B.

Diane Leaman
Safety Project Manager
Division of Medical Imaging and Hematology Products

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/s/

Diane V Leaman
2/10/2009 05:35:37 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on February 9, 2009. The purpose of the meeting was to discuss the February 5, 2009, Clinical Pharmacology discipline review letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: February 9, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Young M Choi

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS

Richard Pazdur, M.D., Director

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwayne) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Clinical Reviewer
Marcus Cato, M.B.A., Regulatory Health Project Manager
Diane Leaman, Safety Project Manager

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION
OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Brian Booth, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/
PHARMACOMETRICS DIVISION

Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL
PHARMACOLOGY/PHARMACOGENOMICS GROUP

Issam Zineh, Ph.D., Associate Director
Rosane Charlab Orbach, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

J&J

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters, MD Franchise Medical Leader
Leonard Oppenheimer, PhD. Statistical Sciences
Mehul Desai MD, Project Physician
Donald L. Heald, Ph.D. VP and Global Head of Clinical PK
Achiel Van Peer, Ph.D. Global Senior Scientific Leader Clinical Pharmacology
An Thyssen, PhD, Clinpharm Leader rivaroxaban
Harry Flanagan, MD Post-Marketing Safety Expert, Benefit Risk Management
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs,
Sigmond Johnson, MS, MBA Program Coordination

BAYER

Andrea Derix, PhD, Sen. Global Regulatory Strategist
Alice Benson Principal Statistician, Global Clinical Statistics,
Martin Homering Statistical Sciences
Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis, Hemostasis, CV and Coagulation
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitz, PhD Global Clinical Pharmacology Project Leader, BSP
Torsten. Westermeier PhD, Statistical Sciences

BACKGROUND:

On February 5, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a Clinical Pharmacology discipline review letter and a request to meet to discuss their pending response.

MEETING OBJECTIVES:

To discuss the February 5, 2009, Clinical Pharmacology discipline review letter.

DISCUSSION POINTS:

Discipline review letter point 1

FDA clarified its position regarding the February 5, 2009, Clinical Pharmacology discipline review letter. FDA emphasized that a clinically relevant increase in systematic exposure was noted in certain patient populations. FDA provided a clinical overview drawing attention to the relatively shallow dose response curve and steep dose bleeding curve for rivaroxaban compared to enoxaparin as well as an almost five-fold risk of major bleeding in subjects receiving a daily dose of 10 mg vs 20 mg in the Phase 2 dose ranging study 11527. FDA identified several special populations (i.e., patients with renal impairment, hepatic impairment, and/or moderate/strong CYP3A4 or P-gp inhibitors) where clinically relevant increases in drug exposure could mimic the exposure difference seen from a doubling of the applicants proposed dose (i.e., 10 mg qd to 20 mg qd) were likely. FDA stated that without the ability for downward dose adjustment to match drug exposure between the general population and these special populations a part of the target population will not be able to utilize this drug. FDA again recommended that the

applicant develop a lower strength or scored 10 mg tablet. FDA also reminded the applicant that the 5 mg dosage form has been extensively studied as noted in the reports submitted in support of this application.

J&J highlighted specific bleeding rates from Phase 2 studies that dosed rivaroxaban bid rather than the proposed daily dosing regimen. FDA stated that a twice-daily dosing regimen is not a proposed drug dosage and that the focus for this product has been on study data using once-daily dosing because the exposure profiles are not the same. FDA reemphasized it does not agree with the J&J position that only a ≥ 2 fold change in exposure is clinically relevant and it believes that a clinically relevant change in exposure is likely lower given the safety data from the Phase 2 dose ranging study 11527. FDA stated that this is a potential labeling issue and if a lower strength were developed it would work with the applicant to match rivaroxaban exposure in the special populations with the general population rather than restrict its use.

FDA asked J&J to clarify its reluctance to downward titrate the dose. J&J expressed concern that matching exposure in subpopulations may not produce the same efficacy and cited efficacy data from the 5mg qd vs. 10 mg qd in the Phase 2 dose ranging study 11527. FDA explained that this comparison was not appropriate because the exposure differences that were being discussed were similar to going from a 10 mg qd regimen to a 20 mg qd regimen and the dose response curve compared to enoxaparin was shallow. J&J also inquired if efficacy studies would be necessary in patient subpopulations using a 5mg dosage form. FDA advised that development of the 5 mg strength could be justified based on the pharmacokinetic/pharmacodynamic (PK/PD) characteristics.

J&J inquired if this was viewed by FDA as an approvability issue. FDA stated that if this issue was not resolved prior to the advisory committee (AC) meeting there may be discussion at the AC and it could be an issue for approval.

Discipline review letter point 2

FDA is not persuaded by the J&J explanation regarding an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups. FDA and J&J discussed details of the FDA data analysis. FDA emphasized that the key point was Figure 3 (see discipline review letter) where Chinese and Japanese subjects show the same PK/PD relationship but different exposure rates. In response, the sponsor inquired if they might submit age differences in a pooled analysis. FDA agreed. FDA also provided additional clarification to the sponsor regarding its request for additional exploration into potential pharmacogenomic causes.

DECISIONS (AGREEMENTS) REACHED:

- J&J to submit pooled analysis of age differences between Chinese and Japanese in studies 11126 and 11608

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- J&J development of a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet

ACTION ITEMS:

- J&J to submit pooled analysis of age differences between Chinese and Japanese in studies 11126 and 11608
- J&J to submit its decision regarding development of a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet.

ATTACHMENTS/HANDOUTS:

February 5, 2009, Clinical Pharmacology discipline review letter

5 pages have been withheld immediately following this page as this is a duplicate of the letter electronically dated 2.5.09 in this Administrative Section

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/s/

Marcus Cato

3/6/2009 06:24:50 PM



NDA 22-406

DISCIPLINE REVIEW LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to your submission dated December 19, 2008.

Our review of the Clinical Pharmacology section of your submission is ongoing, and we have identified the following deficiencies. PK and PD refer to pharmacokinetic and pharmacodynamic, respectively:

1. We have reviewed your response and supporting data addressing the request to develop a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet. Your response indicated that you did not envision a need for a lower strength tablet or a scored 10 mg tablet. You supplied information justifying your perspective. We are not persuaded by your justifications. As outlined in Table 1 and Figure 1 of your response, there is a steep dose response relationship, relative to enoxaparin, for the risk of major bleeding events. These major bleeding events are defined as a fatal bleeding event, bleeding into a critical organ (i.e., retroperitoneal, intracranial, intraocular, or intraspinal bleeding), bleeding that required re-operation, clinically overt extrasurgical site bleeding associated with a ≥ 2 g/dL decrease in hemoglobin concentration, or clinically overt extra-surgical site bleeding leading to transfusion of ≥ 2 units of whole blood or packed cells. Table 1 in your response to FDA reports a greater than 4 fold increase in major bleeding (0.7% vs. 4.3%) when exposure is increased two fold from the proposed dose. This suggests that even a 1.5 fold increase in exposure may double the risk of major bleeding. This is an important safety concern.

Without the ability to downward titrate the proposed dose of rivaroxaban the following populations may be potentially at increased risk for major bleeding based on the exposure and PD data you submitted (i.e., clotting factor Xa (FXa) inhibition and prothrombin time (PT)): 1) moderate to severe renal impairment, 2) mild to severe renal impairment when used with a cytochrome P450 enzyme 3A4 (CYP3A4) inhibitor, 3) moderate to severe hepatic impairment, and 4) concurrent use with a moderate or strong CYP3A4 inhibitor plus a moderate or strong P-glycoprotein (Pgp) inhibitor. Further, the potential increase in exposure from renal impairment combined with a CYP3A4 inhibitor is of particular concern given it was not studied and could be significant given both major elimination pathways are blocked.

Therefore, without downward dose adjustment, a significant part of the target population will not be able to utilize rivaroxaban and inappropriate use of the current strength in these populations could pose an unacceptable risk (e.g., medication error). We again strongly recommend you to develop a lower strength tablet or a scored 10 mg tablet of rivaroxaban and provide adequate data to support bioequivalence between the current formulation and the lower strength or scored 10 mg tablet. We encourage you to promptly obtain this information and submit it as an amendment to your application. Alternative methods to address this safety issue (e.g., restricted distribution or other types of limitations of access) will be considered but we maintain that the issue is best addressed by the development of a lower strength tablet or a scored 10 mg tablet. We suggest having a teleconference to further address our safety concerns. This will afford us an opportunity to further clarify our position and discuss any additional questions or comments you may have on this matter.

2. We have reviewed your response and supporting data regarding an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups including Chinese and we are not persuaded by your explanation. Based on preliminary analysis, we find that the median maximum plasma concentration (C_{max})/Dose and area under the curve (AUC)/Dose were approximately 50% higher in Japanese compared to other ethnicities (see Figure 1).

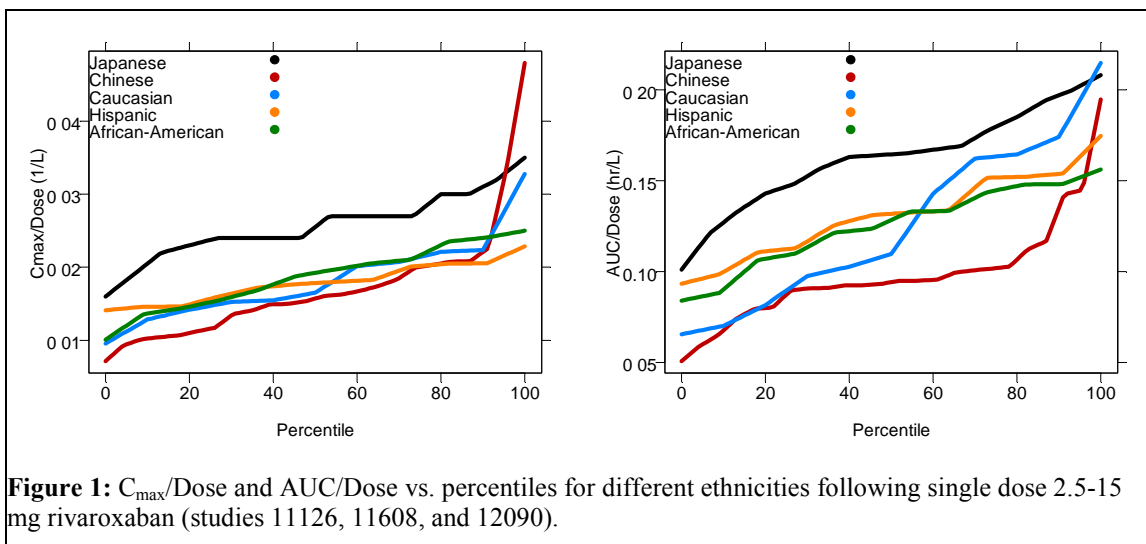
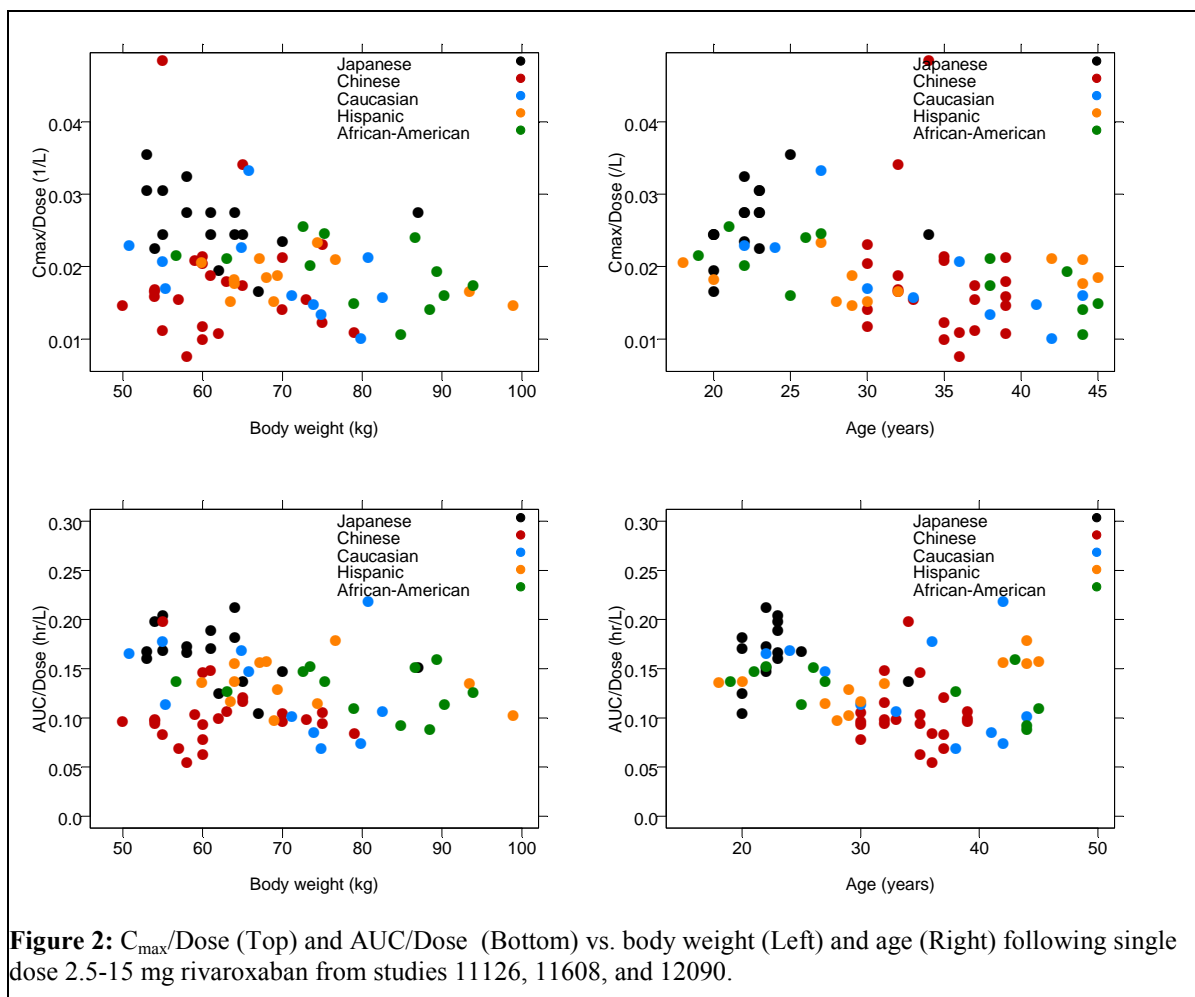


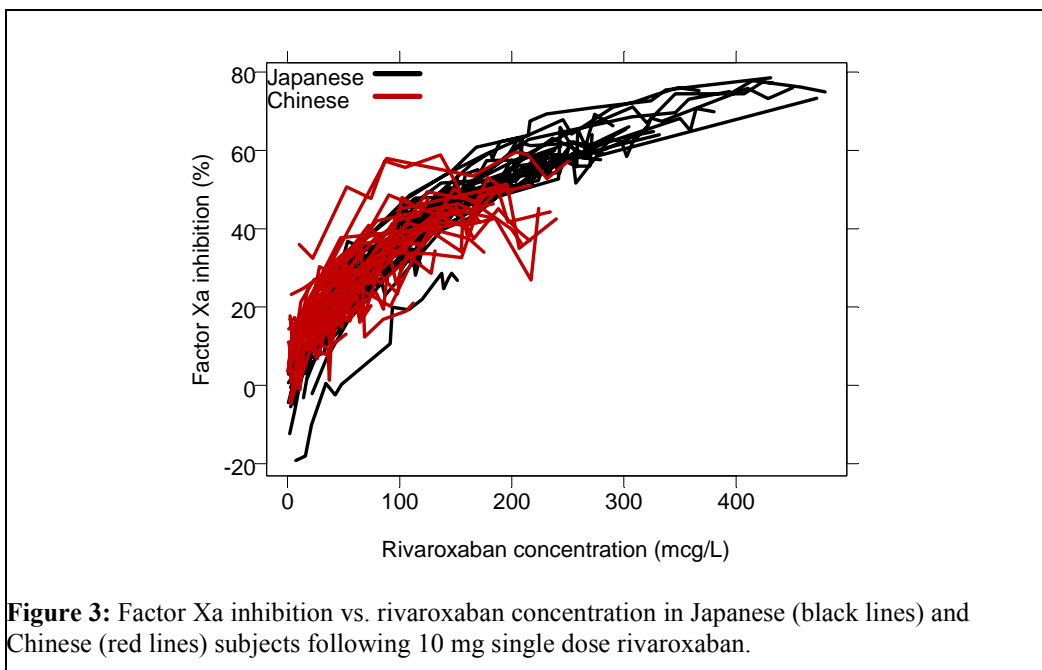
Figure 1: C_{max} /Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-15 mg rivaroxaban (studies 11126, 11608, and 12090).

The only apparent differences in covariates for Japanese compared to other ethnicities are body weight and age where the Japanese were the youngest and "lightest" subjects (see Figure 2) potentially explaining the higher exposure.

However, the exposure in Japanese was approximately 50% higher compared to Chinese subjects weighing the same as Japanese. The Japanese were approximately 10 years younger than the Chinese (mean age of 23 and 34 years for Japanese and Chinese subjects in studies 11126 and 11608, respectively). One would therefore expect the younger Japanese subjects to clear the drug faster (age was found to be a covariate for clearance in population PK) and thus lower exposure (AUC). The opposite was observed in studies 11126 and 11608.



No apparent inter-ethnicity differences were found for Factor Xa inhibition between Japanese (study 11126) and Chinese (study 11608) subjects after adjusting for exposure differences following 10 mg single dose rivaroxaban (see Figure 3).



Based on the PK/PD data from studies 11126 and 11608 in Japanese and Chinese subjects, we conclude that there are significant differences in rivaroxaban pharmacokinetics for Japanese subjects compared to other ethnicities.

Given these preliminary findings and additional clarification we again ask you to provide an additional explanation for the higher exposure in the Japanese population. Pharmacogenetic differences should be considered in detail, in addition to other factors, in your response.

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 questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Young M Choi, Ph.D.
Clinical Pharmacology Team Leader
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Young-Moon Choi
2/5/2009 05:20:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on February 2, 2009. The purpose of the meeting was to provide clarifications in regard to studies in your NDA and discuss expectations for the March 19, 2009, advisory committee meeting.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: February 2, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 1415 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwayne) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager

OFFICE OF TRANSLATIONAL SCIENCE/OFFICE OF BIOSTATISTICS

Ted Guo, Ph.D., Statistician,
Chava Zibman, Ph.D., Staff Fellow
Antonio Paredes, Ph.D., Statistician

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer
Allen D Brinker, M.D., Medical Team Leader

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION
OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

John R. Senior, M.D., Medical Officer (Hepatotoxicity)

EXTERNAL CONSTITUENT ATTENDEES:

J&J

Peter DiBattiste, MD, Therapeutic Area Head Cardiovascular
Gary Peters , MD Franchise Medical Leader
Leonard Oppenheimer, PhD. Statistical Sciences
Mehul Desai MD, Clinical
Jesse A. Berlin, ScD, VP, Epidemiology
G.K. (Dina) Anand MD, Post-Marketing Safety Franchise Leader
Yingshan You, Data Programming
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Steve Miller, VP Global Regulatory Affairs
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs

BAYER

Frank Misselwitz, MD, PhD, VP, Head Therapeutic Area CV and Coagulation
Joseph Scheeren, Pharm.D., SVP Head of Global Regulatory Affairs
Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis, Hemostasis, CV and Coagulation
Gerhard Schlueter,-Global Regulatory Affairs, Head of Therapeutic Area General Medicine
Andrea Derix, PhD, Global Regulatory Affairs,
Alice Benson Principal Statistician, Global Clinical Statistics,
Martin Homering Statistical Sciences
Patricia Hagerty Statistical Analyst - Global Statistical Programming

BACKGROUND:

On January 23, 2009, FDA requested a meeting with Johnson and Johnson Pharmaceutical Research and Development (J&J).

MEETING OBJECTIVES:

To provide clarifications in regard to studies in the NDA and discuss expectations for the March 19, 2009, advisory committee meeting (AC).

DISCUSSION POINTS:

In response to questions about patients who were to receive pneumatic compression J&J provided a written response (see attached). FDA stated that it appears patients who planned to undergo pneumatic compression were excluded from RECORD studies. FDA asked if this was captured in the case report forms. J&J stated that it was and they could submit a summary table to FDA.

FDA stated that in regard to the international aspect of their RECORD studies J&J should be prepared provide comment at the AC about perioperative management and how surgical procedures may vary internationally. FDA noted that approximately 85% of J&J's studied RECORD patients came from outside the United States (US). FDA asked if J&J could comment on how the studies are applicable to the US in their presentation.

J&J noted that they had incorporated tables in the NDA by country and that most of the US data is derived from the Record 4 study and that results had been similar. J&J expected some differences in demographic data and perioperative management but they don't expect significant differences.

FDA & J&J discussed bleeding severity and concomitant medications use. FDA expressed concern for plavix/ticlide use in the US. J&J stated they have some data that they could submit but had not done specific analysis on major bleeding. J&J stated they would gather this data and prepare a submission. FDA stated it would prepare and send specific questions to J&J.

FDA provided its perspective for the AC:

FDA has not completed its review. The AC will be considered part of the review and FDA plans to focus on the major items identified to include:

- A summary of data from major studies
- Major efficacy
- Major safety (i.e., bleeding risks, liver toxicity, etc.)
- Logistical concerns (i.e., presentation, packaging, concomitant medications use, etc.)
- Ongoing clinical studies

FDA noted that its focus will generally be more on safety than efficacy although the totality of originally submitted data will be reviewed. FDA does not anticipate discussing a risk evaluation and mitigation strategy (REMS) in any detail. In general, FDA anticipates that a portion of the questions for AC will focus on the risk vs. benefit of the drug.

FDA & J&J discussed possible packaging and drug presentations that might be less conducive to "off-label" use. FDA advised that the discussion is appropriate to have after the AC, however FDA is concerned and J&J should be prepared to comment.

J&J inquired about FDA liver toxicity concerns. FDA stated that it will attempt to inform J&J of specific cases that might be presented at the AC but that is not certain as of now. FDA stated for the liver cases, there does not generally appear to be a definitive causative relationship based on our preliminary review but the data are still under review; the lack of long term data was of concern with respect to potential liver toxicity. In regard to pre-clinical questions FDA advised J&J to be prepared to address all FDA concerns, and FDA would work to share any specific concerns. J&J stated that it would take a broad approach in its briefing book for the AC.

J&J asked about the need for an orthopaedic surgeon they had consulted to be available at the AC for questions. FDA stated it may be useful for him/her to be there and it may be helpful for him/her to provide comment/a presentation on the international nature/surgical practice correlates for evaluating the RECORD data.

DECISIONS (AGREEMENTS) REACHED:

- J&J stated that they would submit a summary table of pneumatic compression patients excluded from RECORD studies to FDA/as well as a summary of pneumatic compression usage in RECORD studies (consistent with available data).
- FDA stated it would prepare and send specific questions to J&J in regard to bleeding severity and concomitant medications use.

- FDA stated that it will attempt to inform J&J of specific liver cases that might be presented at the AC.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None.

ACTION ITEMS:

- J&J to submit a summary table of pneumatic compression patients excluded from RECORD studies to FDA and pneumatic usage in RECORD studies.
- FDA to prepare and send specific questions to J&J in regard to bleeding severity and concomitant medications use

ATTACHMENTS/HANDOUTS:

J&J written response Intermittent Pneumatic Compression (IPC)

Intermittent Pneumatic Compression (IPC)

While mechanical methods of thromboprophylaxis such as Intermittent Pneumatic Compression (IPC) have been shown to reduce the risk of DVT in a number of patient groups, they have been studied much less intensively than anticoagulant-based approaches and they are generally less efficacious than anticoagulant thromboprophylaxis. The primary reason why the use of IPC devices during the active treatment period was an exclusion criterion in the RECORD studies is that this modality is recommended by the American College of Chest Physicians primarily for use in patients at high risk of bleeding (Grade 1A recommendation). These patients are therefore not eligible for anticoagulant prophylaxis. In addition, although adjunctive use of IPC with anticoagulant therapy is possible, since IPC use would not be randomized it could represent a confounding factor for the primary efficacy analyses. Moreover, the amount of data supporting this combined use is limited. It should also be noted that the benefit of IPC devices was determined years ago when hospital stays were much longer than they are today (now usually only 2-4 days in the United States), and that it is difficult to implement their use effectively (e.g. studies have shown that the devices are often removed for prolonged periods of time even while in the hospital room).

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/s/

Marcus Cato
2/13/2009 12:09:21 PM

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 22-406

Date: January 30, 2009

FDA Participants:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL Participants:

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Andrea F. Kollath, DVM, Regulatory Affairs

Discussion:

Ms. Kollath called to gather information about the upcoming teleconference (February 2, 2009) between FDA and Johnson and Johnson (J&J). Ms. Kollath wanted to know who was invited to the teleconference from FDA and who should be included from J&J. I told her that clinical/chemistry/pre-clinical/clinical pharmacology/statistics and persons from the office of surveillance and epidemiology were invited, however the discussion would center around clarifications regarding liver datasets, clarifications in regard to the international aspect of their RECORD studies/international surgical practices and clarification in regard to why patients who were to receive pneumatic compression were excluded from their RECORD studies.

Ms. Kollath asked would it be appropriate for J&J to ask questions about the upcoming Advisory Committee meeting specifically what to include/focus on in their briefing document. I told her that it would be acceptable to ask that question at the meeting.

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/s/

Marcus Cato
2/3/2009 05:23:38 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 23, 2009. The purpose of the meeting was to discuss our January 21, 2009, clinical information request.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 23, 2009
TIME: 9:20 AM - 10:15 AM EST
LOCATION: CDER WO 2189 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Min Lu

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Min Lu, M.D., Clinical Reviewer
Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Andrea F. Kollath, DVM, Regulatory Affairs
Mehul Desai, MD, Project Physician, Clinical

BACKGROUND:

On January 21, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a clinical information request via e-mail.

MEETING OBJECTIVES:

To Clarify the FDA clinical information request and the timeline for the J&J response.

DISCUSSION POINTS:

FDA & J&J discussed the details of the January 21, 2009, request. FDA provided clarifications. J&J stated that the majority of the information requested was ready and would be submitted on January 23, 2009. J&J further stated that any information that could not be submitted on January 23, 2009, would be submitted on January 26, 2009. FDA agreed.

DECISIONS (AGREEMENTS) REACHED:

- Information that could not be submitted by J&J on January 23, 2009 would be submitted on January 26, 2009.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None.

ACTION ITEMS:

- J&J to submit information requested on January 21, 2009.

ATTACHMENTS/HANDOUTS:

January 21, 2009 FDA clinical information request one

1. For subject 11354-300014007, provide all local and central LFT results including Day 65 and after (not in narrative).
2. For subject 11355-60009-5028, provide LFT data after Day 55 and any additional follow-up information regarding clinical adverse events.
3. For subject 11357-55003-7007, provide hospital summary, all relevant hepatitis and other serology test results.
4. Provide summary tables as Table 1-2 [Pooled Incidence Rates of Liver-related Postbaseline Laboratory Abnormalities – After Day 0 Baseline (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] under ISLS by race (White, Asian, and others as separate tables).
5. For subject 10944-84008, provide hospital summary, liver histological assessment by (b) (4) LFT result link and figure of LFT values over time (similar to LFT figures for other subjects).
6. For adjudicated cardiovascular events that occurred off-treatment, list the days relative to the last dose of active treatment for each event for both treatment group.
7. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 1-11 [Incidence of Postbaseline Hepatic Disorder Adverse Events (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] for subjects under the following categories:
 - MSSO: Cholestasis and jaundice of hepatic origin
 - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
 - MSSO: Hepatitis, non-infectious
 - MSSO: liver infections
 - MSSO: Possible liver-related coagulation and bleeding disturbances
8. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-7 [Incidence of Treatment-Emergent Adverse Events in the MSSO Search Category ‘Hepatic Disorders’ in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects

Valid for Safety in Studies 10942, 10944, 10945, and 11527)] for subjects under the following categories:

- MSSO: Cholestasis and jaundice of hepatic origin
 - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
 - MSSO: Possible liver-related coagulation and bleeding disturbances
9. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-14 [Incidence of Treatment-emergent Adverse Events for “Hepatic Disorders” in Phase 2 Treatment Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11528)] for subjects under the following categories:
- MSSO: Cholestasis and jaundice of hepatic origin
 - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
 - MSSO: Liver infections
 - MSSO: Liver neoplasms, benign

January 21, 2009 FDA clinical information request two

1. For subject 16018-1005 in ongoing study, provide hospital summaries and full autopsy report.
2. Provide summary of Liver Advisory Panel assessment for other cases with increased ALT in RECORD studies (exclude those with ALT >3 x ULN concurrent with TB>2xULN).

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/s/

Marcus Cato
1/28/2009 04:44:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XareltoTM (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 16, 2009. The purpose of the meeting was to discuss our January 12, 2009, clinical information request.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 16, 2009
TIME: 2:30 PM - 3:00 PM EST
LOCATION: CDER WO 2189 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Kathy Robie Suh

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., Clinical Reviewer
Diane Leaman, Safety Regulatory Health Project Manager
Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Andrea Kollath, Regulatory Affairs
Sanjay Jalota, Regulatory Global Regulatory lead

BACKGROUND:

On January 12, 2009 FDA send Johnson and Johnson Pharmaceutical Research and Development (J&J) a clinical information request via e-mail.

MEETING OBJECTIVES:

To Clarify FDA clinical information request

DISCUSSION POINTS:

Request one

In regard to the FDA Request one (see attached clinical information request), FDA stated the subject was incorrectly identified, and the full autopsy report was available. J&J had noted the error and stated a link to the liver function test and any hospital summary would be available the week of January 19, 2009.

Request two and three

J&J stated that FDA Requests two and three (see attached clinical information request) will be available the week of January 19, 2009.

J&J asked if FDA could meet prior to the advisory committee meeting to discuss noted liver cases, liver data, and a proposed Risk Evaluation and Mitigation Strategy (REMS). FDA stated it did not appear likely, but FDA would discuss the request internally and inform J&J if a discussion is deemed necessary.

J&J updated FDA with plans for its upcoming submissions. J&J stated a six-month (6-month is ok here) safety update would be submitted the week of February 16, 2009.

DECISIONS (AGREEMENTS) REACHED:

- None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- REMS Discussion between FDA & J&J prior to the advisory committee meeting.

ACTION ITEMS:

- FDA to discuss meeting internally and inform J&J if a discussion is deemed necessary.
- J&J to make various submissions including a 6-month safety update

ATTACHMENTS/HANDOUTS:

January 12, 2009 FDA clinical information request

1. For subject 11355-140165153 who died of fatal bleeding, provide a full autopsy report, hospital summary, lab data including LFTs and coagulation tests during the treatment and in hospital before death, and investigator assessment for the event.
2. Clarify the number of cardiovascular events in RECORD trials. The discrepancy is noted in the number of events between the individual RECORD study reports and ISS report (Table 1-22).
3. Provide summary of number of patients with maximum ALT>3 ULN and maximum TB>2 ULN (not concurrent) for all completed studies and provide link to narrative and CRF. Also provide this information for ongoing studies if available.

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/s/

Marcus Cato
1/28/2009 04:42:12 PM

RECORD OF TELEPHONE CONVERSATION

NDA: 22-406

Today's date: January 27, 2009

Speakers: Dwaine Rieves for FDA
Michael Kronig for Johnson and Johnson/VP Reg Affairs

I returned a phone call to Dr. Kronig because he had left a voice mail for me yesterday. Dr. Kronig expressed some concern about timeliness of getting feedback from FDA since the company's briefing document is due relatively soon. I noted that we're doing the best we can and have a telephone conference schedule for next week. I noted that in general, the conference will focus upon:

1) clarification of the status of use of pneumatic compression in the RECORD studies/specifically were subjects excluded from all 4 studies if pneumatic compression was planned?/if so, did the case report forms actually capture any use of pneumatic compression/if so what was the usage between treatment groups? I noted that that AAOS regards pneumatic compression as useful in DVT prevention in knee/hip surgery and regards it, in many cases, as preferable to any drug therapy prophylaxis.

2) explanation of why the predominance of patients were enrolled outside of the USA/particularly since surgical and perioperative management may importantly differ in certain countries and hip/knee surgery apparently is very common in the USA. I encouraged them to address the question of the extent to which regional differences in perioperative care impact DVT rates/occurrence.

3) we hope to discuss the "liver data" situation and provide clarification re: our advisory committee focus. I noted that, in general, we will probably focus upon the details within the original NDA plus the summary tabulation/safety updates provided for on-going studies.

I briefly highlighted a few other concerns, as follows:

a) We need a summary of all intracranial hemorrhage across all studies. I expressed particular concern about the reports of intracranial hemorrhage in the ATLAS study that, in multiple cases, appeared related to the concomitant use of Plavix with rivaroxaban and I noted that the company must provide clarity regarding the use of any concomitant anti-platelet (as well as other coagulation-related drugs) throughout the proposed time course of rivaroxaban use. In particular, I expressed concern that, in practice, surgeons may readily direct resumption of concomitant medications within a few days following completion of surgery and, for many patients, these concomitant medication may include Plavix (or other coagulation-related products). I noted the proposed plans do not appear to address this issue.

b) I expressed concern that the logistical packaging programs for rivaroxaban does not appear well thought-out. I noted that, as currently proposed, the packaging appears very conducive to "off label" usage. I noted that the company needs to focus upon package that is more practical and conducive to the "short term" usage proposed in the application. For example, they may wish to consider use of "blister packs" of finite amount of drug or other unique packaging consideration. I noted that I anticipated this topic is likely to come up at the advisory committee and I suggested the company focus upon a well thought out/reasonable answer or justification.

c) I noted that our advisory committee documents and presentation may include discussion of other drugs that had liver-related problems, such as ximelagatran and/or one of the anti-diabetic drugs and potentially other drugs.

d) I noted these are only highlights and we hope to have a useful discussion within the next several days.

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

/s/

Rafel Rieves
1/28/2009 11:28:17 AM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 25, 2008 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 the teleconference between representatives of your firm and the FDA on January 9, 2009. The purpose of the meeting was to discuss the navigation of the Case Report Form (CRF) information in the December 18, 2008 submission to NDA 22-406.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Safety Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 9, 2009
TIME: 2:30 PM to 3:00 PM
LOCATION: White Oak Campus, Bldg 22, Room 2189
APPLICATION: NDA 22-406
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type A, Clinical

MEETING CHAIR: Dr. Min Lu

MEETING RECORDER: Ms. Diane Leaman, Safety Project Manager

FDA ATTENDEES:

Office of Oncology Products/Division of Medical Imaging and Hematology Products (DMIHP)

Min Lu, M.D., Medical Officer
Diane Leaman, Safety Regulatory Health Project Manager
Marcus Cato, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Johnson & Johnson

Andrea Kollath DVM, Director Regulatory Affairs
Sanjay Jalota MRPharms, Senior Director, Regulatory Affairs
Mehul Desai MD Director, Clinical Scientist
Shelly Chandler, Regulatory Operations

BACKGROUND:

On December 18, 2008 (received December 19, 2008), J&J submitted a response to an information request from DMIHP for electronic laboratory data and Case Report Forms (CRFs) relevant to drug-induced liver injury in all completed and ongoing clinical trials with Rivaroxaban.

MEETING OBJECTIVES:

To assist the Medical Officer in navigating the electronic information submitted in the December 19, 2008 submission.

DISCUSSION POINTS:

J&J clarified that central laboratory data were not included in the CRFs; only local laboratory data are in the CRFs. Central laboratory data are in a separate table.

All Phase 3 studies had central and local laboratory data. The sponsor is not sure whether all Phase 2 studies had data from both laboratories. The Medical Officer asked where the liver data was in the CRFs. The sponsor responded that they would research that and get back to the division with a response later.

J&J guided the Medical Officer to several areas in the submission where patient data was to be found. The sponsor noted that there were results from only six autopsies available. The medical officer noted that the submitted autopsy reports did not include two deaths (10844-84008 and 11223-506006) with the autopsies performed. The sponsor indicated that the available autopsy information for the patient who died in the Phase 2 trial is included in the NDA. There is a full, five-page report for patient 10944-84008 in a pdf file. There is a six-page copy of the original autopsy report for patient 11223-506006.

DECISIONS (AGREEMENTS) REACHED:

The sponsor will determine the location of the liver data in the CRFs and update DMIHP with the information.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

The location of the liver data, including chemistry data, in the CRFs needs to be determined.

ACTION ITEMS:

J&J will inform DMIHP of the location of the liver data in the CRFs.

ATTACHMENTS/HANDOUTS:

None.

POSTMEETING ADDENDUM:

On January 9, 2009, at 3:40 PM, J&J provided the following information via electronic mail:

Autopsy report for Subject 10944-84008.

This report is in Appendix 2 of the Integrated Summary of Liver Safety in the initial NDA (Sequence 0000)

Autopsy report for Subject 11223-506006.

This English translation is in the narrative in the MRR for Study 11223 (MRR-00150 ODIXa-DVT: Phase II dose finding and proof of principle trial in patients with acute symptomatic proximal deep vein thrombosis)(pages 1-1211 to 1-1217) in Module 5.3.5.4 of the initial NDA (Sequence 0000). The original report in local language has been requested and will be sent to FDA as soon as received.

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

/s/

Diane V Leaman
1/23/2009 04:05:16 PM

MEMORANDUM OF E-MAIL INFORMATION REQUESTS/CORRESPONDENCE

DATE: January 12, 2009 – April 6, 2009
APPLICATION NUMBER: NDA 22-406

BETWEEN:

Name: Andrea F. Kollath, DVM,
Director, Regulatory Affairs
e-mail: AKollath@its.jnj.com
Representing: Johnson and Johnson Pharmaceutical Research and
Development

AND

Name: Marcus Cato, M.B.A., Regulatory Project Manager
Division of Medical Imaging and Hematology Products
HFD-160

SUBJECT: NDA 22-406 information requests/correspondence

Cato, Marcus

From: Cato, Marcus
Sent: Monday, April 06, 2009 1:34 PM
To: Kollath, Andrea [PRDUS]
Cc: 'Jalota, Sanjay [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following clinical pharmacology information within 10 business days.

Submit a revised file COLLEC.XPT (M5/P3 dataset folder in the 000 submission) in SAS transfer format that includes additional columns identifying patients (based on tables 14.3.5/ 9.1.1 through 14.3.5/ 9.7.2 in the report 35415) who received: 1) any platelet aggregation inhibitor, 2) aspirin or products containing aspirin, 3) clopidogrel, 4) any Non-steroidal anti-inflammatory drugs (NSAID) or combination product containing an NSAID, 5) Any CYP 3A4 inhibitor, and 6) Any P-gp inhibitor. This information should be formatted in a manner similar to CYP3A4 inducers that is already included in this data set. For Items #5 & #6 please also include a column identifying the name(s) of the CYP3A4 inhibitor(s) and a column identifying the name(s) of the P-gp inhibitor(s). In addition please include a revised define.pdf file for this dataset.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
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(301) 796-2050 (phone)
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Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, April 01, 2009 2:20 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22-406 information request
Importance: High

Dear Andrea,

We request that you submit the following information on or before April 2, 2009.

1. Provide a phone number, email address, and FAX number for the following three RECORD 4 investigators: Dr. John Ward site # 14010, Dr. Craig Buettner site # 14004 and Dr. John Schwappach Site # 14045.

We request the following background materials on or before April 10, 2009.

2. Submit the compilation of data listings for use as background material in an upcoming clinical investigator inspection for NDA 22-406, Xarelto. The data listings should include the following parameters:

- Primary efficacy endpoint
- Secondary efficacy endpoint
- Concomitant medications
- Adverse events
- Withdrawals
- Deaths
- Serious Adverse Events
- Protocol violations/deviations
- Randomization list for the site
- Laboratory values (biochemistry, hematology, coagulation parameters, etc.)

The data listings requested are for the following investigators: John Ward, M.D., RECORD 4, Site U.S. 14010; Craig Buettner, M.D. RECORD 4, U.S. Site # 14004 ; and John Schwappach, RECORD 4, U.S. Site #14045.

For each parameter listed in the bullets above, the file should contain a listing of each patient enrolled by that investigator with the pertinent data - e.g., "Primary efficacy endpoint" should contain a listing of Patient 1, 2, 3, 4, etc. with the appropriate outcome of the primary efficacy endpoint.

If you have any questions please feel free to contact me.

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Cato, Marcus

From: Cato, Marcus
Int: Wednesday, March 11, 2009 2:08 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

Regarding the number of deaths in the enoxaparin group in RECORD studies, explain the inconsistency noted between the individual study reports and the integrated analysis. A total of 25 deaths in the enoxaparin group in all RECORD studies were observed, 15 deaths were included in the primary efficacy analysis (treatment period) and 10 deaths in the follow-up. However, your integrated efficacy analysis, showed a total of 16 deaths in the enoxaparin group. It is also noted that a death at Day 151 in the enoxaparin group was included in the RECORD 4 study, explain the reason to include this patient.

If you have any questions please feel free to contact me.

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Cato, Marcus

From: Cato, Marcus
Sent: Tuesday, March 10, 2009 9:21 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

Integrated Analyses of Symptomatic VTE and death in RECORD 1-4

Please provide the dataset containing the following variables for the integrated analyses of RECORD 1-4

- 1 Study Number (Record 1=1, Record 2=2, Record 3=3, Record 4=4)
- 2 Unique Patient ID
- 3 Treatment Group (1=Rivaroxaban, 2=Enoxaparin)
- 4 Treatment Duration (Number of days)
- 5 Dose per day
- 6 Total Dose
- 7 Time to First Symptomatic VTE or Death
- 8 Censoring status for First Symptomatic VTE or Death (1 = censored, 2 = event)
- 9 Time to Death
- 10 Censoring Status for Death (1 = censored, 2 = event)
- 11 Age (continuous)
- 12 Gender (1=Male, 2=Female)
- 13 Race
- 14 Duration of Surgery (1= (<2h), 2= (>=2h))
- 15 Any VTE Risk Factor (1=No, 2=Yes)
- 16 Time to discontinuation
- 17 Reason for discontinuation
- 18 Time-To-First-Event for Major Bleeding (treatment duration)
- 19 Censored Status for Major Bleeding Event (1=Yes, 2=No)
- 20 Time-To-First-Event for Major Bleeding combined with surgical site (treatment duration)
- 21> Censored Status for Major Bleeding combined with surgical site (1=Yes,2=No)
- 22> Time-To-First-Event for Major or clinically relevant Non-Major Bleeding (treatment duration)
- 23> Censored Status for Major or clinically relevant non-Major Bleeding (1=Yes, 2=No)
- 24> Time -To-First-Event for Any Bleeding Event (Treatment Duration)
- 25> Censored Status for Any Bleeding Event (1=Yes, 2=No)

If you have any questions please feel free to contact me.

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Cato, Marcus

From: Cato, Marcus
Int: Friday, March 06, 2009 12:20 PM
J: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

For 2 subjects (#220134004 and #400013004) who had ALT >3xULN Concurrent With TB >2xULN in ongoing EINSTEIN DVT/PE study, provide complete patient narratives with any available follow-up information, hospital summaries, and assessment by the liver advisory panel if available.

If you have any questions please feel free to contact me.

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Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, March 04, 2009 4:15 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Attachments: coverletter.pdf; fda-ir-response-13-feb-2009.pdf

Dear Andrea,

The submitted pooled incidence rates (see attached) for creatinine/urea abnormalities do not match the numbers in ISS Table 1-25 (THR) and 1-26 (TKR) for the pooled treatment-emergent incidence rates. We are looking for the treatment-emergent incidence rate as Table 1-25 and 1-26 but with more categories in creatinine/urea abnormalities.



coverletter.pdf
(123 KB)



fda-ir-response-13-
feb-2009.pdf...

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
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9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, March 04, 2009 11:22 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request
Importance: High

Dear Andrea,

We request that you submit the following information as soon as possible.

Based on the submitted datasets for ROCKET-AF study, 3 additional cases (#101013, #106065, and #100792) of ALT>3xULN either concurrent or preceding total bilirubin values >2xULN were identified which were not included in your 6-month safety update. Please provide explanation, verify the lab values, and submit the patient clinical narratives.

In addition, one case (#101573) of ALT>3xULN non-concurrent with total bilirubin>2xULN was found in the dataset for the ROCKET study. Please verify the lab values and submit the patient clinical narrative.

If you have any questions please feel free to contact me.

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Cato, Marcus

From: Cato, Marcus
Sent: Thursday, February 26, 2009 9:30 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Attachments: N22406 drug dosing modification in pts with and without elevated ALT 022509.doc

Dear Andrea,

We request that you populate the attached table.



N22406 drug dosing
modification...

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
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[illegible]

Cato, Marcus

From: Cato, Marcus
Sent: Friday, February 20, 2009 11:35 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 (Clinical Pharmacology) information request
Importance: High

Dear Andrea,

We request that you submit the following information within 10 business days.

1)

Based on your mass balance study, you report that M2 related metabolites and M8/9 related metabolites account for approximately 27% and 3.7% of total rivaroxaban dose respectively, when 10 mg 14C rivaroxaban is administered orally to healthy volunteers.

Based on your in vitro studies, you report that CYP2J2 and to a less extent CYP3A metabolize rivaroxaban to M2; CYP3A metabolizes parent to M9. In HLM, both M2 and M9 formations are inhibited by ketoconazole and ritonavir. In rCYP experiments, you concluded that CYP2J2 is the high affinity isoform for the formation of M2. You further conclude that 18% and 14% contributions from CYP3A and CYP2J2 respectively. It appears that this conclusion is based on an assumption that M2 formation (and related M1, M5, 6) is equally contributed by CYP3A (page 182 of your summary 2.7.2 Summary of Clinical Pharmacology Studies). Please provide additional justification to support this assumption. If this assumption is based on your estimated total P450 content by CYP2J2 and CYP3A4 are 1-2% and 30% (an approximately 1:30 ratio), please provide justification for this estimation. Also please address the potential effect of extra hepatic CYP2J2 on the metabolism of rivaroxaban.

2)

Please identify the patients used to create table 14.3.1/15.2.8.1 "Incidence of Treatment-Emergent Major or Non-Major Clin. Relevant Bleeding (Central Adjudication) Stratified By Calc. Creatinine Clearance (4 Categories)-Population: Subjects Valid For Safety Analysis Pool of SN 11354 (Record 1), SN 11355 (Record 4), 11356 (Record 3) and 11357 (Record 2)" found in the "Integrated Analysis of Rivaroxaban (BAY 59-7939) Studies 11354 (Record 1), 11355 (Record 4), 11356 (Record 3) And 11357 (Record 2) With Regard To Efficacy And Safety" pages 1857-58. An electronic data set (SAS transfer format) containing the unique patient identifier, study number, treatment group, event (Y/N), and Clcr group would be sufficient.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
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Cato, Marcus

From: Cato, Marcus
Sent: Tuesday, February 17, 2009 11:17 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request: regarding Xarelto lab datasets submitted 30JAN09

Dear Andrea,

We request that you address the following as soon as possible.

- Please clarify the data cut-off dates for ongoing studies for which lab datasets were submitted, and provide a brief statement of how the cut-off dates were decided and implemented.
- Please calculate mean duration of blinded study drug exposure at time of data cut-off for three ongoing studies for which laboratory datasets were submitted:
 - J-ROCKET-AF, (12620)
 - EINSTEIN DVT/PE, (11702)
 - ROCKET-AF, (11630)
- A quick evaluation of the data associated with Study 12620jrocket shows that this study includes a total of 1,185 subjects with a single treatment arm labeled BLINDED and coded 9999. Since there was more than one treatment arm in this study, please re-code the treatments using as an example the ROCKET study where the treatment arms are labeled DUMMY_A and DUMMY_B.

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
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Cato, Marcus

From: Cato, Marcus
Sent: Friday, February 13, 2009 12:37 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 Rivaroxaban information request

Attachments: nda22-406-creatinine-request-table.doc

Dear Andrea,

We request that you fill the attached table regarding the incidence of creatinine/urea abnormalities and renal impairment in RECORD studies as soon as possible.



nda22-406-creatinine-request-t...

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
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**Incidence of Post-Baseline Creatinine and Urea Abnormalities
in Pooled RECORD studies**

Creatinine/Urea Abnormalities	Rivaroxaban	Enoxaparin
Creatinine		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		
Urea		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		

**Incidence of Post-Day 1 Creatinine and Urea Abnormalities
in Pooled RECORD studies**

Creatinine/Urea Abnormalities	Rivaroxaban	Enoxaparin
Creatinine		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		
Urea		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		

Incidence of Post-baseline Renal Impairment Based on Estimated Creatinine Clearance
Rate Using Cockcroft-Gault formula
in Pooled RECORD studies

Creatinine clearance (mL/min/1.73m ²)	Rivaroxaban	Enoxaparin
60 to 89		
30 to 59		
15 to 29		
<15		

Incidence of Post-Day 1 Renal Impairment Based on Estimated Creatinine Clearance
Rate Using Cockcroft-Gault formula
in Pooled RECORD studies

Creatinine clearance (mL/min/1.73m ²)	Rivaroxaban	Enoxaparin
60 to 89		
30 to 59		
15 to 29		
<15		

Cato, Marcus

From: Cato, Marcus
Sent: Friday, February 13, 2009 11:59 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

1. Provide a summary of the number of subjects with elevated liver enzymes at baseline (at Day 0) in RECORD studies.

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Friday, February 06, 2009 7:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: Rivaroxaban letter from DSMB

Attachments: coverletter.pdf; feinbloom-bauer-fda.pdf

Hi Andrea,

Below is your electronic submission dated 2/2/09 (IND 64,892 S1362). The letter (b) (4) mentioned a DSMB report of a death due to liver failure.

Please clarify this case and submit the DSMB report.

Thanks.



coverletter.pdf (93 KB)



feinbloom-bauer-fda.pdf (20 KB...)

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
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4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, January 28, 2009 12:47 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

1. For subject 11702-16018-1005, submit echocardiography reports with clarification of the date (December 1996 or December 2006) and transthoracic echocardiography reports from 1/15/08 to 1/21/08.
2. Provide a summary of outcomes for subjects with ALT>3 xULN for both treatment groups in RECORD studies.

Thanks.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
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Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, January 21, 2009 4:08 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 Additional information request
Importance: High

Dear Andrea,

We request that you submit the following clinical information on or before Friday January 23, 2009.

1. For subject 16018-1005 in ongoing study, provide hospital summaries and full autopsy report.
2. Provide summary of Liver Advisory Panel assessment for other cases with increased ALT in RECORD studies (exclude those with ALT >3 x ULN concurrent with TB>2xULN).

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, January 21, 2009 3:53 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request
Importance: High

Dear Andrea,

We request that you submit the following clinical information on or before Friday January 23, 2009.

1. For subject 11354-300014007, provide all local and central LFT results including Day 65 and after (not in narrative).
2. For subject 11355-60009-5028, provide LFT data after Day 55 and any additional follow-up information regarding clinical adverse events.
3. For subject 11357-55003-7007, provide hospital summary, all relevant hepatitis and other serology test results.
4. Provide summary tables as Table 1-2 [Pooled Incidence Rates of Liver-related Postbaseline Laboratory Abnormalities – After Day 0 Baseline (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] under ISLS by race (White, Asian, and others as separate tables).
5. For subject 10944-84008, provide hospital summary, liver histological assessment by (b) (4) LFT result link and figure of LFT values over time (similar to LFT figures for other subjects).
6. For adjudicated cardiovascular events that occurred off-treatment, list the days relative to the last dose of active treatment for each event for both treatment group.
7. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 1-11 [Incidence of Postbaseline Hepatic Disorder Adverse Events (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] for subjects under the following categories:
 - MSSO: Cholestasis and jaundice of hepatic origin
 - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
 - MSSO: Hepatitis, non-infectious
 - MSSO: liver infections
 - MSSO: Possible liver-related coagulation and bleeding disturbances
8. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-7 [Incidence of Treatment-Emergent Adverse Events in the MSSO Search Category ‘Hepatic Disorders’ in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)] for subjects under the following categories:
 - MSSO: Cholestasis and jaundice of hepatic origin
 - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
 - MSSO: Possible liver-related coagulation and bleeding disturbances
9. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-14 [Incidence of Treatment-emergent Adverse Events for “Hepatic Disorders” in Phase 2 Treatment Studies

in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11528)] for subjects under the following categories:

- MSSO: Cholestasis and jaundice of hepatic origin
- MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
- MSSO: Liver infections
- MSSO: **Liver neoplasms, benign**

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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Cato, Marcus

From: Cato, Marcus
Sent: Monday, January 12, 2009 12:25 PM
To: 'Kollath, Andrea [PRDUS]'
Cc: Leaman, Diane V
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

1. For subject 11355-140165153 who died of fatal bleeding, provide full autopsy report, hospital summary, lab data including LFTs and coagulation tests during the treatment and in hospital before death, and investigator assessment for the event.
2. Clarify the number of cardiovascular events in RECORD trials. The discrepancy is noted in the number of events between the individual RECORD study reports and ISS report (Table 1-22).
3. Provide summary of number of patients with maximum ALT>3 ULN and maximum TB>2 ULN (not concurrent) for all completed studies and provide link to narrative and CRF. Also provide this information for ongoing studies if available.

Thanks.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
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/s/

Marcus Cato
4/14/2009 07:49:06 PM
CSO

Marcus Cato
4/14/2009 07:49:17 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): DDMAC: c/o Michelle Safarik			FROM: Diane Leaman, SRPM, Division of Medical Imaging and Hematology Products	
DATE December 16, 2008	IND NO.	NDA NO. NDA 22-406	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT July 28, 2008
NAME OF DRUG Xarelto (Rivaroxaban) tablets	PRIORITY CONSIDERATIONS Standard		CLASSIFICATION OF DRUG Anti Xa	DESIRED COMPLETION DATE February 9, 2008
NAME OF FIRM: Johnson and Johnson				
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 II 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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II 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 IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV 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 type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please see attached sponsor's draft original package insert labeling for Xarelto™ (Rivaroxaban) tablets for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery. Please provide review and attend labeling meetings as part of review team. Labeling is in EDR at \\CDSESUB1\EVSPROD\NDA022406\0000.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Diane V Leaman
12/17/2008 09:13:27 AM



NDA 22-406

INFORMATION REQUEST LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 25, 2008 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 submission dated July 25, 2008.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a written response in 30 days in order to continue our evaluation of your NDA.

1. Safety Data Request: Laboratory Data Relevant To Drug- Induced Liver Injury In All Completed And Ongoing Clinical Trials With Rivaroxaban

Analysis Datasets to be submitted consistent with the CDISC Standard:

Please provide complete laboratory test results (including lab test results obtained from central **as well as** local laboratories) for subjects during all Phases 1-4 completed and ongoing clinical trials with rivaroxaban, for the following laboratory tests: ALT (serum alanine aminotransferase), AST (serum aspartate aminotransferase), GGT (gamma glutamyl transferase), TBL (total serum bilirubin concentration), DIR (direct bilirubin concentration), ALP (alkaline phosphatase), and INR (international normalized ratio).

Please include in this dataset all results for specified lab tests obtained at any time after initiation of study therapy, or within 30 days after discontinuation of study therapy, regardless of whether the test was specified per protocol.

Please carefully organize your data, including reference ranges, and provide the following data sets consistent with the CDISC standard as SAS transport files:

- a. Liver data set: This data set should include the patients' liver-test results observed over time. The data thus collected should have multiple records per patient.
- b. Patient demographic data set: This data set should include selected patients' characteristics, such as the date of birth, race, sex, etc. The data thus collected should

have a single record per patient for the patients' characteristics do not change over time during the clinical study.

- c. Patient narrative data set: This data set should include the narratives based on CRF and including physician's remarks. Each patient should have a single record consisting of a paragraph in plain text.

Formats for the data sets, above, are specified as follows.

1) Liver data format specification

Requirement	Variable name	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	TRTCD	Treatment Code	Num
4. Required	TRTGRP	Treatment Group	Char
5. Required	EXSTDY	Start Date of Dose	Num (ISO 8601 YYYY-MM-DD)
6. Required	EXDT	Date of Exam	Num (ISO 8601 YYYY-MM-DD)
7. Required	ONPROTOCOL	Is the subject on protocol at the time of exam (Y/N)	Char
8. Required	EXENDT	End Date of Dose	Num (ISO 8601 YYYY-MM-DD)
9. Required	ONPROTOCOL		
10. Required	ALT	Serum alanine aminotransferase activity (U/L)	Num
11. Required	ALT_REF_HIGH	ALT High Normal Range (U/L)	Num
12. Required	BILI	Total serum bilirubin concentration (mg/dL)	Num
13. Required	BILI_REF_HIGH	BILI High Normal Range (mg/dL)	Num
14. Required	AST	Serum aspartate aminotransferase (U/L)	Num
15. Required	AST_REF_HIGH	AST High Normal Range (U/L)	Num
16. Required	ALP	Alkaline phosphatase (U/L)	Num
17. Required	ALP_REF_HIGH	ALP High Normal Range (U/L)	Num
18. Optional	INR	International Normalized Ratio	Num
19. Optional	GGT	Gamma glutamyl transferase	Num
20. Optional	BILIDIRECT	Direct-reacting serum bilirubin (mg/dL)	Num

2) Patient demographic data format specification

Requirement	Variable name	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	INVID	Investigator Identifier	Char
4. Optional	INVNAM	Investigator Name	Char
5. Optional	INVDESC	Investigator Description	Char
6. Required	BIRTHDT	Date of birth	Num (ISO 8601 YYYY-MM-DD)
7. Required	SEX	Sex	Char
8. Optional	RACE	Race	Char
9. Optional	COUNTRY	Country	Char

Requirement	Variable name	The variable means...	Variable-type
10. Required	HEIGHT	Height in Centimeters	Char
11. Required	WEIGHT	Weight in Kilograms	Char
12. Required	COMPLETE	Did the subject complete the study (Y/N)	Char
13. Required	DROPOUTDATE	Date of discontinuation, if applied	Num (ISO 8601 YYYY-MM-DD)
14. Required	DROPOUTREASON	Reason for discontinuation, if applied	Char

3) Patient narrative data format specification

Requirement	Variable name	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	NARRATIVE	Patient's narrative consisting of a paragraph in plain text.	Char

It is not necessary to include all subjects in this patient narrative data set. However, please be sure to include narratives for all subjects with **any** of the following conditions:

- $ALT \geq 5 \times ULN$,
- $TBL \geq 2 \times ULN$,
- Death;
- Discontinuation of study drug after an elevation of serum transaminase or bilirubin.

Individual clinical narratives should include the following information:

- Medical history and concomitant medications;
- Identification of treatment group / study drug (if unblinded);
- Dose, indication, duration of study therapy in days;
- Subject's medical history and concomitant medications;
- Dates and laboratory values for ALT, AST, total bilirubin, serology, and any other diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy;
- Clinical course of any signs or symptoms of liver disease, including jaundice;
- Differential diagnosis and final diagnosis of liver disease;
- Study site investigator, Company, and/or Liver Advisory Board assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events;
- Clinical course of liver-related adverse events including treatment and outcome;
- For deaths, please provide a link to autopsy results/report, if feasible.
- Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation. Please include any

hepatitis serology data and any other data relevant to the clinical course of the patient in the trial.

2. Descriptive Statistics Request: Number and Percent of Study Subjects with ALT (Alanine Aminotransferase) and TBL (Total Bilirubin) in Specified Categories

Populate the following tables with relevant numbers of study subjects from all completed and ongoing (blinded) Phases 1-4 clinical trials with rivaroxaban, using the liver data you submitted to the FDA. Use the row totals to calculate the percentages. Do not combine studies when producing the following tables.

Number (%) of rivaroxaban-treated subjects with maximal TBL by maximal ALT: All completed clinical studies regardless of indication or study duration (includes central + local laboratory data)						
	Maximal TBL (xULN)					
Maximal ALT	0 – 1	>1 – 2	> 2 – 2.5	>2.5 – 3	>3	Total
≤1 xULN						
>1-2 xULN						
>2-3 xULN						
>3-5 xULN						
>5-10 xULN						
>10 xULN						
Total						

Number (%) of comparator-treated subjects with maximal TBL by maximal ALT: All completed clinical studies regardless of indication or study duration (includes central + local laboratory data)						
	Maximal TBL (xULN)					
Maximal ALT	0 – 1	>1 – 2	> 2 – 2.5	>2.5 – 3	>3	Total
≤1 xULN						
>1-2 xULN						
>2-3 xULN						
>3-5 xULN						
>5-10 xULN						
>10 xULN						
Total						

Produce the same tables for ongoing studies in the same fashion.

If you have any questions, call Diane Leaman, Safety Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
 Chief, Project Management Staff
 Division of Medical Imaging and Hematology
 Products
 Office of Oncology Drug Products
 Center for Drug Evaluation and Research

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/s/

Kyong Kang

12/12/2008 02:43:29 PM



NDA 22-406

INFORMATION REQUEST LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 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 submission dated November 25, 2008.

We are reviewing the Statistical, Chemistry, Manufacturing and Controls and Clinical Pharmacology sections 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.

Chemistry, Manufacturing and Quality Control

1. Please submit a copy of your change control protocol for the drug product or an abbreviated version or summary that demonstrates the process.

Statistics

2. Please submit the following data sets (to facilitate these requests, you may request us to arrange a telephone conversation between our statistical team and your representatives):
 - a. Time-to-first event (including treatment phase and follow-up) for major bleeding, major bleeding including surgical site, and major or non-major clinically relevant bleeding.
 - b. We suggest that you use a survival analysis for multiple bleeding events as well. Therefore, submit bleeding data in the multiple event setting. That is, include the starting day of the event and the stopping day of the event in the date-frame.

Clinical Pharmacology

3. We are particularly concerned about the safety and efficacy of Rivaroxaban in certain patients. Specifically, our preliminary review of your application suggests a need for a lower strength tablet or a scored 10 mg tablet of Rivaroxaban to allow for downward dose adjustment in patients with renal impairment, hepatic impairment, and/or concurrent use of a moderate or strong CYP3A4 inhibitor. FDA's preliminary analysis suggests that increasing the dosing interval is not a viable option in these patients. Without downward dose adjustment, a significant part of the target population will not be able to utilize Rivaroxaban and inappropriate use of the current strength in these populations could pose an unacceptable risk. We recommend you to develop a lower strength tablet or a scored 10 mg tablet of Rivaroxaban and provide adequate data to support bioequivalence to the current proposed dose. We encourage you to promptly obtain this information and supply it as an amendment to your application. We ask that you comment upon this request within ten business days. Within your comment, specifically address your ability to supply the information in sufficient time to allow us to review it within this review cycle.
4. A preliminary review of your application indicates there is an approximately 40% higher exposure of Rivaroxaban in Japanese subjects compared to other ethnic groups. We note your assertion that this is related to body weight; however, our preliminary analysis of your population-pharmacokinetic (Pop-PK) data does not suggest this to be the case. We note that age was a significant covariate. Given the results of our preliminary analysis, we ask you to provide an additional explanation for the higher exposure in the Japanese population. Pharmacogenetic differences should be considered, in addition to other factors, in your response. We ask that you submit a response to this request within ten business days.

If you have any questions, call Diane Leaman, Regulatory Health Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Rafel (Dwayne) Rieves, M.D.
Director
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

12/5/2008 05:15:25 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 4, 2008

TO: File

FROM: Diane Leaman, SRPM

SUBJECT: **Xarelto Mid-Cycle Review**
NDA 22-406, Xarelto (rivaroxaban) tablets

The midcycle review for Xarelto™ (Rivaroxaban) tablets was held at 10:00 AM on December 2, 2008 at the FDA White Oak campus in Building 22, Conference Room 1415.

Those in attendance are as follows:

Richard Pazdur, Office Director, Office of Oncology Drug Products
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Division of Medical Imaging and Hematology Products (DMIHP)
Min Lu, M.D., Medical Officer, DMIHP
Diane Leaman, Safety Regulatory Project Manager, DMIHP
Marcus Cato, Regulatory Project Manager, DMIHP
Yash Chopra, M.D., Ph.D., Pharmacologist, DMIHP
Dr. Eldon Leutzinger, Ph.D., Pre-Marketing Assessment Leader, Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V
Aloka Chakravarty, Ph.D., Director, OTS/OB/Division of Biometrics V
Chava Zibman, Staff Fellow, OTS/Office of Biostatistics
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Qing Xu, Ph.D., Statistical Reviewer
Nam Atiqur (Atik) Rahman, Ph.D., acting Deputy Director, Office of Translational Science (OTS), Division of Clinical Pharmacology 5, (DCP5)
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Ph.D., Biopharmaceutics Reviewer
Raj Madabushi, Ph.D., OCP, Clinical Pharmacology Reviewer
Rosane Charlab Orbach, Staff Fellow, OTS/Office of Clinical Pharmacology (OCP)

The following presentations were made:

“NDA 22-406 Xarelto Tablets (Rivaroxaban) Mid-Cycle Review (CMC)” by Josephine Jee, presented by Eldon Leutzinger.

“Xarelto (NDA 22-406) Rivaroxiban IR Tablets Mid-cycle Meeting” by Joseph A. Grillo, Pharm.D., CP Reviewer

“Preclinical Midcycle Review” by Yash Chopra

“MidCycle Meeting December 2, 2008 Statistics” by Qing Xu, Ph.D.

“Xarelto (Rivaroxaban) NDA 22-406 Mid-Cycle Presentation” by Min Lu, M.D., M.P.H.

Action Items:

Statistics: Statistics will request an analysis from the sponsor to analyze recurrent bleeding events to see if there is a significant difference between the proximal and distal DVT in the studies.

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/s/

Diane V Leaman
12/15/2008 09:17:43 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development LLC
Attention: Andrea F. Kollath
DVM Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear M. Kollath:

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 the meeting between representatives of your firm and the FDA on November 17, 2008. The purpose of the meeting was to discuss the needed Chemistry, Manufacturing and Control items to be included in the NDA 22-406.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager,
Division of Medical Imaging and
Hematology
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 17, 2008
TIME: 2:30 PM – 4:00 PM
LOCATION: White Oak, Bldg 22, Room 1313
APPLICATION: NDA 22-406
DRUG NAME: Xarelto™ (rivaroxaban) Tablets
TYPE OF MEETING: NDA Orientation

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Diane Leaman

FDA ATTENDEES:

Office of Oncology Drug Products/Division of Medical Imaging and Hematology Products (DMIHP)

Diane Leaman, Safety Regulatory Health Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance,
Richard Lostritto, Ph.D., Head, Division Pre-Marketing Assessment III and Manufacturing Science (DPAMS)

Division of Pre-Marketing Assessment and Manufacturing Science, Branch V
Eldon Leutzinger, Ph.D., Premarketing Assessment Lead
Josephine Jee, Ph.D., Chemistry Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Johnson and Johnson Pharmaceutical Research and Development LLC (J&J)

Nancy Micalizzi, Chemistry, Manufacturing and Controls
Donald Doyle, Chemistry, Manufacturing and Controls
Sanjay Jalota, Regulatory Global Regulatory Lead, Regulatory Affairs
Andrea Kollath, Regulatory Affairs

Bayer HealthCare (Bayer)

Larry Winick, M.A., Deputy Director U.S. Regulatory Affairs
Robert Kelly, Chemistry, Manufacturing and Controls
Stephen Bartel, Chemistry, Manufacturing and Controls

BACKGROUND:

On July 28, 2008, J&J submitted NDA 22-406. On October 9, 2008, the Agency sent J&J and telefacsimile requesting the following information for NDA 22-406:

Information on the Drug Substance

1. Nomenclature

2. Description
3. Molecular Structure, Molecular Weight and Molecular Formula
4. Physicochemical Properties
5. Specifications (Release and Stability, if different)
6. Stability Protocol and Stability Commitment
7. Stability Data

Information on the Drug Product

1. Description
2. Drug Components and Composition
3. Specifications (Release and Stability, if different)
4. Stability Protocol and Stability Commitment
5. Stability Data
6. Container Closure
7. Container and Carton Labels
8. Environmental Assessment

The Agency also requested the sponsor to implement a Change Control Protocol.

MEETING OBJECTIVES:

To clarify the additional Chemistry, Manufacturing and Control (CMC) information needed in regard to the CMC portion of the Xarelto NDA and to discuss the change control procedures for the NDA.

DISCUSSION POINTS:

In Module 1., the Agency finds that the information in the NDA is elaborate and is concerned that the information that is currently found in Module 1. is merely a list of items in the DMFs. The Agency needs the specific information on the drug product available in the NDA. We need to know that you, as sponsor of the NDA, know what the product is and if the product is changed and if it is living up to specifications.

The sponsor responded that the Reviewer's Guide provided information in the three DMFs.

The Agency clarified that the adequacy of the information in the NDA is a review issue. There is a dearth of CMC information in the NDA. The NDA does not indicate what you, as sponsor, would do if the product becomes out of specification. What change controls do you have? Do you know what is going on? The sponsor said that the change control procedure is at the manufacturing site and that the control is done at inspection. The Agency argued that batch specifications for the drug product need to be placed in the NDA. J&J explained that the reason for having three DMFs is because there are two companies involved with the manufacturing process of the product (J&J and Bayer) and two DMFs are held by one company and the other DMF is held by the other company. J&J further noted that Bayer developed the compound and that Bayer is also an alternate manufacturer of the product. The two companies had a co-development agreement. Both companies DMFs support the required suppliers.

The Agency noted that we have accepted the "process" of submitting several DMFs into an NDA. However, this is a review issue. Multiple DMFS in a submission is acceptable, however,

the sponsor needs to be able to do what the NDA purports the sponsor to do. If there is a gap between the drug owner and the DMF holder, the sponsor needs to know about it. The sponsor is the responsible party. A DMF can be changed at any time. As the sponsor, you can seek drug changes with a DMF. A DMF does not need prior approval to make changes. As NDA sponsor, you need an iron-clad system. Any change has to have proper regulatory oversight. Any change must come from the NDA holder.

The NDA is a link to the CMC information. Access to the CMC information would be unwieldy technically on our end after approval of an NDA that does not contain the necessary information. If there are batches of the product that are out of specification, we need to be able to find the proper information in the NDA to prevent review issues and unfavorable actions in the future. We need a modicum of information in the NDA to ensure the review process.

The sponsor confirmed that the information referenced in Module 3, and previously requested (above) will be submitted to the NDA.

The sponsor will submit Post-approval changes protocol according to 21CFR314 regarding DMF cross reference to the NDA.

Johnson and Johnson and Bayer noted that the Agency request sounds acceptable.

DECISIONS (AGREEMENTS) REACHED:

The Agency minutes will be the final/official minutes of the meeting.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

The sponsor will submit the requested information to the NDA.

ATTACHMENTS/HANDOUTS:

None.

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/s/

Diane V Leaman
12/1/2008 11:26:27 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 1, 2008
TO: File
FROM: Diane Leaman
SUBJECT: November 26, 2008 e-mail and e-mail stream regarding
Clinical information request.

NDA 22-406, Xarelto (rivaroxaban) tablets

Hi Diane,
Thank you the clarification.
We will get started on these.
Happy Thanksgiving!!
Best regards,
Andrea

-----Original Message-----

From: Leaman, Diane V [mailto:diane.leaman@fda.hhs.gov]
Sent: Wednesday, November 26, 2008 9:20 AM
To: Kollath, Andrea [PRDUS]
Cc: sanjay.jalota@its.jnj.com
Subject: RE: NDA 22-406 Xarelto

Andrea,

A list with patient identifier hyperlinked to the CRFs should be fine. If this does not work for us, then, maybe we can look at doing the leaf element.

One thing that you can clarify is the location of the liver data in the CRFs. (when we open the CRF, we do not see the liver values). We want to be sure we can see the CRFs with the data from patients who had ALT > 3 and bilirubins >2. Was there a central laboratory where liver function tests were done? A sampling time is noted, but not the lab values.

For ongoing studies, data should not be unblinded for purposes of satisfying this request (where data are already unblinded, e.g., due to intervention for AE, the SAE data can be presented with the treatment that is known). Please take great care to proceed in responding to our request in such a manner that the integrity of the ongoing efficacy trials is not in any way compromised.

We also want the original, full autopsy results for all death cases, especially Hy's law cases.

I hope this helps you obtain our requests.

In addition, I checked with the CMC group and they want a copy of the change control protocol, if it is not already part of the CMC submission you just sent. If it is too unwieldy for an eCTD submission, you could send us a summary or synopses/overview of the protocol to give us assurance that something is in place for this aspect of the NDA.

Diane

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, November 18, 2008 5:15 PM
To: Leaman, Diane V
Subject: RE: NDA 22-406 Xarelto

Hi Diane,
I will get back to you as to when we can send this.
Kind regards,
Andrea

-----Original Message-----

From: Leaman, Diane V [mailto:diane.leaman@fda.hhs.gov]
Sent: Tuesday, November 18, 2008 3:48 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22-406 Xarelto
Importance: High

Andrea,

When we look in our EDR for the CRFs the pdf files appear to be named with the study number followed by a sequential number from 1 to the total number of CRFs. We can't look at the CRF folder and immediately identify which pdf file is for which subject. We have to open each file and look on the CRF to see the actual patient number. It would be nice to have a table that clearly identifies which pdf file goes with which patient.

Please provide us with a table for each study providing patient identifier for each patient listed in the CRF pdf files such as:

1. CRF file	patient identifier
11354-crf-1	11354-100014022
11354-crf-2	11354-100014032.

2. A separate folder containing the CRF pdf files for all patients in the database who had peak AST>3xULN and total bilirubin >2xULN and patients who had peak ALT>3xULN and total bilirubin >2xULN. For this folder also provide a table identifying the pdf files as described above.

3. Also, clarify whether you have submitted case report files for patients that potentially meet Hy's law criteria and describe how these patients were treated.

Please also provide:

4. Original CRFs for all subjects who had ALT>3x ULN and TB>2x ULN with all central or local LFTs available based on all database (completed and ongoing studies).

5. Full autopsy reports for patients who died with increased LFT's during or after treatment If autopsy was performed.

Thanks.

Diane Leaman, SRPM
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
12/1/2008 11:11:27 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 22, 2008
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf rm Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson (J&J)
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: CMC, Teleconference

MEETING CHAIR: Eldon Leutzing

MEETING RECORDER: Marcus Cato

FDA ATTENDEES:

Office of Pharmaceutical Science / Office of New Drug Quality Assessment/
Division Of Pre-Marketing Assessment And Manufacturing Science Branch V

Josephine M Jee, Ph.D., CMC Reviewer
Eldon E Leutzing, Ph.D., Pharmaceutical Assessment Lead

Office of New Drugs/ Office of Oncology Drug Products/
Division of Medical Imaging and Hematology Products

Marcus Cato, M.B.A., Regulatory Health Project Manager
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager
Florence Moore, M.S., Acting Regulatory Project Management Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Attendees from Johnson & Johnson Pharmaceutical Research and Development

Donald Doyle, ChemPharm Leader
Nancy Micalizzi, CMC Regulatory Affairs
Andrea Kollath, Regulatory Affairs
Kelly Kurtz-Colone, Global Regulatory Dossier Leader

Attendees from BayerHealthCare Pharmaceuticals, Inc.

Robert Kelly, Director, Regulatory Affairs CMC and Marketed Products
Deborah Flint, Associate Director, CMC Regulatory Affairs
Stephan Bartel, Global Regulatory Affairs CMC Manager
Dietmar Boecker, Global Submissions
Larry Winick, Regulatory Affairs
Cesar Vines, Global Submissions
Gerhard Schlueter, Head of General Medicine and Cardiovascular Regulatory Affairs

BACKGROUND:

NDA 22-406 for Xarelto™ (Rivaroxaban) Tablets was submitted July 28, 2008 (received July 28, 2008) for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement therapy and for patients undergoing knee replacement therapy.

MEETING OBJECTIVES:

To clarify the Agency's CMC requests and discuss how to submit the requested information.

DISCUSSION POINTS:

Johnson and Johnson (J&J) referenced a prior agreement with the agency regarding the acceptability of having the CMC information in a Drug Master File (DMF). FDA responded that it is not acceptable to reference a DMF for drug product data, but it is only acceptable to reference the DMF for drug substance data. FDA also reminded J&J that the code of federal regulations (CFR) also requires certain information at a minimum. J&J referenced the pre-NDA meeting with the agency and stated that this was addressed.

FDA commented that usually a firm bringing a product in from a supplier requires a battery of testing and there is particular concern with J&J having two products from different suppliers. FDA also stated that qualification of the drug product is needed. J&J asked if the drug substance information was acceptable in a DMF. FDA indicated that it was acceptable for the drug substance data to be in a DMF but has more concerns regarding the drug product data being in a DMF.

J&J mentioned that in module one of the application, there is product specification information and a reviewers guide to tie together any differences. FDA responded that this information should have been in module three. FDA agreed to check module one for the aforementioned information and asked the sponsor if all the required information is in module one. J&J stated that all required information was in module one and the DMF. J&J further stated that module one also contains the container and carton labels. FDA agreed to go back to verify if the application contained all the CMC information that is required for a NDA submission.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Drug product information submission to the NDA verses what can be referenced in a DMF.

ACTION ITEMS:

FDA agreed to check module one of the submission for the aforementioned information and give the sponsor feedback.

ATTACHMENTS/HANDOUTS:

None.

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/s/

Marcus Cato
11/13/2008 03:16:39 PM

Florence Moore
11/25/2008 02:21:17 PM

Dear Andrea,

We have determined there is information regards Chemistry, Manufacturing and Controls for drug substance and drug product that is missing in your application and that is critical for its review. Accordingly, provide the following information:

- A. Drug Substance
 - 1. Nomenclature
 - 2. Description
 - 3. Molecular Structure, Molecular Weight and Molecular Formula
 - 4. Physicochemical Properties
 - 5. Specifications (Release and Stability, if different)
 - 6. Stability Protocol and Stability Commitment
 - 7. Stability Data
- B. Drug Product
 - 1. Description
 - 2. Drug Components and Composition
 - 3. Specifications (Release and Stability, if different)
 - 4. Stability Protocol and Stability Commitment
 - 5. Stability Data
 - 6. Container Closure
 - 7. Container and Carton Labels
 - 8. Environmental Assessment

We also request that a Change Control Protocol be implemented for covering potential future changes in the manufacturing process for drug substance and drug product, since such changes (if they were to occur) could impact release specifications and ultimately the purity and quality of the drug product. Include the Change Control Protocol along with the other information requested as outlined above.

Since there are two alternate sources of Xarelto™ Tablets, there must be an appropriate mechanism in place to assure that the tablets from all sources used have the same purity and quality. That responsibility is Johnson & Johnson's, and should consist of appropriate monitoring of Xarelto drug substance and drug product for purity and quality, meaning to meet the regulatory specifications (Release and Stability). This is the basis for the requested CMC information.

If you have any questions, call me at (301) 796-1424.

Sincerely,

Diane Leaman, Safety Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
10/9/2008 02:31:25 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-406

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Andrea F. Kollath
DVM Director, Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300 Raritan, NJ 08869-0602

Dear Ms. Kollath:

Please refer to your new drug application (NDA) dated July 22, 2008, received July 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xarelto™ (Rivaroxaban) Tablets.

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 May 28, 2009.

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

The package insert should be revised to be in full compliance with the Physician's Labeling Rule format. Please see preliminary comments below.

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 request that you submit the following information:

Please revise your package insert as follows:

A. HIGHLIGHTS section



- (b) (4)
2. In the **CONTRAINDICATIONS** section, (b) (4)
shorten the bullet to read “Active major bleeding.”
3. In the **CONTRAINDICATIONS** section, (b) (4)
shorten the bullet (b) (4)
4. (b) (4)
5. In the **USE IN SPECIFIC POPULATIONS** section, delete (b) (4)
(b) (4)
- (b) (4)
6. In the **USE IN SPECIFIC POPULATIONS** section, in the Renal impairment (8.6) subsection, shorten the bullets and delete all sub-bullets. We recommend the following:
- “Severe Renal Impairment: Use with caution; use with concomitant medications (e.g., strong CYP3A4 inhibitors); may increase Rivaroxaban plasma concentrations
Kidney failure: Do not use
Hepatic impairment: Association with coagulopathy; may lead to bleeding (8.7).”
7. In the **PATIENT COUNSELING INFORMATION** section, delete the phrase (b) (4)

B. FULL PRESCRIBING INFORMATION section

1. Throughout the labeling refer to Xarelto in title case, not all capital letters.
2. In the **ADVERSE REACTIONS** section, (b) (4)
The contents of the current section may need to be placed in another section of the labeling and this subsection may need to be deleted until data after approval of the drug product has been collected. The corresponding section title in the **FULL PRESCRIBING INFORMATION: CONTENTS** should also match the heading to this subsection.

3. In the **DRUG INTERACTIONS** section, revise the title (b) (4) to clarify more clearly the specific items in this subsection. The corresponding section title in the **FULL PRESCRIBING INFORMATION: CONTENTS** should also match the heading to this subsection.
4. In the **USE IN SPECIFIC POPULATIONS** section, in the **8.1 Pregnancy** subsection, (b) (4) provide an explanation as to why this drug is a Category (b) (4) pregnancy drug.

We have also determined that there is information regarding Chemistry, Manufacturing and Controls for the drug substance and drug product that is missing in your application that is critical for its review. Accordingly, provide the following information:

A. Drug Substance

1. Nomenclature
2. Description
3. Molecular Structure, Molecular Weight and Molecular Formula
4. Physiochemical Properties
5. Specifications (release and Stability, if different)
6. Batch Analysis
7. Stability Protocol and Stability Commitment
8. Stability Data

B. Drug Product

1. Description
2. Drug Components and Composition
3. Specifications (Release and Stability, if different)
4. Batch Analysis
5. Stability Protocol and Stability Commitment
6. Stability Data
7. Container Closure
8. Container and Carton Labels
9. Environmental Assessment

We also request that you implement a Change Control Protocol for covering potential future changes in the manufacturing process for the drug substance and drug product, since such changes (if they were to occur) could impact release specifications and ultimately the purity and quality of the drug product. Include the Change Control Protocol along with the other information requested as outlined above.

If you have not already done so, you must 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/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional 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.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients less than 18 years of age.

If you have any questions, call Mrs. Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

10/1/2008 05:57:17 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2008

To: Linda Rebar	From: Diane Leaman
Company: GlaxoSmithKline	Division of Medical Imaging and Hematology Products
Fax number: (215) 751-4926	Fax number: (301) 796-9849
Phone number: (215) 751-4038	Phone number: (301) 796-1424
Subject: Postmarketing case report of case with aPTT prolongation who died	

Total no. of pages including cover: 3

Comments: Ms. Rebar, In your postmarketing case reports from your safety database for Arixtra, you had one out of eleven subjects who had aPTT prolongation and who died. Please submit the details from the case report of the patient who had prolonged aPTT, was associated with bleeding and organ failure and who subsequently died. The case report was from the September 30, 2006 data lock point.

Document to be mailed: ☐ YES ☒ NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2050. Thank you.

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/s/

Diane V Leaman
10/1/2008 02:19:10 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 18, 2008
TIME: 2:30 PM – 4:00 PM
LOCATION: White Oak, Bldg 22, Room 1313
APPLICATION: NDA 22-406
DRUG NAME: Xarelto™ (rivaroxaban) Tablets
TYPE OF MEETING: NDA Orientation

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Office of Oncology Drug Products

Richard Pazdur, M.D., Director

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwayne) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Officer,
Diane Leaman, Safety Regulatory Health Project Manager
Ebla Ali-Ibrahim, Regulatory Health Project Manager

Division of Drug Oncology Products

Ann Farrell, M.D., Deputy Director

Office of Drug Evaluation I

Division of Cardiovascular and Renal Products

Stephen Grant, M.D., Medical Team Leader

Office of Biostatistics/Division of Biometrics V

Jyoti Zalkikar, Ph.D., Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Qing Xu, Ph.D., Statistical Reviewer

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Sarah Pope, Ph.D., Branch Chief
Josephine Jee, Ph.D., Chemistry Reviewer

Office of Clinical Pharmacology (OCP)

Joseph Grillo, Pharm.D. Pharmacology Reviewer

Office of Translational Science/Office of Biometrics/Division of Biometrics VI

Mark Levenson, Ph.D., Statistician

Chava Zibman, Ph.D., Statistician, Staff Fellow

Office of Surveillance and Epidemiology

John R. Senior, M.D., Medical Officer (Hepatotoxicity)

EXTERNAL CONSTITUENT ATTENDEES:

Johnson & Johnson

Peter DiBattiste, Therapeutic Area Head Cardiovascular

Gary Peters, Franchise Medical Leader

Leonard Oppenheimer, Statistical Sciences

John Zhang, Statistical Sciences

Juliana Ianus, Statistical Sciences

Debra Karvois, Clinical Project Scientist

Mehul Desai, MD, Clinical

Michael Kronig, MD Regulatory CV Therapeutic Area Head Cardiovascular

An Thyssen, Clinical Pharmacology

Sanjay Jalota, Regulatory Global Regulatory lead

Andrea Kollath, Regulatory Affairs,

Andrea Masciale, Regulatory Affairs, FDA Liaison Office

Sigmond Johnson, Project Management

Bode, Nini, Preclinical

Harry Flanagan, Pharmacovigilance

Dina Anand, Pharmacovigilance

Nancy Micalizzi, CMC

Bayer Healthcare, Inc.

Scott. Berkowitz Franchise Medical Leader

Martin. Homering, Statistical Sciences

Dagmar. Kubitza, Clinical Pharmacology

Alice. Benson Statistical Sciences

Volker. Geiss Preclinical

Andrea. Derix Regulatory Affairs,

Sabine Dittmar, Pharmacovigilance

Torsten. Westermeier, Statistical Sciences

Aasia Bhatti, Pharmacovigilance

BACKGROUND:

NDA 22-406 for Xarelto™ (Rivaroxaban) Tablets was submitted July 28, 2008 (received July 28, 2008) for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement therapy and for patients undergoing knee replacement therapy.

MEETING OBJECTIVES:

To provide an avenue for the sponsor to present an overview of the NDA for Xarelto (Rivaroxaban) tablets submitted July 28, 3008. See attached copies of slides presented at the meeting.

ATTACHMENTS/HANDOUTS:

See attached

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/s/

Diane V Leaman
10/9/2008 01:22:28 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: Office of Surveillance and Epidemiology: c/o Dr. John Senior			FROM: Diane Leaman, RPM, Division of Medical Imaging and Hematology Products	
DATE September 17, 2008	IND NO.	NDA NO. 22,406	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT July 22, 2008
NAME OF DRUG Xarelto (rivaroxaban) tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-Xa	DESIRED COMPLETION DATE October 30, 2008
NAME OF FIRM: Johnson and Johnson Pharmaceutical Research and Development, LLC				
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 II 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 checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II 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 IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV 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 type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review data related to liver toxicity. This NDA is submitted for Xarelto (rivaroxaban), an oral anticoagulant for the prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery. Though this NDA is for short-term use of Xarelto, the drug is also being studied for a chronic use (stroke prevention in atrial fibrillation). The NDA contains a report which discusses the liver function SAEs from the controlled studies and a report of an integrated analysis of liver safety in Phase 2. See electronic submission at \\CDSESUB1\EVSPROD\NDA022406\022406.enx. A copy of the proposed labeling is attached.				
SIGNATURE OF REQUESTER Diane Leaman, RPM		METHOD OF DELIVERY (Check one) X DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Diane V Leaman
9/16/2008 06:12:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Mail: CDERDCRPQT attention: Devi Kozeli			FROM: Diane Leaman, SRPM, Division of Medical Imaging and Hematology Products	
DATE September 12, 2008	IND NO.	NDA NO. NDA 22-406	TYPE OF DOCUMENT N	DATE OF DOCUMENT July 28, 2008
NAME OF DRUG Xarelto™ (Rivaroxaban) Tablets		PRIORITY CONSIDERATIONS Standard	CLASSIFICATION OF DRUG Anti Xa	DESIRED COMPLETION DATE March 2, 2009
NAME OF FIRM: Johnson & Johnson				
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 II 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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
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III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV 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 type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS:				
Please review QTC study results. The network location is: \\CDSESUB1\EVSPROD\NDA022406\022406.enx				
In addition, the following submission was received on September 24, 2008:				
ECG Warehouse Notification		Upload ID:	20080721111244	
Sponsor:	Bayer Healthcare Pharmaceuticals	Status:	FDA Access Granted	
Study:	NDA 022406 / 11275	Action:	None (Ready For Regulatory Review)	
Attention: Cesar Vincas, Cesar Vincas, Leaman, Diane V, FDA Reviewers, and ECG Warehouse Administrators				
The study designated as "11275" that is part of FDA application "NDA 022406" has been imported into the ECG				

regulatory review. An e-mail with the attachment was sent to Devi Kozeli on September 24, 2008.

Please also reference (b) (4) that are being reviewed by DCRP and send a copy of your constlt to Alison Blaus, RPM.

If you have any questions, please reply to this message.

If you have any questions, please call Diane Leaman at 301 796-1424.

SIGNATURE OF REQUESTER Diane Leaman, SRPM

METHOD OF DELIVERY (Check one)

☒ DFS

☐ E-MAIL

☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Diane V Leaman
9/25/2008 04:49:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Office/Division): Division of Cardiovascular and Renal Products: c/o Dr. Norman Stockbridge/Stephen Grant			FROM (Name, Office/Division, and Phone Number of Requestor): Diane Leaman/Office of Oncology Drug Products/Division of Medical Imaging and Hematology Products/301-796-1424		
DATE August 26, 2008	IND NO.	NDA NO. 22-406	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT July 22, 2008	
NAME OF DRUG Xarelto (rivaroxaban) tablets		PRIORITY CONSIDERATION Std	CLASSIFICATION OF DRUG Anti Xa	DESIRED COMPLETION DATE	
NAME OF FIRM: Johnson and Johnson Pharmaceutical Research & Development, LLC					
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 checked="" 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 type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: Please provide a general perspective on the major study outcomes for Xarelto. This indicatino is for prophylaxis of deep vein thrombosis and Pulmonary embolism in patients udnergoing hip replacement sruger or knee replacement surgery. See electronic submission at \\CDSesub1\EVSPROD\NDA022406\022406.enx.					
SIGNATURE OF REQUESTOR Diane Leaman, RPM			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input 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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Diane V Leaman
8/26/2008 03:01:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>			
TO (Division/Office): CDER OSE CONSULTS			FROM: Diane Leaman/Office of Oncology Drug Products/Division of Medical Imaging and Hematology Products/301-796-1424		
DATE August 26, 2008	IND NO.	NDA NO. 22-406	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT July 22, 2008	
NAME OF DRUG Xarelto (rivaroxaban) tablets		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG Anti-Xa		DESIRED COMPLETION DATE
NAME OF FIRM: Johnson and Johnson Pharmaceutical Research & Development, LLC					
REASON FOR REQUEST					
I. GENERAL					
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <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 </div> <div style="width: 33%;"> <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT </div> <div style="width: 33%;"> <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): Trade name review </div> </div>					
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II 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 IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV 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 type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the tradename Xarelto (rivaroxaban) tablets. Please find enclosed the proposed package insert and the proposed immediate container and carton labeling. (Note that the name was submitted to IND 64,892 on August 23, 2007). PDUFA DATE: ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND/NDA HFD-160/Division File HFD-160/RPM HFD-160/Reviewers and Team Leaders					
NAME AND PHONE NUMBER OF REQUESTER Diane Leaman, 301 796-1424			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/

Diane V Leaman

8/26/2008 03:00:56 PM



NDA 22-406

NDA ACKNOWLEDGMENT

Johnson and Johnson Pharmaceutical Research and Development LLC
Attention: Andrea F. Kollath
DVM Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear M. Kollath:

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) Tablets

Date of Application: July 22, 2008

Date of Receipt: July 28, 2008

Our Reference Number: NDA 22-406

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 September 26, 2008 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/oc/datacouncil/spl.html>. 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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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 Medical Imaging and Hematology 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/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Acting, Safety Project Manager
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman

8/5/2008 11:53:17 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Mail: ODS: Ms. Janet Anderson, OSE/Dr. Claudia Karwoski, Mary Willy, Susan Berkman, Jody Duckhorn, Mary Dempsey			FROM: Diane Leaman, SRPM, Division of Medical Imaging and Hematology Products	
DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT N	DATE OF DOCUMENT July 28, 2008
NAME OF DRUG Xarelto™ (Rivaroxaban) Tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-Xa	DESIRED COMPLETION DATE February 13, 2008
NAME OF FIRM: Johnson and Johnson				
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 II 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				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
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III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV 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 type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please review the sponsor's Safety Surveillance plan (see attached). It is also located in the EDR at: VCDSesub1EVSPROD\NDA022406\0000 Please also include review of adverse events as related to risk management, particularly with liver injury. Xarelto is a new oral anticoagulant currently under review for a short term indication for the prophylaxis of VTE in patients undergoing hip or knee replacement surgeries. The proposed maximum treatment duration is 35 days for the short term indication. However, the drug may be used off-label as a long-term treatment to replace Coumadin if it is approved. Clinical trials to support long-term indications are currently ongoing. Current data (short-term) have raised some concerns regarding possible liver injury; the review is continuing. This NDA will be presented and discussed at an Advisory Committee meeting on March 19, 2009. Please evaluate the proposed safety surveillance plan and provide comments and any recommendations for a possible risk management plan for this product. Also, we would appreciate your designating an OSE reviewer to attend Xarelto Team meetings on an ongoing basis and to prepare a risk management presentation/comments for the March 19, 2009 advisory committee meeting.				
SIGNATURE OF REQUESTER Diane Leaman, SRPM, DMIHP			METHOD OF DELIVERY (Check one) X DFS <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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Diane V Leaman
12/17/2008 09:10:45 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 29, 2008
TIME: 11:30 AM – 1:30 PM
LOCATION: Room 1419 Building 22, White Oak Campus
APPLICATION: IND 64,892
DRUG NAME: Rivaroxaban, BAY 59-7939
TYPE OF MEETING: Pre-NDA meeting (Type B)

MEETING CHAIR: Dr. Rafel (Dwayne) Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwayne) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Officer,
Diane Leaman, Regulatory Health Project Manager
Adebayo Lanionu, Ph.D., Supervisory, Pharmacologist

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader

Office of Biostatistics. Division of Biometrics V

Jyoti Zalkikar, Ph.D., Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Yuan (Richard) Chen, Ph.D., Statistical Reviewer
Qing Xu, Ph.D., Statistical Reviewer

Office of Business Process Support- Regulatory Review Support Staff (OBPS-RRSS)

Donnovan F. Duggan II, Regulatory Information Specialist
Constance Robinson-Kuiperi, Regulatory Information Specialist

EXTERNAL CONSTITUENT ATTENDEES:

Bayer HealthCare

Dietmar Boecker, Deputy Director, Global Submission Manager
Lawrence Winick, M.A., Deputy Director U.S. Regulatory Affairs
Cesar Vincas, Regulatory Submissions

Johnson & Johnson

Ryan Claringbold, Global Dossier Leader
Joe Donato, Ph.D., Regulatory Submissions
Sanjay Jalota, MRPharmS, Senior Director, Global Regulatory Affairs
Andrea Kollath, DVM, Director, NA Regulatory Affairs

BACKGROUND:

Bayer submitted IND 64,892 on May 29, 2002 (received May 20, 2002) for the treatment and (b) (4) prophylaxis of venous thromboembolism (VTE). Bayer has met with the Agency on several occasions to discuss proposed indications and milestones with the drug development plan for BAY 59-7939 (December 5, 2005; February 15, 2006; August 23, 2006; March 15 and 20, 2007; September 27, 2007; October 9, 2007; November 15, 2007; November 16, 2007 and December 13, 2007).

On August 22, 2007, Bayer requested a meeting to discuss the eCTD content and format of a New Drug Application (NDA) filing to support approval of rivaroxaban for prophylaxis of venous thromboembolism (VTE) in patients undergoing orthopedic surgery of total hip replacement or total knee replacement surgery. On October 17, 2007, DMIHP scheduled the January 29, 2008 meeting. Bayer submitted background information on January 23, 2008. There were no questions in the background package. The purpose of the meeting was to allow Bayer to demonstrate its eCTD submission and allow the Agency reviewers to ask questions during the demonstration.

MEETING OBJECTIVES:

To present a demo eCTD with full structure, but placeholders for some documents, and to spend time navigating through the documentation and allowing Agency reviewers to ask questions of the sponsor regarding the format and structure.

DISCUSSION POINTS:

- Bayer demonstrated the eCTD structure and backbone for the DMIHP reviewers.
- The FDA regulatory review staff reminded Bayer that short descriptive titles in the backbone structure are helpful such as legacy files, xpt export files. The sponsor should define the XML in the submission.
- Discussion touched upon using the copy and paste function from the documentation. Bayer noted that going back and forth between figures and text depends on the reviewer tool used. All the clinical documents will be searchable. The nonclinical pharmacology files will be scanned documents in pdf format.
- The Agency requested the sponsor provide Phase 2, Phase 3 and QTc electronic datasets.

- The sponsor noted that the integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE) will have links to tables in the NDA. Bayer will be submitting the structure of the electronic data-files soon for Agency review. Bayer and Johnson and Johnson will confirm the availability of the data in the ISE. The liver data will be included in the adverse event (AE) electronic datasets from all the studies on rivaroxaban.
- The Agency requests the sponsor provide a cumulative list of all the variables in the electronic datasets (an additional list to support review) across all studies; this cumulative list of all variables should list the variables in alphabetical order.
- For the prophylactic indication, the sponsor should provide full electronic datasets for the integrated Summary of Safety as well as unique electronic datasets for each of the four Phase 3 studies.
- Electronic data sets will be presented individually for each study and also provided for the integrated summary of safety as well as the integrated summary of efficacy. The QTC study will also have unique electronic datasets, as will the Pharmacokinetic/Pharmacodynamic (PK/PD) data that support the clinical pharmacology analyses. Bayer verified that population PK/PD modeling study will be included. The sponsor will include the final protocol and SAP part of the study report supporting documents.
- The sponsor acknowledged an error in 5.2 tagging files in the background package. Bayer will submit an ISS and a separate Liver ISS. The sponsor may have more than one link to a study file. Study files will not be duplicated in the submission.
- The sponsor noted that they will not be including the carcinogenicity study. They will provide a link to Module 2 where they will provide a justification for not including the study.
- Bayer will reference three Drug Master Files (DMF) in the document. They will not include chemistry information in the submission, in deference to the DMF. The DMFs will be in eCTD format.
- Bayer plans to submit the NDA the end of June 2008.

DECISIONS (AGREEMENTS) REACHED:

- Bayer will work on including a comprehensive, alphabetical list of the data set variables in a subfolder in the submission.
- Bayer will work to make navigation of the eCTD, including the electronic datasets, user-friendly.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None.

ACTION ITEMS:

Bayer will be submitting the structure of the data-files soon for Agency review.

The Division will send the sponsor meeting minutes 30 days from the meeting date.

ATTACHMENTS/HANDOUTS:

None.

Linked Applications

Sponsor Name

Drug Name

IND 64892

BAYER
PHARMACEUTICALS
CORP

BAY 59-7939

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

/s/

DIANE V LEAMAN
02/01/2008

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 13, 2007
TIME: 2:00 PM – 3:30 PM
LOCATION: Room 1419 Building 22, White Oak Campus
APPLICATION: IND 64,892
DRUG NAME: Rivaroxaban, BAY 59-7939
TYPE OF MEETING: Pre-NDA meeting (Type B)

MEETING CHAIR: Dr. Rafel (Dwayne) Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwayne) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Officer,
George Shashaty, Medical Officer
Diane Leaman, Regulatory Health Project Manager
Yash Chopra, Ph.D., Pharmacologist

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader

Office of Biostatistics. Division of Biometrics V

Jyoti Zalkikar, Ph.D., Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Qing Xu, Ph.D., Statistical Reviewer

Office of New Drug Quality Assessment

Ravi S. Harapanhalli, Ph.D., Branch Chief, CMC

Office of Surveillance and Epidemiology/Division of Drug Risk Evaluation

Betsy Scroggs, Pharm.D., Safety Evaluator

EXTERNAL CONSTITUENT ATTENDEES:

Bayer HealthCare

Alice Benson, MS, Lead Statistician, Global Clinical Statistics
Scott Berkowitz, MD, Vice President, and Head, Antithrombotic Therapies Group
Dietmar Boecker, Deputy Director, Global Submission Manager
Andrea Derix, PhD., Global Regulatory Strategist
Patricia Hegarty, MS, Expert Statistical Analyst
Harald Kallabis, PhD, Global Project Leader
Rene Kluensch, PhD., Global Regulatory Strategist
Martin Homering, MSPH, Principal Statistician, Hematology/Cardiology
Max Wegner, PhD, Head GRA Therapeutic Area Hematology/Cardiology
Torsten Westermeier, PhD., Therapeutic Area Expert Statistician, Hematology/Cardiology
Lawrence Winick, M.A., Deputy Director U.S. Regulatory Affairs

Johnson & Johnson

Ryan Claringbold, Associate Director, Regulatory Affairs
Sanjay Jalota, MRPharmS, Senior Director, Global Regulatory Affairs
Debra Karvois, MS, Director, Clinical Scientist
Andrea Kollath, DVM, Director, NA Regulatory Affairs
Michael Kronig, MD, Vice President, Internal Medicine TA Regulatory Affairs Head
Andrea Masciale, Senior Director, Regulatory Affairs, FDA Liaison Office
Leonard Oppenheimer, PhD, Senior Director, Statistical Sciences
Gary Peters MD, Vice President, Franchise Medical Leader
John Zhang, PhD, Director, Statistical Leader, Internal Medicine
Sigmond Johnson, Director, Program Manager

BACKGROUND:

Bayer submitted IND 64,892 on May 29, 2002 (received May 20, 2002) for the treatment and secondary prophylaxis of Venous Thromboembolism (VTE). Bayer has met with the Agency on several occasions to discuss proposed indications and milestones with the drug development plan for BAY 59-7939. On October 11, 2007 (received October 15, 2007) Bayer requested a meeting to discuss the eCTD content and format of a New Drug Application (NDA) filing to support approval of rivaroxaban 10 mg for prophylaxis of venous thromboembolism (VTE) in patients undergoing orthopedic surgery of total hip replacement or total knee replacement surgery. The Division of Medical Imaging and Hematology Products (DMIHP) sent Bayer a meeting letter on October 17, 2007 granting the meeting. Bayer submitted a background briefing package on November 9, 2007 (received November 13, 2007). On December 7, 2007, DMIHP sent Bayer a copy of draft responses to questions from the November 9, 2007 background package.

The questions and preliminary responses sent to the sponsor are as follows:

Questions

Pre-Clinical

1. Does the Agency agree that the non-clinical studies listed in the pre-NDA background document are sufficient to support filing and potential approval of the rivaroxaban NDA (Appendix 1)?

FDA Response:

The studies list appears to be sufficient for filing purposes with the exception that the rat and mouse carcinogenicity studies final reports should be submitted with the initial NDA submission.

2. Does the Agency agree with Bayer/J&J's plan to submit data line listings from animal toxicological studies electronically, as scanned attachments to each study report (hyperlinking can be performed from the reports to each document, but not to individual animal data (Section 3.5)?

FDA Response: We strongly encourage you to ensure the quality of your scanned attachments to enable us to search the documents and make legible cut and paste insertions into our documents, if needed, by the reviewer.

Clinical Pharmacology

3. Does the Agency agree that the clinical pharmacology studies listed in the pre-NDA background document are sufficient to support filing and potential approval of the rivaroxaban NDA (see Section 3.2.2 and Appendix 2)?

FDA Response:

The list of the studies in the section 3.2.2 and Appendix 2 of the meeting package appears to be reasonable for submission. The filing and approval of the rivaroxaban will be review issues.

4. For the Phase 1 studies listed in Appendix 2, does the Agency agree with Bayer/J&J that by providing Appendix 16.2. and Appendix 16.4 as part of the individual clinical study reports transfer of electronic data is not required for the clinical pharmacology studies (Section 3.5) with the exception of the QTc study (Study 11275)?

FDA Response: Yes

5. Does the Agency agree that for the QTc study (Study 11275) for which the FDA has requested detailed electronic information, Bayer/J&J will submit the data in CDISC/SDTM(3.1.1) format and Bayer analysis format (Section 3.5)?

FDA Response: Yes

Please keep in mind that the following items should be submitted:

- Electronic or hard copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- Copies of the study reports for any other clinical QT study for this product that has been performed
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Narrative summaries and case report forms for any of the following that occur in this thorough QT study:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study.
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table (see Table 1. below).

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)

Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal $t_{1/2}$	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

6. Does the Agency agree that Bayer/J&J's population PK and PK/PD analyses as outlined in Section 3.5 are acceptable?

FDA Response:

In general, the data submission plan of the population PK / PD analysis as outlined in section 3.5 appears reasonable. Consider the following comments to support the PK/PD review:

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as

CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Clinical and Statistical

7. Does the Agency agree that the Phase 2 and Phase 3 studies listed in Appendix 3 and 4 of this pre-NDA background document are sufficient to support the filing and potential approval of the NDA?

FDA Response:

The listed completed studies are sufficient for NDA submission. Filing and approval decisions are contingent upon review findings.

8. For the Phase 1 studies, does the Agency agree with the planned pooling strategy for presenting the adverse event and laboratory data from these studies based on an integrated analysis with three dose groups of rivaroxaban (less than 10 mg, 10 mg, greater than 10 mg) (Section 3.2.5.1)?

FDA Response: It is acceptable.

9. For Phase 2 studies, does the Agency agree with the following planned pooling strategy (Section 3.2.5.1):

- a). present an integrated analysis of the adverse event data for the four orthopedic surgery studies:

FDA Response: It is acceptable for submission.

- b). present an integrated analysis of efficacy and adjudicated bleeding event data for the three twice daily dosing Phase 2 orthopedic surgery studies, and discuss these findings in relation to the Phase 2 once daily dosing study.

FDA Response: It is acceptable.

- c). present a separate integrated analysis of adverse event data from the two DVT treatment studies.

FDA Response: It is acceptable.

- d). to not integrate the efficacy and safety data from the Phase 2 orthopedic surgery studies with those from Phase 3 studies (since the Phase 3 program used a different venography adjudication group, had some changes to the endpoint definitions (e.g. major bleeding) and was solely once daily dosing while most of the Phase 2 data was with twice daily dosing)?

FDA Response:

A separate efficacy analysis for phase 2 and 3 studies for each indication is acceptable. However, the integrated safety summary should include all clinical studies by dose regimen.

e.) to discuss the 3 Japanese Phase 2 atrial fibrillation studies individually?

FDA Response: It is acceptable.

Phase 3

10. Does the Agency agree with pooling the Phase 3 data from the RECORD 1, 2, 3 and 4 studies using the "Total Duration Pool" as the primary pool for the integrated analysis? [The "Total Duration Pool" is defined as events occurring during the double-blind study medication (active and placebo control treatment) from all four Phase 3 studies of the RECORD program)].

FDA Response: It is acceptable to pool studies for safety analyses. Pooling studies for efficacy analysis will be problematic and it is considered as a post-hoc analysis. Additional analyses may be requested during NDA review.

11. Are there alternative supportive pooling strategies the Agency would prefer in addition to those proposed in the updated SAP (i.e., the pooled RECORD 1 and 2 populations; the pooled RECORD 3 and 4 populations; and RECORD 1, 2, 3 and 4 studies through Day 12 \pm 2)?

FDA Response: See response to question 10 (above).

12. Does the Agency agree that pooled analyses using "post-tablet" and "active control" pools are not required? ("Post-tablet" refers to treatment-emergent events that occur after initiation of rivaroxaban (tablet or matching placebo); "active control" refers to the common treatment period where active rivaroxaban and active enoxaparin were administered, i.e., does not include Day 12 to Day 35 in RECORD 2 where placebo was administered in the enoxaparin treatment group).

FDA Response:

Multiple analyses are necessary to fully explore the data. A safety analysis should include a comparison of the study drug with all comparators (active control drug and placebo). Use total treatment duration, regardless of active or placebo treatment, in the safety comparison.

13. Does the Agency agree with the integrated efficacy analyses in the RECORD 1, 2, 3 and 4 SAP (Appendix 5)?

FDA Response: The proposed pooled analysis is considered to be a post-hoc hypothesis-generating analysis.

14. Can statistically significant results from the prespecified composite endpoint of symptomatic VTE and death be included in the Clinical Studies section of the USPI?

FDA Response: This will be a review issue.

15. Does the Agency agree with the integrated safety analyses in the RECORD 1, 2, 3, and 4 SAP (Appendix 5)?

FDA Response: It appears to be acceptable for submission.

16. Does the Agency agree that a comprehensive discussion of bleeding related parameters can be a section of the Integrated Summary of Safety and not a stand alone document?

FDA Response: It is acceptable.

17. Does the agency agree with the proposed subgroups for the efficacy, bleeding, and adverse events analyses, as per Tables 2.1, 2.2 and 2.3?

FDA Response: They are acceptable.

ISS for Liver Safety

18. Is the separate comprehensive "liver" ISS analysis summarizing the Phase 1, 2, and 3 liver laboratory and adverse event safety data from completed and ongoing studies, which will be placed in Module 5.3.5.3 of the NDA (Reports of Analyses of Data From More Than One Study), acceptable to the Agency?

FDA Response: It is acceptable. However, it should be referenced in the ISS laboratory evaluation section. Please provide appropriate links between the documents.

19. Does the agency agree that only ALT laboratory abnormalities will be presented (except for cases with ALT > 3X ULN and total bilirubin > 2X ULN where all liver enzymes will be reported) in the updated liver ISS?

FDA Response: No, all liver test results should be presented.

Adverse Reaction Section of USPI

20. Does the Agency agree with the use of investigator-assessed causality as the primary determinant for identifying ADRs?

FDA Response: No. Evaluation of ADRs, regardless of attribution, will be an important part of the safety review. Labeling regarding adverse events is contingent upon the numeric comparison of the adverse event rates.

21. Does the Agency agree that the primary source for selecting ADRs to report in the label is the pooled analysis of the RECORD 1, 2, 3, and 4 studies?

FDA Response: No. All safety data will be considered for the labeling.

22. Does the Agency agree with the information proposed to be included in the Adverse Reactions section of the label including a table of adjudicated bleeding event rates?

FDA Response: It is acceptable for submission.

23. Does the agency agree with a cutoff of $\geq 1\%$ frequency for describing ADRs in the Adverse Reaction section of the USPI?

FDA Response: It is acceptable for submission.

24. Does the Agency agree with the use of Medical Entities (grouped Preferred Terms) for the adverse event portion of the label (Section 3.2.6.1)?

FDA Response: It is acceptable for submission.

25. Does the Agency agree with the list of proposed Medical Entities (Appendix 6)?

FDA Response: It is acceptable for submission.

PHASE 2 AND PHASE 3 ONGOING STUDIES IN OTHER INDICATIONS; RESULTS FROM LONG-TERM SAFETY DATABASE

26. Does the agency agree with the proposal to provide best available "snapshot" results from ongoing studies for the initial filing and the safety update (Section 3.3.2)?

FDA Response: It is acceptable, as described on page 23 of the meeting background package.

27. Does the Agency agree with the proposal as outlined for unblinded safety results from the EINSTEIN-DVT, EINSTEIN-PE and ATLAS-ACS studies (Section 3.3.2.1)?

FDA Response: It is acceptable for submission.

28. Does the Agency agree with the proposal as outlined to provide the blinded results from the ROCKET –AF, JAPAN-AF, EINSTEIN-Extension and MAGELLAN studies along with unblinded results for SAEs unblinded according to standard procedures (Section 3.3.2.2)?

FDA Response: It is acceptable for submission.

RISK MANAGEMENT PLAN

29. Is the Agency amenable to a separate dedicated meeting at a future date to discuss the details of the Risk Management Plan (Section 3.4)?

FDA Response: Yes.

GENERAL NDA AND ECTD FORMAT QUESTIONS (SECTION 3.5)

30. Does the Agency agree that Bayer/J&J can submit an eCTD adhering to current guidelines and specifications, without submitting another pilot eCTD?

FDA Response: Yes.

31. Does the Division agree that the proposed content and eCTD format of the NDA, as outlined in this pre-NDA background document, are acceptable?

FDA Response: Yes.

32. Does the Agency agree with the proposal to submit non-clinical and clinical study reports and tagging files as single PDFs using the "legacy-clinical-study-report" file-tag value.

FDA Response: Yes, of course legacy reports will create difficulties when attempting to replace any individual parts of the report. If you think that nothing will ever change in these reports, then a legacy report format is fine.

33. Does the Agency agree with the proposal for the definition of the element "duration" in the STF (short/medium/long studies for non-clinical studies as follows: <4 week studies = "short"; 1 & 3 month studies = "medium"; 6 & 12 month studies = "long", in accordance with prior submissions)?

FDA Response: There is no attribute within the xml backbone for defining the exact duration. You could, however, designate this in the leaf title and/or the document title. We recommend that you indicate the specific duration of each of the studies in the leaf/document title. The variable terms (short-term, medium-term, and long-term) can be included in parenthesis, if needed.

34. Does the Agency agree that Bayer/J&J can restrict transfer of electronic datasets to the 5 studies (QTc study and the 4 pivotal Phase 3 studies) listed in Table 5, Section 3.5?

FDA Response: No. Submit all datasets electronically.

35. Does the Agency agree that Bayer/J&J can submit two types of electronic datasets [CDISC/SDTM(3.1.1)] and Bayer Analysis?

FDA Response: CDISC is the FDA standard.

36. Does the Agency agree to the proposed documentation of the key primary and secondary efficacy analysis: Detailed analysis results metadata will be in the format of a Microsoft Word or Excel table and will contain the following information organized by table: table number, table description, Bayer analysis dataset(s) used, and documentation containing information about how the analysis was performed?

FDA Response: Please send the information in PDF format. Do not send in Excel spreadsheets or Microsoft Word documents- convert these to PDF.

37. Does the Agency agree with Bayer/J&J's plan to provide the NONMEM datasets in .xpt format and the NONMEM control streams and output in .pdf format, as is detailed in the eCTD format guidelines?

FDA Response: Please see Clinical Pharmacology comment to Question 6.

38. Does the Agency agree with Bayer/J&J's plan to submit some SAS transport files that could be up to 300MB in size?

FDA Response: 300MB should be the largest.

39. Does the Agency agree with the proposal to submit narratives and case report forms for deaths, discontinuations due to adverse events, serious adverse events including all liver related SAEs and all cases of ALT > 3xULN plus Total Bilirubin > 2xULN from the completed Phase 1, 2, and 3 studies?

FDA Response: It is acceptable for submission.

40. Does the Agency agree with the proposal to submit narratives for all cases of ALT > 3xULN plus Total Bilirubin > 2xULN from all ongoing studies?

FDA Response: It is acceptable for submission.

41. The Summary of Clinical Efficacy (SCE) for the rivaroxaban NDA will be prepared in accordance with regulation 21 CFR 314.50(d)(5)(v) calling for an integrated summary of efficacy (ISE) and will be provided in Module 2.7.3. Based on Guidance for Industry (M4: The CTD – Efficacy Questions and Answers), the SCE provided in Module 2.7.3 will contain the level of detail expected for an ISE. Therefore, a separate ISE will not be provided in Module 5.3.5.3, Reports of Analyses of Data From More Than One Study. Is the proposal to submit the SCE in Module 2 and not to submit an ISE in Module 5 acceptable to the Agency?

FDA Response: The ISS and ISE DO NOT BELONG IN MODULE 2. They belong in Module 5. The level of detail that is required for the ISS and ISE take it out of the

summary category. The ISS and ISE are integrated analyses not really summaries. Do not get confused by the word "summary." Please put the ISS and ISE in 5.3.5.3.

5.3.5.3 Reports of analyses of data from more than one study

Integrated analysis of safety

Integrated summary of safety report

Analysis datasets

Analysis programs

Integrated analysis of efficacy

Integrated summary of efficacy report

Analysis datasets

Analysis programs

The only time it is acceptable for the ISS and ISE to be in Module 2 is if there is only one study.

42. The Summary of Clinical Safety (SCS) for the rivaroxaban NDA will be prepared in accordance with regulation 21 CFR 314.50(d)(5)(vi) calling for an integrated summary of safety (ISS) and will be provided in Module 2.7.4. Based on Guidance for Industry (M4: The CTD – Efficacy Questions and Answers), the SCS provided in Module 2.7.4 will contain the level of detail expected for an ISS. Therefore, a separate ISS will not be provided in Module 5.3.5.3, Reports of Analyses of Data From More Than One Study. Is the proposal to submit the SCS in Module 2 and not to submit an ISS in Module 5 acceptable to the Agency?

FDA Response: See Question 41 (above).

PRIORITY REVIEW

43. Does the Agency concur that a request for priority review is justified and will the Agency give consideration to a priority review once the application is filed?

FDA Response: The decision will be made at the filing meeting.

44. Assuming the Agency grants a 6-month priority review, does the Agency agree with a 4 month safety update after the original NDA submission date?

FDA Response: Yes.

45. If the Agency accepts a 4-month safety update date, will the Agency agree that the update is not considered a major amendment?

FDA Response: Additional major clinical data will be considered to be a major amendment.

46. Will the Agency give consideration to reviewing the MRRs for RECORD 1, 2 and 3 and the pre-clinical module (Module 2: Section 2.4 and 2.6 and Module 4) prior to the NDA submission to facilitate review by the primary reviewers?

FDA Response: All studies to support the proposed indication should be submitted in the NDA submission.

ADVISORY COMMITTEE

47. Does the Agency anticipate that rivaroxaban would be the subject of an Advisory Committee meeting for the prophylaxis of VTE in patients undergoing total hip replacement or total knee replacement surgery?

FDA Response: We anticipate the need for an advisory committee discussion, barring review findings that would preclude a substantive discussion.

PUBLISHED LITERATURE

48. Does the Agency agree with Bayer/J&J's plans to submit published literature according to the following proposal?

- Bayer/J&J will submit in Module 5, Section 5.4 copies of all published literature cited in Module 2.5, Clinical Overview and in Module 2.7, Clinical Summaries in accordance with ICH guideline M4E.
- Bayer/J&J will perform a search of the published scientific literature for reports relevant to the clinical safety and effectiveness of rivaroxaban using an appropriate cut-off date. Relevant published literature identified by the search will be summarized in a report to be included in Module 5, Section 5.3.5.4, copies of all relevant references will be provided in Module 5, Section 5.4.
- References cited in the individual study reports will not be included in the submission but will be available upon request.
- All references that are not provided in Module 5 will be available upon request.

FDA Response: It is acceptable for submission.

FINANCIAL DISCLOSURE

49. As per 21 CFR 54, Sponsors are required to provide certification of financial disclosure in an NDA for any studies FDA will rely on to establish a product is effective in a claimed indication. As such, Bayer/J&J plans to provide financial disclosure information from the Record 1, 2, 3 and 4 Phase 3 key efficacy trials only in the NDA.

Is Bayer/J&J's proposal to supply financial disclosure information acceptable to the Agency?

FDA Response: It is acceptable for submission.

CMC Comment

"Submit a detailed pharmaceutical development report tracing the design and development of the drug product and the process. Refer to ICHQ8 for the details. Also, submit the stability data in

SAS transport files or Excel spreadsheet format along with statistical analysis of all stability-indicating quality attributes."

On December 11, 2007, Bayer/J&J submitted "clarifying questions/positions" in reply to the FDA's preliminary responses. They are seeking clarity and follow-up to questions 19, 20, 21, 41/42, and the CMC Comment. The Division did not have time to review the December 11, 2007 list of questions. The meeting served to discuss these questions.

MEETING OBJECTIVES:

To discuss the outstanding questions from the November 9, 2007 background package regarding the eCTD content and format of a New Drug Application (NDA) filing to support approval of rivaroxaban 10 mg for prophylaxis of venous thromboembolism (VTE) in patients undergoing orthopedic surgery of total hip replacement or total knee replacement surgery.

DISCUSSION POINTS:

Question 1. The sponsor asked if they would be required to complete the carcinogenicity study before submitting the NDA. The Division responded that because this is a short-term indication, the sponsor can indicate in the submission that the carcinogenicity studies are ongoing in the NDA submission.

Question 2.

Bayer will submit the one Phase 1, Phase 2 and the four Phase 3 studies in STDM format. Bayer will submit analysis sets for Phase 2 and Phase 3 and liver study data.

Question 9e.

Bayer should include data from Japanese (Phase 2) studies in the ISS.

Bayer does not need the ISE to be fully integrated since the patient populations/indications somewhat differ. However, the ISS does need to be fully integrated (to include integrated analyses of important safety outcomes). Bayer should (as customary) provide separate reports for the Phase 2 and the Phase 3 studies. The Division recommends that Bayer analyze the Phase 2 and Phase 3 studies by dose regimen (for major safety outcomes). Bayer can break down the regimens in the Phase 2 studies by daily dosing.

Question 19:

FDA Response: All liver test results should be presented.

Clarification response to Question 19:

Bayer/J&J is providing descriptive statistics of all liver parameters in the general ISS.

The intent of the initial proposal for the liver ISS was to provide a more detailed summary of selected liver parameters (ie: ALT abnormalities > 3xULN [either alone or in conjunction with total bilirubin 2x ULN], > 5xULN, > 8xULN, > 10xULN, > 20xULN). We will now add similar summaries for AST. We propose these summaries because ALT and AST are the most sensitive

indicators for potential hepatocellular injury. For subjects with an ALT or AST > 3x ULN in conjunction with a total bilirubin > 2x ULN, our proposal is to provide additional liver laboratory data that could aid in the clinical interpretation of such cases. Such laboratory tests, as collected in the RECORD program, may include direct/indirect bilirubin, alkaline phosphatase, GGT, and LDH.

Descriptive statistics of non-transaminase laboratory parameters will be included as part of the general ISS, and there will be cross-references between the general ISS and liver ISS. In addition, narratives for specific subjects with pre-specified liver function abnormalities in the individual study reports will be cross-referenced. We are not proposing a detailed narrative for individual subjects with isolated bilirubin increases (or isolated alkaline phosphatase increases) that are not accompanied by ALT or AST elevations > 3x ULN because these cases are generally not indicators of severe drug-induced liver injury.

Does the Agency concur with this approach?

FDA Response: No, all relevant liver test results including direct/indirect bilirubin, alkaline phosphates, GGT, and LDH should also be presented in the liver ISS, as well as INR as a measure of liver function in cases with available data.

Question 20: Causality

FDA Response: Evaluation of ADRs, regardless of attribution, will be an important part of the safety review. Labeling regarding adverse events is contingent upon the numeric comparisons of the adverse event rates.

Clarification response to Question 20:

We (Bayer) will provide summaries and listings of both all treatment emergent and drug related (by investigator) treatment emergent adverse events. We will propose an algorithm to determine which of these are ADRs based on comparison of event rates and biologic plausibility. We believe this is consistent with your preliminary response.

Does the Agency concur with this approach?

FDA Response: Bayer should provide shift tables for ALT, GGT, LDH and any other laboratory tests they regard as important. Bayer should perform analyses of major safety outcomes by the lot of drug used. Document the detailed analysis. Bayer may submit draft (liver safety) tables to Agency to examine and comment upon. The Division is skeptical of investigational assessments of causality as the definitive determination of drug relatedness.

Question 21: Primary source for ADRs

FDA Response: All safety data will be considered for the labeling.

Clarification response to Question 21:.

As stated in the background package, we agree that all safety data from all clinical studies will be

considered for the labeling. Since the vast majority of the safety data available for the 10 mg once daily dose will be from the RECORD 1, 2, 3 and 4 studies (approximately 6200 patients for this dose compared with approximately 142 patients in Phase 2 studies), we propose that the primary source for ADRs to included in the incidence tables will be from the integrated analysis of these 4 studies.

All other data sources (e.g. Phase 1 and Phase 2 which include different strengths) will also be reviewed for ADRs, and appropriate ones included in the label. These data sources are considered supplemental since their robustness will be limited due to the much smaller numbers of exposures. Bayer/J&J believe that this approach is consistent with the FDA's preliminary response of "all safety data" will be considered for labeling.

This is consistent with our response to Q20

Does the Agency agree with this reply?

FDA Response: Yes

Question 41/42: ISS and ISE

FDA Response: The ISS and ISE DO NOT BELONG IN MODULE 2. They belong in Module 5. Please put the ISS and ISE in 5.3.5.3. Reports of analyses of data from more than one study.

Supply electronic datasets for both Phase 2 and Phase studies.

The Division prefers xpt format and one record per patient. In addition, we prefer a derived data set with demographics and efficacy and safety information in two part file format (stand alone derived dataset and detailed dataset).

FDA Statistical reviewer, Satish Misra, met with the Bayer's statistical reviewers and eCTD personnel on the side after the meeting to discuss the derived dataset for this submission. A derived dataset along with the definition files should be submitted for both primary and secondary efficacy analyses and should include information about demographics, efficacy, baseline, subgroups, and all the key variables, etc. Bayer's statistical reviewers and eCTD personnel agreed to provide the details of this request for FDA's review.

OIT Clarification response to Question 41 and 42

We acknowledge the Agency's response - we did not mean to imply we would place the ISS and ISE in module 2. The ISS and ISE and all datasets, attachments and appendices would be placed in module 5. Our intent is to use the text of the ISE and ISS text for module 2.7.3. and 2.7.4 respectively.

Per draft FDA guidance, released in June 2007, entitled "Integrated Summaries of Effectiveness

and Safety: Location within the Common Technical Document,". Page 7, example 4, of this draft guidance indicates that it is possible to use the same text in Module 2.7.3 and 5.3.5.3 for the ISE, and 2.7.4 and 5.3.5.3 for the ISS. Therefore, if the text portion of the ISE also meets the requirements of 2.7.3, and the text portion of the ISS also meets the requirements of 2.7.4, we would like to make use of this.

Is this approach to follow example 4 for this NDA acceptable to the Agency?

FDA Response:

The bottom line is that Module 2 is a summary of the Integrated Analyses in Module 5. "...the ISE and ISS are not summaries but rather detailed integrated analyses of all relevant data from the clinical study reports that belong in Module 5." If they meet the conditions outlined in "C. Exceptions" then they have an argument. So if the application consists of a single study or a number of small studies then they may meet the conditions for an exception. If they do not meet the conditions for an exception then they should place the ISS and ISE in Module 5 and place a summary of the ISS and ISE in Module 2.

C. Exceptions

There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2. *This situation is rare but can occur if the application is small and consists of a single study or a number of small studies.* In our experience, the narrative portion of the ISE often is more amenable for inclusion in Module 2 than is the ISS. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical that a clear explanation of where the parts are located be included. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3).

New CMC Comment: Submit a detailed pharmaceutical development report tracing the design and development of the drug product and the process. (Submitting stability data in SAS transport files or Excel spreadsheet format along with statistical analysis of all stability-indicating quality attributes was previously agreed to)

Clarification response to New CMC Comment: Pharmaceutical Development Report

The NDA, will be submitted in CTD- format; the chapter corresponding to pharmaceutical development ICH Q8 will be:

3.2.P.2.1 Component of the Drug Product

3.2.P.2.2 Drug Product

3.2.P.2.3 Manufacturers Process Development

3.2.P.2.4 Container Closure System

Section 3.2.P.2.1 will contain reports on: Choice of Drug Substance and Choice of Excipients

Section 3.2.P.2.2 will contain reports on: Formulation Development

Section 3.2.P.2.3 will contain reports on: Manufacturing Process Development and Proof of Product Equivalence after Change of Production Process/Site

Section 3.2.P.2.4 will contain reports on: Suitability of Container Closure System

A separate document "Pharmaceutical Development Report" will not be submitted with the NDA

Is this approach acceptable to the Agency?

FDA Comment:

Please consider scheduling a separate meeting with the Quality Reviewers for further clarification.

DECISIONS (AGREEMENTS) REACHED:

- If the carcinogenicity study is not completed upon NDA filing for the prophylaxis indication, the sponsor can indicate in the submission that the carcinogenicity studies are ongoing in the NDA submission.
- All safety data for Rivaroxaban should be included in the NDA submission (see questions 19-21 for details.)
- If the NDA is determined to be a "standard review submission," a four-month safety update will be submitted. An additional safety update may be requested by the reviewing division later during the review process. If the NDA is determined to be a "priority review submission," the sponsor may consider submitting a three-month safety update. The determination of the safety update as a major or minor amendment will be determined upon the size and complexity of the submission if it is received within the last three months of the review cycle.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Submission of a CMC Pharmaceutical Development Report.

ACTION ITEMS:

The Division will send the sponsor meeting minutes 30 days from the meeting date.

ATTACHMENTS/HANDOUTS:

None.

Post-meeting note on CMC pharmaceutical development. Yes, we agree that the proposed approach to describing the pharmaceutical development report within the section 3.2.P.2 is acceptable and that we don't need a new section.

Linked Applications

Sponsor Name

Drug Name

IND 64892

BAYER
PHARMACEUTICALS
CORP

BAY 59-7939

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

/s/

DIANE V LEAMAN
01/11/2008

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 23, 2006
TIME: 11:00 AM – 12:30 PM
LOCATION: White Oak Conference Room 1315
APPLICATION: IND 64,892
DRUG NAME: Rivaroxaban
INDICATION: Treatment and Secondary Prophylaxis of Venous Thromboembolism (VTE)
TYPE OF MEETING: End of Phase 2 (Type B)

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Dwaine Rieves, Deputy Division Director

Min Lu, Medical Officer

Diane Leaman, Regulatory Project Manager

Yash Chopra, Pharmacology/Toxicology Reviewer

Division of Cardiovascular and Renal Products (DCRP)

Tom Marciniak, M.D., Clinical Team Leader,

Patricia Harlow, Ph.D., Pharmacology/Toxicology Reviewer, DCRP

Division of Clinical Pharmacology V, Office of Clinical Pharmacology (OCP)

Young Moon Choi, Clinical Pharmacology Team Leader,

Rajnikanth Madabushi, Ph.D., Pharmacometrics Reviewer,

Office of Biometrics V

Jyoti Zalkikar, Mathematical Statistician

Satish Misra, Mathematical Statistician

Samesh Chattopadhyay, Mathematical Statistician

EXTERNAL CONSTITUENT ATTENDEES:

Bayer HealthCare Pharmaceuticals Corporation (Bayer)

Frank Misselwitz, M.D., Therapeutic Area Head, Cardiovascular Global Clinical

Anthonie Lensing, M.D., Global Clinical leader

Andrea Derix, M.D., Global Regulatory Strategist

Joseph Scheeren, PharmD., Head Global Regulatory Affairs

Larry Winick, M.A., Deputy Director, U.S. Regulatory Affairs

Torsten Westermeier, Ph.D., Global Clinical Statistician
Scott Berkowitz, M. D., Global Clinical Leader
Paul MacCarthy, M. D., Vice President, Head Medical Affairs North America
Reinhard Fescharek, M. D., Global Drug Safety
Dagmar Kubitz, M.D., Clinical Pharmacologist
Volker Geiss, Ph.D., Veterinary Pathologist/Toxicologist
Max Wegner, Ph.D., head GRA Global Strategy

Johnson and Johnson

Peter M. DiBattiste, M.D., FACC, Vice President, Associate Therapeutic Area Head
Lloyd Haskell, M.D., MBA, Vice President, Compound Development Team Leader
Christopher Nessel, M.D., Senior Director, Global Clinical
Gary Peters, M.D., FACP, Vice President, Franchise Medical Leader
Sanjay Jalota, MRPharmS., Director, Global Regulatory Affairs
Leonard Oppenheimer, Ph.D., Senior Director, Statistical Sciences

Outside Consultant:

(b) (4)

BACKGROUND:

Bayer submitted IND 64,892 on May 29, 2002 (received May 20, 2002) for the treatment and secondary prophylaxis of Venous Thromboembolism (VTE). On October 10, 2002, Bayer met with the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) to discuss Bayer's proposed Phase 1 and Phase 2 clinical trials. On July 5, 2005, Bayer met with DGCDP in an End-of-Phase 2 meeting to discuss the clinical development program for oral, BID dosing of BAY 59-939 in the prevention of VTE in patients undergoing (b) (4) hip replacement surgery or knee replacement surgery. On November 18, 2005, Bayer met the Division of Medical Imaging and Hematology Products (DMIHP) to discuss liver function monitoring plan and a once-daily dose choice of BAY 59-7939 for the Phase 3 clinical development program. On February 15 and 23, 2006, Bayer and DMIHP held teleconferences to discuss the statistical analysis plans and additional information on the RECORD 1, RECORD 2, RECORD 3 and RECORD 4 protocols. On June 1, 2006, Bayer and DMIHP held a teleconference to discuss the revisions proposed for the carcinogenicity protocol for BAY 59-3979 in the March 28, 2006 submission. On June 16, 2006, Bayer submitted an End-of-Phase 2 meeting request to discuss the clinical program for oral once daily dosing of rivaroxaban (BAY 59-7939) for the treatment and secondary prophylaxis of VTE. Bayer submitted the background package on July 20, 2006.

MEETING OBJECTIVES:

Agreement to the proposed Phase 3 development program including use of one open-label Vitamin K Antagonist (VKA)-controlled, non-inferiority study and one placebo-controlled, double-blind superiority extension study, dosing strategy and regimen, comparator, end points, inclusion and exclusion criteria.

Agreement to the proposed liver safety monitoring plan for the Phase 3 development program.

Agreement to the proposed statistical methods, including the non-inferiority margin in the study.

DISCUSSION POINTS:

Items discussed during the meeting were as follows:

1. The robustness of findings from an open-label, non-inferiority trial that uses a “symptom-directed” primary endpoint.
 - The sponsor should detail, to the extent possible, à priori the analyses they plan to use to assess the robustness of the proposed studies. Specifically, the sponsor should be aware that the determination of efficacy from this study will not rely solely upon the single pre-stated statistical test of the primary endpoint. Instead, multiple exploratory/sensitivity analyses must provide consistent evidence of a retained primary endpoint treatment effect. Failure of these exploratory/sensitivity analyses to maintain consistency with the single, pre-stated primary endpoint statistical test may result in a non-persuasive interpretation of the primary endpoint result.
2. Multiple comparators in the proposed Phase 3 clinical trials:
 - The sponsor proposes to restrict the number of active comparators in the Phase 3 trials.
 - The Agency acknowledged the sponsor’s remarks, but expressed concerns that the proposed study design may not result in persuasive results (see prior comments). The use of a non-inferiority margin with four comparators needs to be justified, especially with respect to the differential treatment effect of each comparator versus a putative placebo. The Agency is not objecting to the major architectural aspects of the trial but presented items for the sponsor to consider in order to enhance the potential persuasiveness of the study results. Bayer acknowledged the risks and assumptions in the study design and noted that they will try to minimize these problems.
3. Use of a drug that is not approved in the US:
 - The sponsor proposes to include acenocoumarol as a comparator in the clinical trial because it seeks to study rivaroxaban globally.
 - The Agency is not objecting to having acenocoumarol in the study.
4. Mortality Considerations:
 - In regard to fatal PE, Bayer will provide plans for the diagnosis of PE leading to death.
5. Bias from open-label studies:

Regarding the importance of the limitations of the open label study, the Agency reminded the sponsor that other drug development programs have used similar Phase 3 study designs that culminated in non-persuasive results. The Agency encouraged the sponsor to seriously consider the recommendations, as outlined below, in order to optimize the potential for a successful drug development program.

6. Dose:

A flat dose-VTE incidence rate relationship was seen over a range of 2.5 mg to 30 mg BID (12 fold) for VTE prevention in major orthopedic surgery (four trials) and from 10-30 mg BID/20-40 mg OD in the dose-selection trials for the treatment of acute symptomatic DVT (two trials). However, a dose response with increased bleeding at higher doses was noticed. Hence, the Agency suggested that a lower dose may be more appropriate in the studies. The potential for liver toxicity in the form of transient elevations of liver function tests seen in previous trials is a concern for the Agency. The dosing regimen was discussed regarding BID versus OD dosing. Bayer suggested that patients could be dosed at 15 mg BID during the limited initial treatment period and at 20 mg OD for secondary prevention as the AUC is similar to that of 10 mg BID. The Agency is concerned that chronic OD treatment may have long-term hazards as it is associated with higher maximum concentrations (30% higher) and less than half of trough concentrations when compared with BID regimen and hence encourages a 10 mg BID dosage regimen. Also, in light of the flat dose-response in the dose-selection trials, the Agency asked the sponsor if they had considered a lower dose arm/dose range for their pivotal trial. Bayer said that the option of a lower dose arm was discussed internally and the sponsor concluded to not have one.

7. Pre-clinical studies:

In the June 1, 2006 teleconference between representatives from Bayer and DMIHP, the sponsor clarified that the sponsor proposed a 20 mg dose limit for chronic clinical dosing, but proposed a higher clinical dose for short-term administration.

DECISIONS (AGREEMENTS) REACHED:

In response to the questions in the June 16, 2006, meeting request, and the July 20, 2006, background package, the following agreements were reached after discussion. The format provides the firm's questions in italics followed by DMIHP's responses in bolded lettering. Headings, agreements and additional discussion are underlined.

1. Dose Selection, Dose Regimen

Based on the results from the Phase 2 VTE treatment studies with rivaroxaban, Bayer proposes to use a dosage regimen of [REDACTED] (b) (4)

Does the Agency concur with the above mentioned dosing strategy and regimen in the Phase 3 study?

FDA Response:

No, we do not concur.

- **Instead of your current dose plans, we recommend that you propose a dose of 10 mg BID for your Phase 3 studies based on the following:**
 - **The potential for organ toxicity at the higher dose (e.g., liver toxicity),**

- Similar pilot efficacy yet more bleeding events in the higher dose experience (20 mg and 30 mg BID), and
- A more favorable PK profile for the 10 mg BID dose when compared to 20 mg OD (i.e., higher C_{max} and lower C_{trough} using 20 mg OD).
- The PK profile in moderately impaired renal patients appears to be similar to that in severely impaired renal patients and both PK profiles differ from those of subjects with normal renal function. Please propose a dose adjustment plan for moderate-to-severe renally-impaired patients.
- In the recent rat and mouse carcinogenicity protocols dated June 26, 2006, you stated that the clinical dose will be limited to 20 mg/day. (b) (4)
Please clarify this inconsistency, especially with respect to the utility of your carcinogenicity studies to support the “clinical dose.” In general, we anticipate that, based on the animal carcinogenicity proposals, all clinical dose proposals would not exceed 20 mg/day.
- We note that Rivaroxaban is to be administered with food in the Phase 3 trials. Please clarify whether Rivaroxaban was administered with food or without food in the two dose selection Phase 2 trials (11223 and 11528).

Bayer clarified that the Phase 2 trials were performed with food.

2. Choice of Comparator

The proposed open-label Phase 3 VTE treatment study will evaluate rivaroxaban versus low molecular weight (LMW) heparin /VKA with a target International Normalized Ratio (INR) of 2.5 (range of 2.0-3.0). The proposed double-blind extension study will evaluate rivaroxaban versus placebo.

Does the Agency concur with the selection of (LMW) heparin/VKA as the active comparator in the open-label study and with placebo in the double-blind extension study?

Does the Agency agree that a choice of heparin limited to only one type of heparin per center (i.e., centers will have to use only one type per study) and a choice of VKA limited to Warfarin or acemocoumarol (i.e., centers will have to use only one type) is acceptable?

FDA Response:

- Regarding the open label, noninferiority study (Study 11702); while we do not object to these plans for the comparators, we recommend the use of a single comparator for the initial treatment period and for the VTE treatment period. You should be aware that the use of multiple comparator agents may confound both the safety and efficacy findings from your studies if the comparator agents do not demonstrate consistent effects and the constancy (of comparator effect) assumption is violated. Confounding effects may necessitate the need for additional randomized clinical trials to definitively establish the safety and efficacy of your study agent.
- You proposed a single non-inferiority trial for acute treatment of VTE. Two adequate and well-controlled studies are generally needed to support a new indication. There is a risk in performing a single trial that may not have convincingly positive results to support the proposed indication. In addition, a non-

inferiority trial is less likely to be persuasive. The acceptance of the single study as a sufficient scientific and regulatory basis for approval of a new indication will be determined by its adequacy to support the efficacy claim based on strength of the results. See “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products” and “Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials.” Consistent with the information in this guidance, we are very concerned that your proposed open label, non-inferiority study (Study 11702) will not provide robust evidence of safety and efficacy.

- Use of a placebo is appropriate for Study 11899.
- Patient management needs to be the same in both arms and the clinical protocols should clearly outline the procedures that will be performed in order to maintain this expectation. For example, VTE symptom ascertainment bias (based upon more frequent healthcare provider visits for one group compared to another) must be minimized. We recommend a double-blind design.

3. Inclusion and Exclusion Criteria

Does the Agency concur with the proposed inclusion and exclusion criteria as described in the briefing package?

FDA Response:

- The proposed inclusion and exclusion criteria are acceptable.
- Regarding Study 11899 and potential product labeling considerations, please be aware that designating the target patient population as one consisting of all patients “[REDACTED]” is not acceptable text for a product label. The clinical data from this study must be sufficient to identify the target patient population based upon readily familiar patient/conditions (for example, “patients with metastatic cancer and VTE”). (b) (4)

4. Primary Efficacy Endpoint

Does the Agency concur that the proposed, composite primary efficacy endpoint (recurrent symptomatic VTE including fatal PE and unexplained death) will be sufficient to support the approval of rivaroxaban in the desired indication?

FDA Response:

- No. We reiterate the design limitations associated with Study 11702 (open label, multiple comparator agents, non-inferiority design). We are especially concerned regarding the subjectivity associated with “unexplained death” and “symptomatic VTE” in an open label study. The evaluation of symptoms, as well as assignment of a cause for death, is very vulnerable to knowledge of the treatment assignment and physician bias regarding the safety and efficacy of the treatment assignment. We request that you redesign the analytical aspects of this study to use a superiority approach on a primary endpoint that includes a composite of symptomatic VTE or

death for any cause. Given an open label design and your proposal for a single confirmatory study, we have substantial concerns that a noninferiority analytical approach to the primary endpoint would result in non-persuasive results.

- Regarding Study 11899, we anticipate that mortality outcomes may highly compete with symptomatic VTE outcomes (the study allows the enrollment of cancer patients who may have very limited survival). Hence, please revise this primary endpoint to include all-cause mortality.

5. Primary Safety Endpoint

Does the Agency concur with the proposed definitions of 'major bleeding' and 'clinically relevant non-major bleeding'?

FDA Response:

- The proposed definitions of major bleeding and clinically relevant non-major bleeding are acceptable.

Does the Agency concur that the primary safety endpoint, defined as a composite of major and clinically relevant non-major bleeding, is acceptable for the prespecified superiority analysis in the large open-label VKA-controlled, non-inferiority study?

FDA Response:

- We reiterate the limitations associated with this study (Study 11702). We do not regard this study design as sufficient to support a claim of superior safety, predominately due to the use of multiple comparator agents in the control arm as well as the analytical approach.
- You appear to indicate that you propose co-primary endpoints—the efficacy endpoint assessed by non-inferiority analyses and the safety endpoint by superiority analyses. This analytical approach does not preserve the Type 1 error and we request clarification of your endpoint goals and statistical methodology.
- The comparator agents may differ in safety outcomes that fail to be detected due to sample size considerations (under powering). Additionally, the open label nature of the study is conducive to undetectable bias in patient management that may impact safety outcomes.
- Please be aware that claims in a product label are contingent upon the totality of the findings from clinical studies. Hence, a robust superiority primary efficacy result, combined with consistent findings of less risk for major bleeding (when the active study agent is compared to each comparator agent) may provide sufficient evidence to support a claim of superior efficacy and safety, especially when these findings are duplicated in clinical studies.

6. Major Bleeding-Expedited Reporting

With regard to reporting procedures for serious adverse events (SAEs) that are also potential study endpoints, does the Agency concur that these events should be treated as study endpoints only, and that the requirement for SAE reporting be waived?

FDA Response:

- **SAEs that are also study endpoints do not need to be submitted in an expedited report. However, these events/reports should be included in your periodic safety reports. All deaths should be reported as expedited reports.**
- **Major bleeding should be considered an SAE as well as a safety endpoint.**

7. Monitoring of Liver Function Tests

Bayer proposes the liver function monitoring plan as described in the briefing package for the Phase 3 study. *Does the Agency concur with the proposed liver function monitoring plan?*

FDA Response:

The proposed liver function monitoring plan is acceptable.

8. Long-term/chronic VTE Prophylaxis and Safety Database

Does the Agency concur that the proposed numbers of exposed patients and the duration of dosing, considering both the initial non-inferiority study period and the extension study period, are sufficient to support approval of rivaroxaban for the chronic use in secondary prophylaxis of recurrent VTE?

Does the Agency concur this constitutes adequate safety information for rivaroxaban in this population?

FDA Response:

- **No. Please be aware that the sufficiency of an overall sample size is heavily contingent upon the study findings and it is impossible to definitively identify an acceptable safety population database *a priori*. The detection of important safety signals (even if rare or uncommon) may necessitate a larger safety database than originally planned.**
- **It is unclear how many patients will be treated for 12 months in the acute treatment trial. The proposed number of patients who will be exposed to Rivaroxaban in the treatment extension trial is 650. These patients may also be from the acute treatment trial.**
- **The proposed number of patients appears to be insufficient to adequately evaluate the possible liver toxicity of this product in the proposed patient population who may use this product chronically for an extended period.**

9. Statistical Plan

Does the Agency concur that the proposed statistical methods for both studies will be sufficient to evaluate rivaroxaban for the proposed indication?

Specifically does the Agency concur

a) *with the proposed non-inferiority margin in the open-label VKA-controlled, non-inferiority study?*

b) *with the proposed one-sided alpha of 0.025 (two-sided alpha of 0.05) for both studies?*

FDA Response:

- **No.** Please see our prior comment about Study 11702 (where you imply that you will assess co-primary endpoints—one an efficacy endpoint and the other a safety endpoint). We reiterate the limitations of the Study 11702 design and the high likelihood that this type of study design will not provide robust evidence of efficacy (even with a reasonable quantitative justification for the non-inferiority margin and for the assumption of constancy of comparator effect).

10. Clinical Development Plan

The proposed indication for rivaroxaban is "(b) (4) Prophylaxis of Venous thromboembolism (VTE)"

Bayer proposes on open-label VKA-controlled, non-inferiority study (with central randomization and blind adjudication) to support the indication for a treatment duration up to 12 months and one placebo-controlled, double-blind superiority extension study (providing additional data to support chronic use of rivaroxaban in patients with persistent risk of VTE recurrence).

Does the Agency concur that these studies in addition to the Phase 2 studies in VTE treatment will support approval for the proposed indication?

FDA Response:

No. Please see our prior comments regarding the limitations of your clinical development program. Please be aware that text for product labeling is contingent upon the study results.

Does the Agency agree with the following labeling proposal for Rivaroxaban:

"(b) (4) prophylaxis of venous thromboembolism. The duration of therapy with rivaroxaban should take account of the patients' individual risk for VTE recurrence. Patients should be treated with rivaroxaban for a minimum of (b) (4). The overall treatment duration should be as long as the risk persists. A chronic prophylaxis with rivaroxaban may be indicated in patients with permanent or persisting risk factors?"

FDA Response:

No. The final wording in the labeling will reflect the study results and will be review-dependent.

Does the Agency concur:

a) *That an open-label, confirmatory study with central randomization and blind adjudication is acceptable to support approval of rivaroxaban in the desired indication?*

FDA Response:

No. You proposed a single trial each for acute treatment of VTE (PE and DVT) and for treatment extension of VTE. Two trials are generally required to support each indication. See responses to Question 2.

b) *that (b) (4) patient management before diagnostic confirmation and randomization does not impact the evaluation of rivaroxaban and supports approval for the proposed indication?*

FDA Response:

No. We cannot be certain that there will be no impact.

c) *with the definition of baseline risk factors for VTE recurrence, as described in the briefing package and the consequent three, six or 12-month dosing durations in the open-label VKA controlled non-inferiority study are acceptable to support approval for the proposed indication?*

FDA Response:

The definitions of the baseline risk factors appear reasonable.

11. Pediatric Plan

There are currently no plans to conduct clinical studies of rivaroxaban in the pediatric population. Bayer proposes to request a waiver for pediatric data at the time of registration. *Does the Agency concur with this approach?*

FDA Response:

- **A decision will be made at the time of filing. A waiver is unlikely to be granted but a waiver may be requested. You should submit a plan.**
- **You do not plan to conduct clinical studies of rivaroxaban in the pediatric population at present. In the future, if you propose to use study agent in a pediatric population, you will need to conduct the preclinical 3-month toxicity studies in juvenile rodent and non-rodent species and submit the data to the Agency. If you plan to use the study agent in neonates, you will need to submit the toxicity studies performed in neonate rodents or non-rodents.**

Summary

FDA noted that multiple items for consideration were provided to the sponsor and the sponsor acknowledged those considerations. FDA did not object to the clinical development program but did express concerns related to the potential persuasiveness of the data.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Additional items for clarification focusing on preclinical considerations related to drug distribution and metabolism should be submitted to the IND for review.

ACTION ITEMS:

Bayer should submit background information and specific questions regarding any outstanding preclinical issues to the Division for consideration.

ATTACHMENTS/HANDOUTS:

Expected distribution of study patients

4900	Warfarin	Acenocoumarol
	2900	2000
Enoxaparin		
3300	1950	1350
UFH		
1250	750	500
Fondaparinux		
125	75	50
Tinzaparin		
225	125	100

Measures to minimize open label bias

- ▶ central randomization by IVRS
- ▶ patients are provided with information on the symptoms of safety and efficacy outcomes and instructions to contact the study site (using patient diaries)
- ▶ prescheduled fixed assessments in both treatment groups in a standard, systematic manner
- ▶ central independent blinded adjudication of all suspected efficacy and safety outcomes including death
- ▶ each patient will be followed up to the planned theoretical end of the study including those who will discontinue prematurely
- ▶ only confirmed outcome events will be used for the analyses
- ▶ close monitoring of protocol adherence in the trial to confirm compliance with the bias safeguards
- ▶ comparison of the ratio of central, independent, adjudication committee confirmed events to reported suspected events between treatment groups
- ▶ monitoring VKA compliance by plotting INRs

Rate of bleeding OD vs. BID regimen

Results after 3 months' treatment

Rivaroxaban

Total Daily Dose (TDD)	20 mg (10 BID)	30 mg	40 mg (20 BID)	40 mg (40 OD)	60 mg (30 BID)
BID dosing					

Major bleeding, n/N (%)	2/119 (1.7%)	-	2/117 (1.7%)	2/121 (1.7%)	4/121 (3.3%)
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Major + Non-major bleeding, n/N (%)	6/119 (5.0%)	-	11/117 (9.4%)	14/121 (11.6%)	13/121 (10.7%)
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OD dosing

Major bleeding, n/N (%)	1/135 (0.7%)	2/134 (1.5%)	0	-
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Clinically relevant bleeding n/N (%)	7/135 (5.2%)	6/134 (4.5%)	3/136 (2.2%)	-
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ODIXa-DVT – regression of thrombus and recurrent VTE after 3 weeks

	Rivaroxaban				VKA+enox
	10 mg bid (n=100)	20 mg bid (n=98)	30 mg bid (n=109)	40 mg od (n=112)	(n=109)
Improvement of thrombotic burden* (95% CI)	53.0% (43, 63)	59.2% (49, 69)	56.9% (47, 66)	43.8% (34, 53)	45.9% (36, 56)
Recurrent or extended DVT, PE or VTE- related death, n (%)	1 (1.0%)	1 (1.0%)	0	0	0

*≥4-point improvement in thrombus burden by (b) (4) without recurrent VTE
Per-protocol population (n=528)

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/s/

Diane V Leaman
9/5/2006 02:12:22 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 5, 2005
TIME: 11:00 AM – 1:00 PM
LOCATION: Parklawn Building, Chesapeake Room
APPLICATION: IND 64,892
DRUG NAME: BAY 59-7939
TYPE OF MEETING: End of Phase 2 (Type B)

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Diane Moore

FDA ATTENDEES:

Office of Drug Evaluation III

Florence Houn, M.D., Director

Division of Gastrointestinal and Coagulation Drug Products

Kathy Robie-Suh, M.D., Ph.D., Hematology Team Leader

Min Lu, M.D., Medical Officer

Diane Moore, Regulatory Project Manager

Sushanta Chakder, Ph.D., Pharmacologist

Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

Suresh Doddapaneni, Ph.D., Pharmacokinetic Team Leader

Division of Biometrics II (DBII)

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EXTERNAL CONSTITUENT ATTENDEES:

Bayer HealthCare Pharmaceuticals

Tiemo Bandel, M.D., Global Clinical Leader

Pam Cyrus, M.D., Vice President, U.S. Medical Affairs

Andrea Derix, M.D., Global Regulatory Strategist

Christoph Dierig, M.D., Global Biometry Leader

Margaret Foley, Assistant Director, U.S. Regulatory Affairs

Volker Geiss, D.V.M., Ph.D., Expert in Veterinary Pathology

Kenneth Harris, M.D., Associate Director, U.S. Medical Affairs

Dagmar Kubitz, M.D., Global Project Leader

Paul Mac Carthy, M.D., Vice President, U.S. Medical Science

Frank Misselwitz, M.D., Head Global Clinical Development CV

Ed Tucker, M.D., Vice President, Drug Safety Assurance
Klaus Wehling, Ph.D., Global Project Manager
Corinna Weinz, Ph.D., Principal Staff Scientist Drug Metabolism and Preclinical
Joseph Scheeren, PharmD., Head Global Regulatory Affairs
Reinhard Fescharek, M.D., Global Drug Safety
Michael Rozycki, PhD, Director, Regulatory Affairs

BACKGROUND:

On April 22, 2005, Bayer Healthcare Pharmaceuticals (Bayer) requested an End of Phase 2 meeting to discuss the clinical development program for oral, BID dosing of BAY 59-7939 in the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery such as hip replacement surgery or knee replacement surgery. The background package was submitted on June 2, 2005.

MEETING OBJECTIVES:

To discuss the clinical program for oral, BID dosing of BAY 59-7939 in the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery such as hip replacement surgery or knee replacement surgery.

DISCUSSION POINTS:

FDA statement: Because this is an oral anticoagulant, a safety study to support long term use will be required for approval for any use.

- Please explain your long-term plans for this drug product.

DECISIONS (AGREEMENTS) REACHED:

In response to the questions in the June 2, 2005, background package, the following agreements were reached after discussion. The format provides the firm's questions in *italics* followed by DGCDP's responses in **bolded** lettering.

Question 1. *Does the Agency agree that these pivotal trials (Trial 11354, 11357 and Trial 11356) could generate information to support the following indication:* (b) (4)
thromboembolism (b) (4) *undergoing* (b) (4) *hip* (b) (4)
replacement surgery or knee replacement surgery? (b) (4)

FDA Response:

- No.
- You are proposing three indications. Generally, two adequate and well-controlled trials are needed to support each indication. You are proposing two non-inferiority trials for hip replacement and knee replacement. (Please refer to Guidance for Industry "Establishing Effectiveness . . ." on why two studies are recommended and what otherwise would be needed.) Therefore, there is a risk in performing a single study that may not have convincingly positive results. In addition, non-inferiority studies are less likely to be persuasive. Also, while these two indications are related, it cannot be

determined a priori whether and/or how well one study may support the other. For extended treatment, one superiority trial may suffice if the results are convincing and demonstrates a favorable benefit-risk and the results from the hip replacement prophylaxis program are favorable.

- (b) (4) is not acceptable for the proposed indication. "Prophylaxis" should be used.
- (b) (4) is not acceptable for the proposed indication. Specific surgery such as hip replacement or knee replacement should be used.

Question 2. Does the Agency agree with the selection of the comparator and its dose regimen (BAY 59-7939 at 5 mg bid given for 5-6 weeks compared with enoxaparin 40 mg qd with first administration pre-operatively, given for 5-6 weeks); (BAY 59-7939 at 5 mg given for 5-6 weeks with short-term prevention with enoxaparin 40 mg qd with first administration pre-operatively for 10-14 days followed by placebo in patients undergoing elective total hip replacement surgery) and (BAY 59-7939 at 5 mg bid given for 10-14 days compared to enoxaparin 40 mg qd with first administration pre-operatively, given for 10-14 days.)?

If no, could the Agency elaborate why this would not be appropriate (e.g., comparator, dose regimen)?

FDA Response:

- No. Comparative trials with non approved U.S. dose regimens should use a superiority design. Labeling may not refer to the specific unapproved drug regimen.
- The proposed comparator enoxaparin dose regimen of 40 mg qd given for (b) (4); in Trial 11354 is not an approved dose regimen for prophylaxis of DVT in patients undergoing hip replacement surgery in the U.S. The efficacy of Bay 59-7939 can not be supported by a non-inferiority study using this regimen as comparator.
- Enoxaparin is approved for three weeks for extended prophylaxis of DVT in patients undergoing hip replacement surgery. Use of comparator enoxaparin 40 mg for (b) (4) since we know enoxaparin, given for three weeks, is efficacious.

• (b) (4)

Sponsor Commented that the proposed knee replacement study and extended versus short total hip replacement study will be superiority design studies. (See attached slide).

Question 3. Does the Agency agree that the comparator, enoxaparin, sourced from (b) (4), is equivalent to the US marketed enoxaparin and is appropriate to use for the studies with US centers?

FDA Response:

- We do not have any information about the equivalency between enoxaparin drug products marketed in (b) (4), and enoxaparin drug products marketed in the USA. Therefore, you should use enoxaparin drug products approved in the U.S.A.

- To use enoxaparin drug products marketed in (b) (4), provide a side-by-side comparison of all CMC specifications with the U.S. marketed drug products. The attestation statement in Appendix 3 is inadequate.

Question 4. Does the Agency concur that for the Phase 3 studies in (b) (4), the same dose is used in all patients?

FDA Response:

- Yes. It is acceptable not to dose-adjust individuals in your proposed studies with 5 mg.

Question 5. Does the Agency agree with the dose of 5 mg bid and the proposed dose regimen?

FDA Response:

- We strongly recommend you consider adding a 2.5 mg dose arm to your study of 5 mg because of the potential for serious side effects, e.g., bleeding and liver toxicity. Based on the available data it is not clear that the 2.5 mg dose is not effective. Where possible, it usually is preferable to use the lowest effective dose, especially for agents where there are safety concerns and use may be long-term.

Question 6. Does the Agency agree to the definitions of primary and secondary endpoints and to the statistical analysis plans? (primary efficacy endpoint in superiority trials (a composite of all cause mortality, non fatal pulmonary embolism, total deep vein thrombosis) in non-inferiority trials a composite of VTE-related mortality, non fatal PE, proximal deep vein thrombosis and symptomatic DVT; secondary endpoints in superiority trials include VTE-related deaths, separate analysis of the components of the composite especially of the proximal and distal DVT, all cause deaths and separate analyses of the components of the composite. In the short term TKR trial 11356, a non-inferiority/superiority switch will be used. A hierarchical test procedure will first confirm non-inferiority based on the endpoint total VTE deviation from the definition given above and thereafter a test will be performed for superiority using the same endpoint total VTE.

FDA Response:

- In these elective orthopedic surgery thromboprophylaxis trials, clearly VTE-related death is the relevant mortality parameter to include in the primary efficacy endpoint. However, in these trials where the overall death rate is expected to be very low, there should not be a great numerical difference in total mortality and VTE-related mortality. If non-VTE related mortality is noticeably greater with BAY 59-7939 treatment, this will be a cause for concern and will need to be explained.
- Criteria for designating VTE-related mortality should be clearly described in the protocol.
- Explain why different components of primary endpoint should be allowed to be used in between superiority and non-inferiority trials.

Question 7. Does the Agency agree to the statistical plan of the TKR study 11356, specifically with respect to the hierarchical testing and the endpoint?

FDA Response:

From a statistical perspective, the hierarchical testing proposed for TKR study 11356 is acceptable. However, the issues raised in our responses to previous questions may make it a moot point.

The study will now be a superiority study.

Question 8. *Does the Agency agree to this method of determination of the DVT endpoint and its central adjudication?*

FDA Response:

- **Yes. It is acceptable. An independent, blinded adjudication committee should be used.**

Question 9. *Does the Agency agree to this definition of major bleeding? (fatal bleeding, bleeding into a critical organ, bleeding requiring re-operation, clinically overt severe extrasurgical site bleedings resulting in a drop of Hb > 2 g/dl, clinically overt severe extrasurgical site bleedings requiring transfusion of 2 or more units of whole blood or packed cells)*

FDA Response:

- **Yes. It is acceptable.**

Question 10. *Does the Agency agree that all other bleeding events should be classified as minor? (All other bleeding events not listed in question 8)*

FDA Response:

- **All other bleeding events should be considered non-major. Hemorrhage at the surgical site may be clinically significant. Occurrences of loss of substantial amounts of blood due to bleeding at the surgical site should be captured in the case report form and included as appropriate in the presentation of the bleeding data.**

Question 11: With regard to reporting procedures for major bleeding events, Bayer proposes the following: if not reported as SAEs by the investigator, major bleedings are generally exempted from expedited reporting, but they are closely monitored by the sponsor as alert terms or adverse events of special interest. Further details regarding major bleeding are in section 7.4.5.4. Does the Agency agree to this procedure?

FDA Response:

- **Yes. It is acceptable. However, all deaths occurring during the study (regardless of cause) should be reported as expedited events.**

Question 12. *Does the Agency concur with this plan for monitoring of liver function tests? (ALT, AST, GGT, Lipase, Amylase, total and direct Bilirubin, AP at baseline, after surgery and at the end of treatment, in trial 11356 at end of treatment 14 +2 days, in all trials, at end of 30 day clinical follow up period; automated alert from central laboratory of increases >3x ULN; weekly follow-up investigations of increased lab parameters until resolution. Stopping rules include combined increase of ALT>3xULN and BILI>2 x ULN if reconfirmed within 3 days and persistently high or increasing ALT/AP/Lipase>8xULN if re-confirmed and no alternative explanation*

FDA Response:

- No. Liver function should be monitored more closely in the trials, e.g., at the first week, at 14 days, at one month, at the end of treatment, and 30 days after discontinuation of the drug.
- Drop-outs and withdrawals should have liver testing 30 days from last drug dose or clinical outcomes follow-up.
- Define “persistently”.
- Drug should be stopped if transaminases $>5 \times \text{ULN}$ at any time.
- Provision should be made for more frequent monitoring of transaminases and/or bilirubin if a rapid rate of rise is observed.
- “Reconfirmation within 3 days” should refer to the actual time of availability of the result of the repeat laboratory test, not to the time of the blood draw for the test.

Sponsor will provide proposal and rationale for monitoring of hepatic transaminases and bilirubin during the short term and long term trials and provide stopping rules and rationale.

Question 13. *Does the Agency concur with the exclusion criteria proposed for all pivotal trials? (see bg pkg)*

FDA Response:

- Patients with transaminases and/or serum bilirubin $>2 \times \text{ULN}$ should be excluded from the trials.

Sponsor will exclude patients with serum bilirubin $> 2 \times \text{ULN}$ from the trials.

Question 14. *Does the Agency agree that after therapeutic ranges of PT prolongation have been established, assessment of PT is an appropriate and sufficient measurement to assess anticoagulation in specific patients with high monitoring need?*

FDA Response:

- The plan appears to be acceptable. However, please clarify your definition of “high monitoring need”.

Question 15. *Does the Agency agree that this follow-up period and procedure are appropriate? (Patients in the Pivotal studies will be followed for 30 days after treatment cessation. If clinical adverse events occur up to the 30 day follow-up, the cardiovascular or VTE related events will be adjudicated by an Adjudication Committee)*

FDA Response:

- Yes. It is acceptable for the proposed trials. Any adverse events including clinical laboratory abnormalities (e.g., elevation of hepatic enzymes) should be followed to resolution.

Question 16. *Does the Agency concur with this plan and that it would provide appropriate guidance in the labeling? (guidance for overdose -treatment discontinuation, screening of the source of bleeding, appropriate symptomatic treatment such as surgical hemostasis, and/or transfusion of fresh (frozen) plasma and/ or 4-factor concentrate, sufficient diuresis.)*

FDA Response:

- Because use of your drug as an oral formulation, there is concern for overdose (accidental or intentional). Therefore, we encourage you to develop an antidote or steps to take in the event of overdose.

Question 17. *Does the Agency agree with this approach? (Waiver for pediatric data at the time of registration)*

FDA Response:

- At this time, we would defer requirement for pediatric data for BAY 59-7939.

Question 18. *Does the Agency agree with this approach? (No specific ECG monitoring to assess potential effects on QTc will be performed)*

FDA Response:

No

- We recommend that prior to phase 3 studies you conduct a 'thorough QT/QTc study' as described in section 2.1.2 of the draft concept paper "The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs" (June 10, 2004). If this study is negative, required monitoring of ECGs in phase 3 studies would be minimal.

Sponsor will submit the report of their QTc study for review (11275)

Question 19. Does the Agency agree that the series of completed and ongoing preclinical safety studies and the results seen are sufficient to support the clinical program outlined in this submission and in addition will form an adequate basis to reach a decision regarding registration?

FDA Response:

- Yes

Question 20: *Does the Agency agree that the series of completed and ongoing preclinical pharmacokinetic and drug metabolism investigations are sufficient to support the clinical program outlined in this submission and in addition will form an adequate basis to reach a decision regarding registration?*

FDA Response

- Yes

Question 21: *Does the Agency agree that the interaction program described in the briefing package, the proposed design of interaction studies (see also question 22) and the data generated will form an adequate basis for drug interaction recommendations in the labeling and for a decision regarding registration?*

FDA Response

- The proposed program may provide adequate information.

Question 22: *All interaction studies have been performed with international accepted model drug representatives of the potential interaction mechanism. Our drug interaction recommendation will be based on the information obtained in the interaction studies above. No further testing will be done on individual drugs, which may be widely used in the targeted indications. Does the Agency concur with this proposal?*

FDA Response

- **In general, the proposal is acceptable with respect to the CYP3A4 and P-gp inhibition related drug interactions.**

Question 23. *Would the Agency grant a meeting to discuss the dose and questions related to the necessary revisions to the Phase 3 protocols if the dose regimen in the Phase 3 program is revised to a once daily regimen?*

FDA Response:

- **We will determine the need for a meeting when you submit your meeting request.**

Question 24: *If so, would the Agency agree to a type B meeting?*

FDA Response:

- **Meeting type is determined at the time of granting the meeting.**

Additional Comments:

- **Please request an End of Phase 2 Chemistry and Manufacturing meeting per the Guidance for Industry "INDs for Phase 2 and Phase 3 Studies" May 2003.**

OUTSTANDING ITEMS:

- Discussion regarding liver function monitoring after sponsor submits the following:
 - Proposal for stopping rules with justifications
 - Safety assessment with consultant package

ACTION ITEMS:

- Sponsor will submit a package, including the statistical analysis plan, for the three trials with proposal for long-term safety data, for Agency review and comment.
- Sponsor will submit QTc report

ATTACHMENTS/HANDOUTS: (see attached)

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this page is the manifestation of the electronic signature.**

/s/

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