CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215859Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 7, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 215859
Product Name and Strength:	Xarelto (rivaroxaban) for oral suspension, 1 mg/mL (after reconstitution)
Applicant/Sponsor Name:	JANSSEN PHARMACEUTICALS INC
OSE RCM #:	2021-1248-1
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Instructions for Use (IFU), container label, and carton labeling received on November 24, 2021 for Xarelto. The Division of Non-Malignant Hematology (DNH) requested that we review the revised IFU, container label, and carton labeling for Xarelto (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We determined that the revised IFU, container label, and carton labeling are acceptable from a medication error perspective, and we do not have additional recommendations at this time.

Regarding the revised IFU, we note the Applicant did not increase the prominence of the caution statement in IFU Step 4 as previously recommended. The Applicant noted that they

[a] Whaley, E. Human Factors Results and Label and Labeling Review for Xarelto (NDA 215859). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 15. RCM No.: 2021-1248 2021-1257.

previously implemented post-validation revisions to make the caution statement more noticeable (i.e., addition of the Caution symbol and removal (b) (4)). We acknowledge the Applicant's previously implemented revisions are intended to increase the prominence of the caution statement and to address performance in the HF validation study. As such, in this instance, we determined that additional IFU revisions to IFU Step 4 are not needed at this time.

Regarding the revised container label and carton labeling, we note the Applicant did not implement our recommendation to include the total volume after reconstitution on the container label and carton labeling. The Applicant stated that inclusion of the total volume after reconstitution could cause confusion to the pharmacist (e.g., a pharmacist who sees the (b) (4) mL total volume on the label may be confused about how much water to use and could incorrectly reconstitute with (b) (4) mL of water). We note the carton labeling and Prescribing Information inform users of the volume needed for reconstitution (i.e., 150 mL) and the total contents of the bottle (i.e., 155 mg of rivaroxaban). In this instance, we determined that additional container label and carton labeling revisions are not needed at this time.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
12/07/2021 08:58:28 AM

COLLEEN L LITTLE
12/07/2021 09:38:25 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 15, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 215859
Product Type: Drug Constituent Name and Strength Device Constituent:	Combination product Xarelto (rivaroxaban) for oral suspension, 1 mg/mL (after reconstitution) Oral syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
Submission Date:	6/22/2021; 8/30/2021
OSE RCM #:	2021-1248; 2021-1257
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors :	Lolita White, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 215859 for Xarelto (rivaroxaban) for oral suspension.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed oral syringe device constituent part that is intended to support the proposed indications of (a) treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment and (b) thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure. The proposed product will be supplied in a 200 mL glass bottle containing rivaroxaban granules along with two 5 mL oral dosing syringes and a press in bottle adapter (PIBA). After reconstitution with 150 mL water, the concentration of the suspension is 1 mg/mL. The oral syringe includes both graduation marks in milliliter units and color bands to facilitate dosing. Pediatric doses range from 0.8 mg to 20 mg administered up to three times a day. Users must perform the measurement and administration process multiple times to achieve the 7.5 mg, 10 mg, 15 mg, and 20 mg doses. See Figure 1 below and Appendix A.

Figure 1. Proposed oral syringe graduations, cap, bottle and PIBA

(b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

Xarelto (rivaroxaban) tablets was approved on 7/1/2011 under NDA 022406, and is available as 2.5 mg, 10 mg, 15 mg, and 20 mg tablets. Xarelto is currently approved for the treatment of the following indications in adults:

- to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation
- for treatment of deep vein thrombosis (DVT)
- for treatment of pulmonary embolism (PE)
- for reduction in the risk of recurrence of DVT or PE
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients
- to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)

On August 6, 2019, we provided comments for the Type B Pre-NDA meeting under IND 064892 requesting the Applicant determine whether the results of a HF validation study need to be submitted to support safe and effective use of their proposed granules for oral suspension

[redacted] (b) (4)

product.[b] We also provided risks and potential errors for the Applicant's consideration including the following:

- Evaluate the color of the plunger with respect to the readability of the dose markings.
- If the proposed oral syringe will support accurate measurement of all potential doses (i.e., will some patients require more than 5 mL).
- Consider any issues that may arise from not incorporating any unit graduation marks on the oral syringe and forcing your intended users to rely on a purely color-based perception model.
- Consider confusion by your intended users who are color vision deficient (color blind) and not color vision deficient and how that user characteristic may influence user interaction with the proposed product.

On August 24, 2020, the Applicant submitted a HF validation study protocol under IND 064892 for the proposed granules for oral suspension. We completed our review of the HF validation study protocol on October 21, 2020[c] and provided recommendations for the Applicant. On December 11, 2020, the Applicant submitted a response to our October 22, 2020 HF Validation Study Protocol Advice Letter, which included the Applicant's justification to enroll adolescent participants 14 to 17 years old instead of 10 to 17 years. Subsequently, we completed an HF protocol memo on May 10, 2021[d] and provided additional recommendations to the Applicant regarding the pediatric user group, the product design, and the Instructions for Use (IFU).

On June 22, 2021, the Applicant submitted the results of the HF validation study under NDA 215859, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

[b] Chon, W. Meeting- Preliminary Comments for rivaroxaban (IND 064892). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2019 JUL 31. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80509c0a

[c] Oguntimein, O. HF Validation Study Protocol Review for rivaroxaban granules for oral suspension (IND 064892). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 21. RCM No.: 2020-1767.

[d] Yokum, A. HF Protocol Memo for rivaroxaban granules for oral suspension (IND 064892). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 13. RCM No.: 2020-2641.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed , and our analysis to determine if the results support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

We previously reviewed the HF validation study protocol, and we note that the Applicant did not implement our recommendation to include HF validation study data for pediatric users. Specifically, the Applicant noted that they conducted additional HF studies with children aged 10-17 years to assess the usability of the product by that age group. However, the results from the HF studies did not support self-administration by children aged 10-17 years. As such, the Applicant proposes to include labeling statements to indicate the product should be administered by adults only.

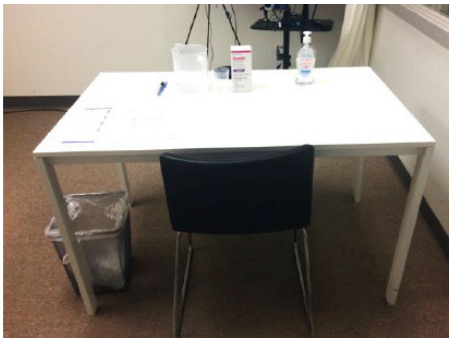
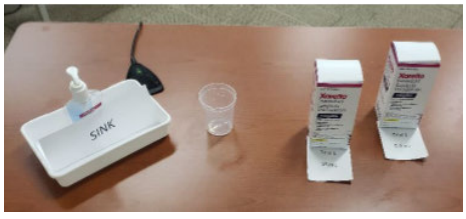
Additionally, we note the Applicant did not implement our recommendations for improvement to the oral syringe labeled graduations or for revisions to add units of measure to the IFU labeling. The Applicant determined that the HF validation testing demonstrated that the revisions are not needed.

Overall, we determined the aforementioned deviations from Agency recommendations do not preclude our review of the results.

We also note that following our HF protocol review, the Applicant revised the protocol to add a IFU mandatory testing scenario (Trial 2) in which caregiver participants simulated administration of a second dose and were required to refer to the IFU during testing. Additionally, the Applicant revised the protocol to include a caregiver user group that received pharmacist consultation prior to testing. See Table 2 below for additional details. Because Trial 1 is simulated before Trial 2 and participants were not directed to use the IFU, we find the addition of Trial 2 acceptable. However, we find the methodology for

pharmacist to consult the caregiver user group unacceptable because with real-world use, training or pharmacist counseling may not consistently or routinely occur. As such, this review does not consider the data for the 15 participants in the pharmacist consultation caregiver user group.

Table 2 presents a summary of the HF validation study design. See Appendix D for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	Pharmacists/pharmacy technicians, n = 16 - 15 participants completed simulated use and 1 pharmacist participant provided the consultation to caregivers Lay Caregivers, n = 30 - Group 1, n = 15 - received no consultation from a pharmacist prior to testing - Group 2, n = 15 - received a consultation from a pharmacist prior to testing
Training	No formal training was provided. However, caregiver group 2 received a consultation from a pharmacist prior to testing.
Test Environment	The test environment included a well-lit room with flat working surface, background noise (typical of an office setting). - Simulated pharmacy environment  - Simulated home environment 
Sequence of Study	Pharmacists/pharmacy technicians - Simulated use (reconstitution for either 0.9 mL or 15 mL doses)

- Knowledge tasks
- Root cause analysis (RCA)
- Subjective feedback

Lay Caregivers
- Pharmacist consultation (pharmacist consultation caregiver group only)
- Simulated use Trial 1 (IFU optional): The IFU was available, but participants were not directed to use it unless they indicated they would in actual use
- Simulated use Trial 2 (IFU Mandatory): Participants were asked to use the IFU step-by-step to administer the second dose.
    - Note: All caregiver participants simulated the administration of two doses (i.e., first dose in Trial 1 followed by a second dose in Trial 2)
- Knowledge tasks
- RCA
- Subjective feedback

	Non-Consultation Caregiver Group (N = 15)		Consultation Caregiver Group (N = 15)	
	Trial 1	**Trial 2**	**Trial 1**	**Trial 2**
Pharmacist Consultation	No	No	Yes	Yes
IFU use	Optional	Mandatory	Optional	Mandatory
Dose (mL)	0.9 or 15	15 or 0.9	0.9 or 15	15 or 0.9
Counterbalance	Yes	Yes	Yes	Yes

3 RESULTS AND ANALYSES

Section 3.1 describes the analyses of use errors, close calls, and use difficulties identified with critical tasks in the HF validation study. Section 3.2 describes use errors, close calls and use difficulties with non-critical tasks in the HF validation study. As previously noted, this review does not consider the data for the 15 participants in the pharmacist consultation caregiver user group to be representative of real use; thus, the data was excluded.

3.1 ANALYSIS OF CRITICAL TASK ERRORS

Table 3 describes the study results, the Applicant's analyses of the results, and DMEPA's analyses and findings for use errors, close calls and use difficulties with critical tasks.

Table 3. Identified Issues and DMEPA's Findings * indicates pharmacist/pharmacist technician only task - Note: In Trial 1, caregiver participants simulated administration of a first-time dose and use of the IFU was optional. In Trial 2, caregiver participants simulated administration of a second dose and use of the IFU was mandatory.		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
Pharmacists/pharmacy technicians		
1.	For the task "Check expiration date of granules"*, there were 5 use errors (5 failures) in which pharmacy participants did not check the expiration date. Regarding subjective feedback, participants noted that they either check expiration date separate from preparation steps, the product is new, or that dry powders have a long shelf life. The Applicant's RCA attributed the use errors to the nature of the study environment. The Applicant did not propose mitigations in response to the use errors and noted that pharmacists have internal workplace procedure to check expiration dates of medications.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (e.g., if pharmacist uses expired granules to prepare medicine and the suspension does not have the specified potency resulting in repetitive underdoses). Our review of the study results identified subjective feedback that indicated that users would check the expiration date in a separate step or expected that the product would have a long shelf life. Our review of the labels and labeling finds that the carton labeling and container label include expiration dates. Additionally, we find that it is standard practice to check the expiration in the pharmacy setting prior to dispensing. Thus, based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
2.	For the task "Tap bottle until all granules flow freely"*, there was 1 use error (1 failure) in which the pharmacy participant did not tap the bottle. Regarding subjective feedback, the participant noted that tapping the bottle is not a typical reconstitution step and that the information about flavoring is unusual and draws more attention. The Applicant's RCA attributed the use error to the information being difficult to locate due to the presence of other information.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (i.e., if the granules do not fully suspend due to clumping resulting in underdose). Our review of the study results identified subjective feedback that indicated the participant noted the prominence of the information could be improved.

	In response to the use error, the Applicant revised the carton labeling to relocate the information about flavoring to a separate area above the reconstitution steps so the information about tapping the bottle is more noticeable. The Applicant determined that this labeling revision did not require validation.	Our review of the labels and labeling finds that the Applicant revised the carton labeling to relocate the information about flavoring to a separate area above the reconstitution steps in order to make the information about tapping the bottle more noticeable. We also note this information appears in the Prescribing Information (PI). However, we find the Applicant's post-validation carton labeling revision can be improved to increase the prominence of this step and decrease the prominence of the information regarding flavoring the product. We provide a recommendation in Table 5 to address this concern We have determined that this change can be implemented without additional HF validation testing data to be submitted for review.
3.	For the task "Shake for 60 seconds until all granules wetted and suspension is uniform"*, there were 10 use errors (10 failures). Specifically, 5 pharmacy participants shook the bottle ~40-50 seconds, 4 pharmacy participants shook the bottle ~30 seconds or less, and 1 pharmacy participant rolled the bottle upside down for ~20 seconds and then shook the bottle for ~40 seconds. Regarding subjective feedback, participants indicated that shaking the bottle for the time designated doesn't seem important as long as the medication is fully resuspended and that they counted too quicky or estimated the time. The Applicant's RCA attributed the use errors to participants incorrectly estimated the 60 second shaking time. The Applicant did not propose mitigations in response to the use errors and noted that the 60 seconds instruction is a guideline, but the key endpoint is that reconstitution is complete, which all participants successfully completed. The Applicant also noted that if the granules are not resuspended, additional shaking and a visual check later in the process assures proper mixing and homogeneity of the suspension.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (e.g., due to low drug concentration resulting in an underdose). Our review of the study results identified subjective feedback that indicated that participants who experienced use errors were aware they needed to shake the bottle; however, they did not shake for the full 60 seconds. We also note that all participants successfully suspended the product. Our review of the labels and labeling finds that the carton labeling, and Section 2.7 of the PI include instructions to shake the product for 60 seconds until the granules are wetted and the suspension is uniform. Additionally, the IFU and container label instruct users to shake the bottle for 10 seconds prior to each use; as such, ideally, patients and caregivers will also shake the bottle which helps to mitigate the risk of administered granules that are not wetted/uniform suspension. Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

4.	For the task "Apply use-by date on bottle"*, there were 2 use errors (1 failure and 1 close call). One pharmacy participant said they would apply a use-by sticker to the carton but not on the bottle, and 1 pharmacy participant expressed concern that caregivers would miss the use-by date (post-reconstitution expiration date) on the container label and would use a sticker instead. Regarding subjective feedback, the participants indicated applying a sticker to outer packaging is more convenient and that the post-reconstitution expiration date is not noticeable on the container label. The Applicant's RCA attributed the use errors to the participants thinking that the area to apply the post-reconstitution expiration date would not be noticeable. The Applicant did not propose mitigations in response to the use errors and noted that placement of the post-reconstitution expiration date is dependent on pharmacy practice and all pharmacists applied a post-reconstitution expiration date in the study.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (e.g., due to use of expired granules which may result in reduced drug potency and a repetitive underdose). Our review of the study results identified subjective feedback that indicated the location of the use-by date labeling could be improved. Our review of the labels and labeling finds that the proposed container label includes a space for the pharmacist to write in the post-reconstitution expiration date. However, the prominence and format can be improved. We also find the carton labeling can be improved to include a space for the post-reconstitution expiration date. Additionally, instructions for the post-reconstitution expiration date in the PI can be improved. We provide recommendations in Tables 4 and 5 to address these concerns. We have determined that these changes can be implemented without additional HF validation testing data to be submitted for review.
5.	For the knowledge task "Do not add flavor as product is already flavored"* (Question: Is the product already flavored?), there was 1 use error (1 use difficulty). One pharmacy participant did not locate relevant information on the carton but reported would not add any additional flavor without confirming compatibility. Regarding subjective feedback, the participant noted that the instruction is located between 2 steps that draw more attention because they begin with action words. The Applicant's RCA attributed the use error to the information being difficult to locate due to presence of other information. In response to the use error, the Applicant revised the labeling to make the instruction more prominent. The Applicant determined that this labeling revision did not require HF validation.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis because added flavor dilutes the formulation and could impact the stability of the formulation. Our review of the study results identified subjective feedback that the participant considered the labeling information difficult to locate. Our review of the labels and labeling finds that the Section 2.7 of the PI and the carton labeling instruct users not to add flavor to the product. We also note the Applicant revised the carton labeling following the HF validation study; specifically, the Applicant moved the guidance to not add flavoring (previously Step 2) to a separate area above the reconstitution steps and used red font with bolding. However, as previously noted, we find the Applicant's post-validation revision can be improved to decrease the prominence of the information regarding

		flavoring the product and we provide a carton labeling recommendation in Table 5 to address this concern.
6.	For the knowledge task "Product must be dispensed in original bottle"* (Question: Can the product be dispensed in a bottle other than the original bottle?), there 1 use error (1 failure). One pharmacy participant reported they would transfer the medication to another amber bottle. Regarding subjective feedback, the participant stated that transferring to another bottle is common practice. The Applicant's RCA attributed the use error to the information being difficult to locate due to presence of other information. In response to the use error, the Applicant moved the information about flavoring to a separate area of the labeling above the reconstitution steps so the information about dispensing in original bottle is more noticeable. The Applicant did not validate the revision.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (e.g., if stored in a bottle leading to underdosing due to stability, extractables or leachables issues) or bleeding (e.g., if stored in plastic bottle leading to water evaporation and higher concentration resulting in repetitive large overdoses). Our review of the study results identified subjective feedback that indicated the use error may have occurred in part due to negative transfer. Our review of the labels and labeling finds that Section 2.7 of the PI and the carton labeling state the product should be dispensed in the original bottle. We also note the Applicant revised the carton labeling; specifically, the Applicant revised the "dispensing the product" section (previously Step 7) and moved it to a new section with red colored font. We have determined that this change can be implemented without additional HF validation testing data to be submitted for review. We did not identify any other areas of improvement.
7.	For the knowledge task "Store the granules and reconstituted suspension"* (Question: What are the storage conditions for the granules and reconstituted suspension?), there was 1 use error (1 close call). The pharmacy participant reported the medication should be stored from 59 to 86 degrees, and then self-corrected. Regarding subjective feedback, the participant said the temperature range permitted for excursions is the first temperature range encountered when reading the carton label from the bottom up. The Applicant's RCA attributed the use error to the pharmacist reading the label from the bottom up. The Applicant stated this was a "one-off event," and did not propose mitigations in response to the use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis due to reduced potency. Our review of the study results identified subjective feedback that indicated the participant was reading the labeling in reverse order than typically expected. However, we note that the response provided is listed as a permissible storage temperature excursion on the carton labeling and the participant was able to self-correct and provide the correct answer. Our review of the labels and labeling finds that the carton labeling and container label include product storage information. Based on our review of the user interface, subjective feedback, and RCA, we agree

		with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
Lay Caregivers		
8.	For the task "Check 'use-by' date on bottle", there were 8 use errors (8 failures). Specifically, 7 caregiver participants in Trial 1 (IFU optional) did not check the post-reconstitution expiration date and 1 caregiver participant in Trial 1 referred to the expiration date for the granules instead. Regarding subjective feedback, the participants indicated they did not read the instructions, focused on administration, assumed they had just come from the pharmacy and expired medication wasn't provided, and first saw expiration date and did not look further. The Applicant's RCA attributed the use errors to participants not reading the IFU and did not recognize the need to check the post-reconstitution expiration date. The Applicant did not propose mitigations in response to the use errors and noted that reading the IFU was effective in checking the post-reconstitution expiration date and that the reconstituted medication is good for 60 days which is longer than the expected duration of the longest prescription period (50 days).	Based on the URRA, if this task is omitted or not performed correctly there is risk of biocontamination or thrombosis (i.e., expired suspension may result in reduced drug potency and a repetitive underdose). Our review of the study results identified subjective feedback that indicated some participants did not read the instructions and that study artifact might have also contributed to some use errors. Also, we disagree with the Applicant's assertion that the longest prescription period is 50 days. Specifically, we note that if a patient is prescribed 2.2 mL daily, their prescription would last approximately 70 days. However, we note there are other approved products in which users may need to discard product that remains after the post-reconstitution date; as such, this characteristic is not unique. Our review of the labels and labeling finds that the container label includes a space for the post-reconstitution expiration date. Additionally, IFU Step 1 instructs users to check the (b) (4) date. However, as previously noted, we recommend revisions to the post-reconstitution expiration date on the container label and inclusion of the post-reconstitution expiration date on the carton labeling to address this use error concern (see Row 4 in this table (b) (4)
9.	For the task "Shake bottle slowly for 10 seconds before each use", there were 6 use errors (6 failures). Three caregiver participants in Trial 1 (IFU optional) did not shake the bottle prior to withdrawing the medication and 3 caregiver participants in Trial 1 shook the bottle aggressively.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (i.e., due to low drug concentration resulting in underdose). Our review of the study results identified subjective feedback that indicated that the language in the IFU could be improved upon.

	Regarding subjective feedback, participants stated they did not read the instructions, focused on administration, shook aggressively out of habit or misinterpreted the meaning of "slow". The Applicant's RCA attributed the use errors to participants not reading the IFU and negative transfer from other medications. The Applicant did not propose mitigations in response to the use errors and indicated reading the IFU was effective.	Our review of the labels and labeling finds that the IFU and container label include instructions to shake the bottle slowly. However, we find that the corresponding graphic on the container label can be relocated to mitigate the risk of users shaking the bottle vigorously. We provide a recommendation in Table 5. We have determined that this change can be implemented without additional HF validation testing data to be submitted for review.
10.	For the task "Check suspension. If lumps or granules are on the bottom of the bottle, shake slowly again for 10 seconds" there were 6 use errors (6 failures). Specifically, 6 caregiver participants in Trial 1 (IFU optional) did not check for lumps or granules. Regarding subjective feedback, the participants indicated they did not read the instructions, would rely on pharmacy consultation in actual use, or did not check out of habit or not usually shaking oral liquid medication. The Applicant's RCA attributed the use errors to negative transfer from other medications. The Applicant did not propose mitigations in response to the use errors and indicated reading the IFU was effective.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (i.e., due to low drug concentration resulting in underdose). Our review of the study results identified subjective feedback that indicates not reading the IFU, relying on pharmacy consultation, and negative transfer contributed to the use errors. None of the subjective feedback points to any one piece of labeling for improvement. Our review of the labels and labeling finds that IFU Step 2 instructs users to check the suspension. However, to increase prominence, we find that the container label can be improved to include this task. We provide a recommendation in Table 5. We have determined that this change can be implemented without additional HF validation testing data to be submitted for review.
11.	For the task "Push the plunger all the way in to remove air", there were 4 use errors (2 failures and 2 use difficulties). Specifically, 2 caregiver participants in Trial 1 (IFU optional) did not push the plunger all the way in, 1 caregiver participant in Trial 1 was confused about pushing the plunger in, and 1 caregiver participant in Trial 2 (IFU mandatory) was confused about pushing the plunger in. Regarding subjective feedback, participants in Trial 1 indicated they did not read the instructions, had no previous experience with bottle adaptors, or did not think to invert the bottle. Participants in Trial 2 indicated they did not read this step in the IFU and thought to push	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (i.e., air remaining in the syringe could lead to a single or repetitive underdose). Our review of the study results identified subjective feedback that indicated not reading the IFU and negative transfer contributed to the use errors. We note that a participant in Trial 2 (IFU mandatory), did not read this step in the IFU, which resulted in confusion. However, the participant understood that air had to be removed.

	air into the bottle. The Applicant's RCA attributed the use errors to negative transfer from other medications. The Applicant did not propose mitigations in response to the use errors and indicated reading the IFU was effective in performing this task.	Our review of the labels and labeling finds that IFU Step 4 provides instructions and a graphic for this task. Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
12.	For the task "Insert syringe into bottle adaptor", there was 1 use error (1 failure). One caregiver participant in Trial 1 (IFU optional) poured the medication, with bottle adaptor still in bottle, into the bottle cap and withdrew the medication from there. Regarding subjective feedback, the participant indicated they did not have previous experience with bottle adaptors and would consult with a pharmacist. The Applicant's RCA attributed the use error to negative transfer from other medications. The Applicant did not propose mitigations in response to the use error and indicated reading the IFU was effective in performing this task.	Based on the URRA, if this task is omitted or not performed correctly there is risk of irritation if the medication leaks from the PIBA resulting in accidental dermal or ocular exposure. Our review of the study results identified subjective feedback that aligns with the RCA. For example, the participant noted previous experience. Our review of the labels and labeling finds that IFU Step 4 provides instructions and a graphic for this task. In addition, a bottle adapter and syringe are routinely used to facilitate administration of pediatric doses. We note the participant who experienced a failure with this task was able to draw up the dose. Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
13.	For the task "Fill syringe slightly past the prescribed dose line", there was 1 use error (1 close call). One caregiver participant in Trial 1 (IFU optional) first attempted to draw medication without inverting the bottle. The participant then self-corrected. Regarding subjective feedback, the participant indicated they did not read the instructions and that the flat top gave the impression that the bottle did not need to be inverted. Additionally, the participant noted that they have not needed to invert a bottle with past medications. The Applicant's RCA attributed the use error to negative transfer from other medications.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis due to underdose. Our review of the study results identified subjective feedback that aligns with the RCA. For example, the participant noted experience with past medications. Our review of the labels and labeling finds that IFU Step 4 provides instructions and a graphic for this task. In addition, we note the participant was able to self-correct. Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

	The Applicant did not propose mitigations in response to the use error and indicated reading the IFU was effective in performing this task.	
14.	For the task "Tap syringe to move air bubbles to the top", there were 4 use errors (4 failures). Specifically, 3 caregiver participants in Trial 1 (IFU optional) did not tap the syringe to remove air bubbles and 1 caregiver participant in Trial 2 (IFU mandatory) misinterpreted the steps in the IFU related to overfilling, tapping, and readjusting. Regarding subjective feedback, participants in Trial 1 indicated they did not read instructions or did not notice air bubbles that were in the syringe. A participant in Trial 2 indicated they filled the syringe past the dose line to account for air bubbles, which is their standard practice for current medications. The Applicant's RCA attributed the use errors to negative transfer from other medications. The Applicant did not propose mitigations in response to the use errors and noted that the dose administered was within acceptable limits based on estimating the amount of air bubbles in the syringe. The Applicant also noted that the instruction covers this topic extensively and no further action is required.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis (i.e., air bubbles remain in the syringe resulting in an underdose). Our review of the study results and subjective feedback finds that the Applicant's RCA regarding negative transfer applies primarily to the Trial 2 results. We identified subjective feedback from Trial 1 participants indicating that participants were not aware that the air bubbles should be removed or did not see the air bubbles. Our review of the labels and labeling finds that IFU Step 4 provides instructions and a graphic for this task. However, should the air bubble not be visualized in the syringe, we have been informed by our clinical review team that a dosing error within 15% of the intended dose is not likely to result in clinical harm. Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement based on the study results and. However, we recommend additional labeling mitigations to the IFU to improve prominence of this task. We provide a recommendation in Table 5 for the Applicant to update the IFU to better depict how to identify air bubbles in the syringe.
15.	For the task "Adjust to your prescribed dose", there were 6 use errors (3 failures, 2 close calls, and 1 use difficultly). Specifically, 1 caregiver participant in Trial 1 (IFU optional) and 2 caregiver participants in Trial 2 (IFU mandatory) did not deliver the prescribed dose. Additionally, 1 caregiver participant in Trial 1 and 2 caregiver participants in Trial 2 almost delivered an inaccurate dose but self-corrected. Regarding subjective feedback:	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis or bleeding. Our review of the study results identified subjective feedback indicating that participants were not aware that the air bubbles should be removed. We also consulted the clinical review team, and they confirmed that a dosing error within 15% of the intended dose is not likely to result in clinical harm.

	- Trial 1: 1 participant who did not deliver the prescribed dose set the plunger to 0.8 mL instead of 0.9 mL. The participant did not know why they did that but thought possibly due to nervousness. The participant believed they administered the prescribed dose. Additionally, 1 participant set the plunger at 1.1 mL instead of 0.9 mL; however, the participant corrected after rereading the IFU. - Trial 2: Two participants who did not deliver the prescribed dose set the plunger to (a) 15.1 mL instead of 15 mL and (b) 15.3 mL instead of 15 mL. One of the 2 participants indicated the syringe may not have been held at eye level well enough, and the other participant noted they accounted for air bubbles and some medication remaining in the syringe post-administration by aligning the top of the syringe past the prescribed dose line, a participant realized they had to administer two more 5 mL doses (for the 15 mL dose) after putting the medication away. Additionally, 1 additional participant withdrew more than 5 mL and readjusted the plunger to 5 mL, but noticed medication in the tip of syringe and attempted to remove it. The Applicant's RCA attributed the use errors to nervousness and attempting to account for air bubbles by aligning the syringe past the prescribed dose line. The Applicant noted re-reading the IFU helped participants recover from drawing an incorrect dose. The Applicant also noted that participants were more likely to use the color scale for the smaller, more granular 0.9 mL dose (16/30=53%) as it did not require counting markings and were likely to use the mL scale for the larger 15 mL doses (mL: 18/30=60%) that aligned with the major graduation markings. Some participants used both scales to double-check their set dose (9/60=15%). The Applicant did not propose mitigations in response to the use errors and noted that the dose delivered was within the accepted margin.	Our review of the labels and labeling finds that IFU Step 4 provides instructions and a graphic for this task. Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.

16.	For the task "Store syringe", there were 2 use errors (2 failures). Specifically, 1 caregiver participant in both Trial 1 (IFU optional) and Trial 2 (IFU mandatory) indicated an improper storage procedure. Regarding subjective feedback, the participant saw the IFU statement but indicated they would still discard the box to avoid clutter and store syringe on a paper towel in a cabinet. The Applicant's RCA attributed the use errors to the participant not seeing the need to store syringes in the carton. The Applicant did not propose mitigations in response to the use errors and noted that the participant's performance was a one-off event and no further action is required.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis. Our review of the study results finds the subjective feedback indicates the participant intentionally deviated from the intended use of the product. Our review of the labels and labeling finds that the first page of the IFU states "Store the bottle upright with the oral dosing syringes in the original carton". Based on our review of the user interface, subjective feedback, and RCA, we agree with the Applicant that the residual risk is acceptable for this task. We did not identify areas of improvement and have no recommendations at this time.
17.	For the knowledge task "Knows not to take a partial dose" (Question: What would you do if there is not enough medication in the bottle for a full dose?), there were 3 use errors. Specifically, 3 caregiver participants in Trial 1 (IFU optional) could not find the caution statement in the IFU. Regarding subjective feedback, the participants indicated the statement was not easy to find and that the statement should be closer to the beginning of the IFU when first inspecting the medication. The Applicant's RCA attributed the use errors to participants being unable to locate the warning statement in the IFU. In response to the use errors, the Applicant revised the IFU to remove the boxed statement and added "Caution" and a caution symbol to make the statement more noticeable in the IFU. The Applicant determined no additional validation testing is needed as further highlighting the information improves the opportunity to locate the warning statement in the IFU.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis. Our review of the study results finds the subjective feedback indicates participants noted difficulty locating the IFU statement. Our review of the labels and labeling finds that IFU Step 4 states "Do not take a partial dose. Make sure you have enough medicine for a full dose". However, the prominence of the statement could be improved. We provide a recommendation in Table 5. We also note the Applicant implemented a post-validation revision to the IFU to include a triangular symbol and the word "Caution" ( ) prior to the partial dose caution statement. We acknowledge the triangular symbol is not a universal symbol and may not be understood by patients with low literacy. However, we note that the post-validation revision also includes the word "Caution" which will assist in users' understanding of the symbol and corresponding statement. As such, we find the post-validation revision acceptable.

18.	For the knowledge task "Knows to use provided syringes" (Question: Can you use syringes other than those provided to administer the medication?), there were 6 use errors. Specifically, 6 caregiver participants could not find the warning statement in the IFU. Regarding subjective feedback, the participants indicated they could not find the warning statement. The Applicant's RCA attributed the use errors to the participants being unable to locate the warning statement in the IFU. In response to the use errors, the Applicant repeated the statement in Step 3 enclosed in a box to make the statement more noticeable in the IFU. The Applicant determined no additional validation testing is needed because the revision is repeating information.	Based on the URRA, if this task is omitted or not performed correctly there is risk of thrombosis or bleeding. Our review of the study results finds the subjective feedback indicates participants noted difficulty locating the IFU statement. Our review of the labels and labeling finds that the beginning of the IFU and IFU Step 3 contain the statement "Only use the oral dosing syringe provided with XARELTO oral suspension", which incorporates the Applicant's revision to repeat the information. We have determined that this change can be implemented without additional HF validation testing data to be submitted for review. We did not identify any additional areas of improvement.

3.2 ANALYSIS OF NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the following non-critical tasks; however, based on our review of the available participants' subjective feedback, the Applicant's root cause analysis, and the Applicant's proposed risk mitigation strategy, we determined the residual risk is acceptable. Specifically, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the four noncritical tasks below. We also find the labels and labeling are in alignment with best labeling practices. In addition, we considered the use tasks of the proposed product as compared with the use tasks in similar marketed products with the same user groups to determine if there are any known concerns of vulnerability to use error and did not identify any concern. Subsequently, we did not identify further need to implement additional risk mitigation strategies at this time to address the use errors related to the following non-critical tasks:

- Push adaptor into bottleneck and recap
- Place bottle into carton (as well as syringes and IFU, if removed)
- Wash hands
- Disposal

3.3 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Division of Non-malignant Hematology (DNH)			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information- Section 2 Dosage and Administration			
1.	In Tables 2 and 3 in Section 2.2 Recommended Dosage for Pediatric Patients, each numerical value in the "Body weight" column does not include units of measure.	Confusion regarding the body weight in the dosing table might result in wrong dose errors.	Consider revising Tables 2 and 3 to include units of measure (i.e., kg) after each numerical value in the "Body weight" column. For example, in Table 2 "2.6" should be revised to "2.6 kg".
2.	Tables 2 and 3 in Section 2.2 include error prone symbols (i.e., <, ≥).	The symbols may be mistaken as opposite of intended, which could result in wrong dose errors.	Consider replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.[e] Alternatively, if appropriate, consider revising the body weights to as follows: - Revise "2.6 to <3 kg" to "2.6 kg to 2.9 kg", revise "3 to <4 kg" to "3 kg to 3.9 kg", etc.
3.	Tables 2 and 3 in Section 2.2 include trailing zeroes (e.g., 2.0).	To avoid ten-fold misinterpretation, trailing zeroes should be eliminated from dose expressions.[f]	Remove all instances of trailing zeroes in Tables 2 and 3.

[e] Error-Prone Abbreviations, Symbols, and Dose Designation: ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [2021 SEP 27]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

[f] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 SEP 29]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4.	Table 4: Reference Values of Serum Creatinine in Pediatric Patients <1 year of age in Section 2.2 can be improved to mitigate the risk of confusion.	Users might be more familiar with serum creatinine values presented in mg/dL (versus micromole/L). Additionally, the values for creatinine in micromole/L overlap with plausible creatinine clearance values, which may lead to confusion resulting in wrong dose errors.	Consider revising Table 4 to delete the 2nd column, which contains serum creatinine values in micromole/L. Alternatively, if you choose to retain both columns in Table 4, consider relocating the 2nd column (micromole/L) to appear after the 3rd column (mg/dL).
5.	The presentation of the instructions in Section 2.7 Preparation Instructions for Pharmacy of XARELTO for Oral Suspension can be improved to increase the prominence of the critical preparation instructions.	If preparation instructions are overlooked, there is risk of wrong technique in drug usage process errors.	Consider revising the 1st paragraph in Section 2.7 to present the preparation step/instructions in number or bullet format.
6.	The presentation of the dispensing information in Section 2.7 is not cohesive because the dispensing information appears out of sequence and in multiple locations.	If dispensing instructions are overlooked, there is risk of wrong technique in drug usage process errors.	Consider revising this section so that all dispensing instructions appear after the preparation instructions and in close proximity to each other. We specifically note the following dispensing instruction statements "Dispense in the original bottle", "Dispense the bottle upright with the syringes provided in the original carton", and " Reconstitute before dispensing".
7.	The instructions for the post-reconstitution expiration date can be improved. Specifically, we are concerned that the term (b) (4) might confuse users.	Based on subjective feedback from the HF validation study, we are concerned the term (b) (4) may be misinterpreted to mean (b) (4) which is inconsistent with the intended action of writing the (b) (4) date.	Revise the statement (b) (4)

Medication Guide			
1.	The proposed Medication Guide for both Xarelto tablets and for oral suspension contains the newly added negative statement [redacted] (b) (4) " to inform users that Xarelto tablets should not be split but does not inform users of the appropriate action.	We are aware of post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked, and the warning may be misinterpreted as an affirmative action.[g]	Consider revising the statement [redacted] (b) (4) to read "If your child is taking the tablet, the tablet should be taken whole and should not be split in an attempt to provide a [redacted] (b) (4) dose" so that the affirmative statement appears before the negative statement.

[g] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Table 5: Identified Issues and Recommendations for Janssen Pharmaceuticals Inc (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The IFU Step 4 graphic regarding air bubble removal can be improved to better visually present the task.	Failure to remove air bubbles in the syringe might result in thrombosis (i.e., air bubbles remain in the syringe resulting in an underdose).	For the IFU Step 4 task, "Tap syringe to move air bubbles to the top", consider including a syringe graphic that is larger and clearly depicts air bubbles.
2.	The prominence of the partial dose caution statement in IFU Step 4 could be increased.	In the HF validation study, there were 3 use errors with the task "Knows not to take a partial dose" in which 3 caregivers participants could not find the caution statement in the IFU. Increasing the prominence of the statement might mitigate the risk of use errors with this task. If users administer a partial dose, there is risk of thrombosis (i.e., due to underdose).	For IFU Step 4, increase the prominence of the statement and revise to read "Caution Make sure you have enough medicine for a full dose. Do not take a partial dose."
Container Label (bottle)			
1.	The location of the container label graphic depicting shaking the bottle can be improved.	In the HF validation study, there were 6 use errors with the task "Shake bottle slowly for 10 seconds before each use" in which participants either did not shake the bottle or shook the bottle aggressively.	Relocate the "Shake slowly before each dose" graphic closer to the PDP so it's more likely to appear in the end user's view on the cylindrical bottle. For example, see image below and please note that this image is solely for the

		Failure to perform this task correctly might result in thrombosis (i.e., due to low drug concentration resulting in underdose).	purpose of demonstrating our recommendation only: (b) (4)
2.	The container label does not include instructions for users to check if the suspension has lumps and granules and to shake the bottle again if they are present.	In the HF validation study, there were 6 use errors with the task "Check suspension. If lumps or granules are on the bottom of the bottle, shake slowly again for 10 seconds" in which the participants did not perform the task and did not read the IFU. The presence of the instruction and/or a graphic on the container label might mitigate the risk of use errors with this task. Failure to perform the task correctly might result in thrombosis (i.e., due to low drug concentration resulting in underdose).	If space permits, revise the container label to include a graphic, text, or both for the task of checking the suspension for lumps or granules.
3.	The container label does not include the total volume after reconstitution.	Inclusion of the total volume after reconstitution on the container label might mitigate the risk of product preparation errors.	Revise the label to include the total volume after reconstitution on the PDP. For example, XXX mL (when reconstituted).

4.	A statement such as "For Oral Administration Only" or "For Oral Use Only" is not present on the label.	Post-marketing experience has indicated that wrong route of administration errors have occurred when oral liquid products have been inadvertently administered as injections.[h]	To minimize the risk of wrong route of administration medication errors, consider inclusion of the statement "For Oral Use Only" on the PDP.
5.	The format of the post-reconstitution expiration date on the container label can be improved.	In the HF validation study, there was subjective feedback that indicated the post-reconstitution expiration date labeling on the container label is not prominent. We are concerned that confusion regarding the post-reconstitution expiration date might result in deteriorated drug medication errors.	We recommend you revise the post-reconstitution expiration date labeling from [redacted] (b) (4) date here" to "Discard after __/__/__" since "Discard after" is an affirmative statement, and has been shown to result in the desired action. The "__/__/__" statement will alert the healthcare provider to write a complete date (month, day, and year) on the container label. Additionally, we recommend you consider methods to increase the prominence of the post-reconstitution expiration date labeling (e.g., boxing, bolding, etc.).
6.	The storage information can be improved to align with the Prescribing Information.	The storage information on the container label should be aligned with the Prescribing Information to minimize confusion and reduce the risk for deteriorated drug medication errors.	Revise the storage information to read: "Store granules and reconstituted suspension at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F)."
Carton Labeling			
1.	Refer to container label recommendations #3, #4,		

[h] Institute for Safe Medication Practices. Avoiding inadvertent IV injection of oral liquids. ISMP Med Saf Alert Acute Care. 2012;17(17):1-3.

	and #6 and revise accordingly.		
2.	We note you implemented a post-validation revision to the "Pharmacy Use Only" section of the carton labeling. However, we find the labeling can be further improved to increase the prominence of the reconstitution steps and decrease the prominence of the information regarding flavoring the product.	In the HF validation study, there was 1 use error for the task "Tap bottle until all granules flow freely", and the subjective feedback indicated that the information about flavoring is more prominent than the reconstitution steps. Failure to perform the task correctly might result in thrombosis (i.e., if the granules do not fully suspend due to clumping resulting in underdose).	In the "Pharmacy Use Only" labeling section, relocate the two bulleted statements (i.e., "Do not add flavor…" and "Dispense in the original bottle") to the end of the section (after the reconstitution steps) and remove the bolding from the two bulleted statements. Additionally, consider revising the statement "Do not add flavor…" to "XXX flavor. Do not add flavor…" to provide the flavor information.
3.	The carton labeling does not include space for the pharmacy to indicate the post-reconstitution expiration date.	In the HF validation study, there were 2 use errors for the task (b) (4) and the subjective feedback indicated that including the post-reconstitution expiration date on the carton labeling may mitigate risk of failure with this task. Failure to place the post-reconstitution expiration date on the labeling might result in deteriorated drug medication errors.	Revise the carton labeling to include a space for the post-reconstitution expiration date. We recommend, "Discard after __/__/__" since "Discard after" is an affirmative statement, and has been shown to result in the desired action. Additionally, the "__/__/__" statement will alert the healthcare provider to write a complete date (month, day, and year) on the carton labeling.
4.	The "Pharmacy Use Only" instructions regarding the post-reconstitution expiration date can be improved to clarify the intended action.	As noted in the recommendations above, the carton labeling will be updated to include post-expiration date labeling and the "Pharmacy Use Only" instructions should be updated accordingly.	Revise the carton labeling text from (b) (4) date to bottle" to "Write the "discard after" date on the bottle and carton".

5.	The description of the dosing device in the list of carton contents can be improved to clarify the route of administration.	Post-marketing experience has indicated that wrong route of administration errors have occurred when oral liquid products have been inadvertently administered as injections.[i]	Revise “2 Dosing Syringes” to “2 Oral Dosing Syringes”.

[i] Institute for Safe Medication Practices. Avoiding inadvertent IV injection of oral liquids. ISMP Med Saf Alert Acute Care. 2012;17(17):1-3.

4 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation study identified use errors with critical tasks. However, taking into consideration the review of the subjective feedback, root cause analysis, and our independent review of the proposed user interface, the risk mitigations implemented, and our postmarketing experience with similar currently approved products, we find residual risks associated with these use errors acceptable. Thus, in this specific instance, we accept the simulated HF validation study results.

We determined that the additional label and labeling revisions should be implemented to further reduce the residual risk associated with the design of the user interface. Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. These revisions can be implemented without submission of additional results of HF validation testing. Above, we have provided recommendations in Table 4 for the Division and Table 5 for the Applicant. We ask that the Division convey Table 5 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA 215859.

4.1 RECOMMENDATIONS FOR JANSSEN PHARMACEUTICALS INC

Our evaluation of the proposed Xarelto (rivaroxaban) for oral suspension packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Table 5 and we recommend that you implement these recommendations and submit your revised labels and labeling prior to approval of this NDA 215859. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation data for Agency review.

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On September 23, 2021, we searched the L:drive and AIMS using the terms, rivaroxaban and NDA 215859, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 3 previous reviews[j][k][l], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\CDSESUB1\evsprod\nda215859\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\vte-tx-prev-ped\5354-other-stud-rep\human-factor\legacy-study-human-factor.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On August 25, 2021, we sent an Information Request to the Applicant to request a side-by-side comparison of the labeling that was tested in the HF validation study and the intend-to-market labeling, along with tracked edits on the changes, and justification for any changes. The Applicant responded on August 30, 2021:
\\CDSESUB1\evsprod\nda215859\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\vte-tx-prev-ped\5354-other-stud-rep\human-factor\reponse-fda-25aug2021.pdf

[j] Rimmel, S. Use related risk analysis review for rivaroxaban granules for oral suspension IND 064892. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 24. RCM No.: 2017-54.

[k] Oguntimein, O. HF Validation Study Protocol Review for rivaroxaban granules for oral suspension (IND 064892). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 21. RCM No.: 2020-1767.

[l] Yokum, A. HF Protocol Memo for rivaroxaban granules for oral suspension (IND 064892). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 10. RCM No.: 2020-2641.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[m] along with postmarket medication error data, we reviewed the following Xarelto labels and labeling submitted by Janssen Pharmaceuticals Inc.

- Container label received on June 22, 2021
- Carton labeling received on June 22, 2021
- Instructions for Use received on June 22, 2021. Available from:
  - \\CDSESUB1\evsprod\nda215859\0001\m1\us\ifu-manuscript.pdf
- Prescribing Information (Image not shown) and Medication Guide received on June 22, 2021. Available from:
  - \\CDSESUB1\evsprod\nda215859\0001\m1\us\draft-labeling-text-marked-pediatric.pdf

F.2 Label and Labeling Images

Container label (bottle)

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[m] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EBONY A WHALEY
11/15/2021 12:29:24 PM

COLLEEN L LITTLE
11/15/2021 03:03:04 PM

LOLITA G WHITE
11/17/2021 03:14:40 PM

CHI-MING TU
11/17/2021 03:34:17 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 22, 2021
To:	Carleveva Thompson, MS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	XARELTO (rivaroxaban)
Dosage Form and Route:	for oral suspension
Application Type/Number:	NDA 215859
Applicant:	Janssen Research & Development, LLC

1 INTRODUCTION

On June 22, 2021, Janssen Research & Development, LLC., submitted for the Agency's review an original New Drug Application (NDA) 215859 for XARELTO (rivaroxaban) oral suspension to support inclusion of the proposed new indications in pediatric patients in the Prescribing Information. This submission serves as the Applicant's response to a Written Request for pediatric studies of rivaroxaban (XARELTO) for the purpose of pediatric exclusivity determination, and to fulfill the Pediatric Research Equity Act (PREA) and Post-Marketing Requirements (PMRS) under XARELTO (rivaroxaban) tablets, NDA 022406**.**

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on July 14, 2021 and August 6, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for XARELTO (rivaroxaban) oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft XARELTO (rivaroxaban) oral suspension MG and IFU received on June 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 14, 2021.
- Draft XARELTO (rivaroxaban) oral suspension Prescribing Information (PI) received on June 22, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 14, 2021.
- Approved XARELTO (rivaroxaban) tablets, NDA 022406, labeling dated August 23, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG or IFU.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 20, 2021

To: Carleveva Thompson
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for XARELTO (rivaroxaban) tablets, for oral use and XARELTO (rivaroxaban) for oral suspension

NDA: 215859

In response to DCN's consult request dated August 6, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Xarelto.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN on October 14, 2021, and are provided below.

OPDP comments on the proposed PPI/Medication Guide/IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 2, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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CLINICAL INSPECTION SUMMARY

Date	September 20, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Ann Farrell, M.D., Division Director Carleveva Thompson, M.S., Project Manager Division of Nonmalignant Hematology Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
NDA	215859
Applicant	Janssen Pharmaceuticals, Inc.
Drug	Xarelto® (rivaroxaban)
NME	No
Division Classification	Direct Factor Xa inhibitor (oral anticoagulant)
Proposed Indications	(1) For treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years. (2) For thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure
Review Type	Standard
Consultation Request Date	July 1 2021
Summary Goal Date	October 22, 2021
Action Goal Date	December 20, 2021
PDUFA Date	December 22, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 14372 and Study 39039039CHD3001 were submitted to the Agency in support of a New Drug Application 215859 for the drug rivaroxaban, proposed: (1) for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years, and (2) for thromboprophylaxis in pediatric patients two years and older with congenital heart disease after the Fontan procedure. Four clinical investigator sites, Riten Kumar, M.D., Joseph Palumbo, M.D., Biagio Pietra, M.D., and Andrew van Bergen, M.D. were inspected in support of NDA 215859.

Based on these inspections, the conduct of the above studies appears to be adequate. The study data derived from these clinical investigator sites are considered reliable: Riten Kumar, M.D., and Joseph Palumbo, M.D. for Study 14372, and Biagio Pietra, M.D. and Andrew van Bergen, M.D. for Study 39039039CHD3001. The study data submitted to the Agency for assessment appear acceptable in support of the proposed indication.

II. BACKGROUND

The sponsor submitted this priority pediatric application for rivaroxaban, an oral, direct Factor Xa inhibitor. For this NDA pediatric supplement, Study 14732 and Study 39039039CHD3001formed part of the FDA submissions for which domestic clinical study site inspections were requested.

Study 14372

Study 14372 was a Phase 3, multicenter, open-label, active-controlled, randomized study. Children received body weight-adjusted rivaroxaban in a once-daily, twice-daily or thrice-daily regimen. The main study treatment period was three months, which could be extended at the discretion of the treating physician within three blocks of three months each, followed by an observational period of another 30 days.

The primary objectives of this study were the following: (1) to assess the incidence of symptomatic recurrent venous thromboembolism, and (2) to assess the incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging. The principal safety objective was to assess the incidence of overt major and clinically relevant non-major bleeding.

The primary efficacy endpoint was symptomatic recurrent venous thromboembolism. The secondary efficacy outcome was the composite of symptomatic recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging. The principal safety outcome was the composite of overt major and clinically relevant non-major bleeding.

A total of 520 children were screened in 109 study centers in 28 countries. The first subject was enrolled on November 13, 2014. The end of study was on January 30, 2019.

Study 39039039CHD3001

Study 39039039CHD3001 was an open-label, active-controlled, multicenter study conducted at multiple sites in North America, Latin America, Western Europe, and in Asia-Pacific countries to evaluate the pharmacokinetic and pharmacodynamic profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in pediatric subjects two to eight years of age with single-ventricle physiology who had completed the Fontan procedure within four months prior to enrollment. Subjects were to be enrolled and randomized to receive the first dose of study drug on Visit 2 after meeting all of the inclusion and none of the exclusion criteria. Subjects could be enrolled and randomized on the business day prior to Day 1 of study drug administration.

The primary objective of the study were (1) to characterize the single- and multiple-dose pharmacokinetic and pharmacodynamic profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 years of age with single ventricle physiology who had completed the Fontan

procedure within four months prior to enrollment, and (2) to evaluate the safety and efficacy of rivaroxaban, administered twice daily (exposure matched to rivaroxaban 10 mg once daily in adults) compared to acetylsalicylic acid (ASA), given once daily (approximately 5 mg/kg) for thromboprophylaxis in same population.

The primary efficacy outcome was any thrombotic event (venous or arterial). All thrombotic events and the primary cause of death were adjudicated by a central and independent adjudication committee.

Safety was evaluated based on bleeding events, adverse events, clinical laboratory tests (hematology, serum chemistry, prothrombin and activated partial thromboplastin times), also adjudicated by an independent committee.

A total of 112 subjects were enrolled in this study in 10 countries including the US. The date the first parent or caregiver signed the informed consent was on November 17, 2016. The date of last observation recorded was on July 16, 2020.

III. RESULTS (by site)

1. Riten Kumar, M.D.
700 Childrens Drive
Columbus, OH 43205

Inspection dates: August 16 to 20, 2021

For Study 14372 (Site 14005), 23 subjects were consented and screened, and 20 subjects were enrolled and randomized into the study. A single subject discontinued (withdrew parental consent) from the study. There were 19 study subjects who completed the treatment phase.

Specifically, the following records were evaluated: study subject eligibility; protocol-required procedures; serious adverse event reporting; study efficacy endpoints; patient clinical progress notes; electrocardiographic reports; central laboratory reports; protocol adherence, relevant regulatory documents and study drug accountability.

All the records for the 20 enrolled and randomized study patients were evaluated. The primary efficacy endpoint data were verified against the data line listings. No discrepancies in the endpoint data were noted. There was no under-reporting of serious adverse events.

There were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued.

2. Joseph Palumbo, M.D.
3333 Burnet Avenue, ML 7015
Cincinnati, OH 45229

Inspection dates: August 2 to 10, 2021

For Study 14372 (Site 14023), 28 subjects were screened and enrolled. There were 28 study patients who were enrolled and randomized. All the study participants completed the treatment phase of the study.

The following regulatory documents were assessed: IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, dosing records, site signature and responsibility logs, and site training documentation. All the enrolled subjects' records were audited for eligibility, protocol adherence and adverse event reporting.

There were 24 of the 28 enrolled source records that were evaluated. The primary endpoint data were verified against the data line listings. No discrepancies were noted. There was no evidence of under-reporting of adverse events or protocol deviations.

There were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued.

3. Biagio Pietra, M.D.
1600 SW Archer Rd
Gainesville, FL 32610

Inspection dates: August 2 to 6, 2021

For Study 39039039CHD3001 (Site US10010), there were six subjects were consented and screened. All the six study patients were enrolled and completed the study.

The study records audited at Dr. Pietra's site included, in part, the following review: IRB approval letters, correspondence between sponsor and study site, site signature and responsibility logs, and site training documentation informed consent forms, monitoring reports, subject medical records, case report forms, study visit source documents, laboratory test results, dosing records, investigational drug accountability records.

Source records at the site for the six enrolled and randomized study patients were examined and verifiable, for primary endpoint data against the data line listings. No discrepancies were observed. There was no evidence of under-reporting of adverse events.

There were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued.

4. Andrew H. van Bergen, M.D.
4440 West 95th Street
Oak Lawn, IL 60453

Inspection dates: August 4 to 13, 2021

For Study 39039039CHD3001(Site US10013), there were 20 subjects were consented and screened, 20 subjects were enrolled and randomized. Of the 20 subjects who were randomized, 18 study subjects completed the treatment phase. Two subjects discontinued, due to increased study drug (rivaroxaban) exposure, and due to thrombosis, respectively.

The study records audited at Dr. van Bergen's site included, in part, the following review: IRB approval letters and correspondence, site signature and responsibility logs, and site training documentation informed consent forms, monitoring reports, protocol adherence, subject medical records, case report forms, study visit source documents, laboratory test results, dosing records, investigational drug accountability records.

Source records at the site for the 20 enrolled and randomized study patients were examined and verifiable, for primary endpoint data against the data line listings. No discrepancies were observed. There was no evidence of under-reporting of adverse events.

There were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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