CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217003Orig1s000

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:	August 23, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217003
Product Name and Strength:	Imbruvica (ibrutinib) oral suspension, 70 mg/mL
Applicant/Sponsor Name:	Pharmacyclics LLC
OSE RCM #:	2022-410-1
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted their response to the Agency's container label and carton labeling recommendations for Imbruvica on August 18, 2022 in response to recommendations that we made during a previous label and labeling review[a], as well as a recommendation from the Office of Pharmaceutical Quality (OPQ) regarding the consistency of storage statements across all labels and labeling.[b] The Applicant also submitted their revised container label and carton labeling for Imbruvica on August 22, 2022. The Division of Hematologic Malignancies 1 (DHM 1) requested that we review the aforementioned submissions (Appendix A and B, respectively) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

Regarding the expiration date format, the Applicant clarified that the format will be "YYYY-MM-DD" and will appear in the in the variable data/black laser print field on the carton labeling and

[a] Whaley, E. Human Factors Study Results and Label and Labeling Review for Imbruvica (NDA 217003). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 AUG 8. RCM No.: 2022-410 2022-416.

[b] Lee-Alonzo, R. Labeling PMR/PMC Discussion Comments for Imbruvica (ibrutinib). Silver Spring (MD): FDA, CDER, OND, DHM1 (US); 2022 AUG 17. NDA 217003. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8067d829.

container label. Regarding the location of the [redacted] (b) (4) The Applicant also noted that a 2D data matrix barcode product identifier will appear in the variable data/black laser print field on the carton labeling in accordance with the Drug Supply Chain Security Act.

We find the Applicant's response regarding the expiration format and location of the 2D data matrix acceptable. As such, we conclude that the proposed container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

APPENDIX A. APPLICANT'S RESPONSE RECEIVED ON AUGUST 18, 2022

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APPENDIX B. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 22, 2022

Container Label

(b) (4)

1 Page(s) 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/

COLLEEN L LITTLE on behalf of EBONY A WHALEY
08/23/2022 01:25:57 PM

COLLEEN L LITTLE
08/23/2022 01:26:06 PM

HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW
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)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 8, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217003
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength:	Imbruvica (ibrutinib) oral suspension, 70 mg/mL
Device Constituent:	Oral Syringe
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pharmacyclics LLC
FDA Received Date:	February 24, 2022; May 12, 2022; May 24, 2022; July 7, 2022; July 25, 2022
OSE RCM #:	2022-416, 2022-410
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 Director:	Danielle Harris, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 217003 for Imbruvica (ibrutinib) oral suspension.

1.1 PRODUCT INFORMATION

This is a combination product with a proposed oral syringe device constituent that is intended to treat pediatric patients aged 1 year and older with chronic graft-versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

The proposed combination product is supplied in a carton containing: (a) one amber glass bottle of ibrutinib oral suspension and (b) two 3 mL reusable oral syringes. The dosing range is 0.4 mL to 6 mL administered once daily. Users must perform the measurement and administration process two times to achieve doses above 3 mL. The proposed combination product is intended for use by lay caregivers, pediatric patients, and healthcare professionals (HCPs). See Appendix A and Figure 1 for more information.

Figure 1 : Imbruvica oral suspension oral syringes

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

- Imbruvica (ibrutinib) capsules were approved on November 13, 2013 under NDA 205552, and Imbruvica tablets were approved on February 16, 2018 under NDA 210563. Imbruvica

capsules and tablets are currently approved for the treatment of the following indications in adults:
  - mantle cell lymphoma (MCL)
  - chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
  - CLL/SLL with 17p deletion
  - Waldenström's macroglobulinemia (WM)
  - marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
  - chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy
- On February 25, 2021, the Applicant submitted a HF validation study protocol under IND 147315 for the proposed oral suspension. We completed our review of the HF validation study protocol and issued comments to the Applicant on May 21, 2021.[a]
- On July 16, 2021, the Applicant submitted a response to our May 21, 2021 HF Advice and we provided additional comments regarding the HF validation study protocol methodology on November 2, 2021.[b]
- On February 24, 2022, the Applicant submitted the results of the HF validation study under NDA 217003, which is the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous DMEPA HF Reviews	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

[a] Vora, N. Human Factors Validation Study Protocol Advice for ibrutinib. Silver Spring (MD): FDA, CDER, OSE (US); 2021 MAY 21. IND 147315. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805f2422
[b] Vora, N. Human Factors General Advice for ibrutinib. Silver Spring (MD): FDA, CDER, OSE (US); 2021 NOV 02. IND 147315. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80624cbd

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

3 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 indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

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

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• Adult caregivers of children (n = 15) o Six of the 15 caregivers were caregivers of children that do not have a chronic condition (i.e., general population) • Adult caregiver-pediatric patient dyads (n = 15) o Pediatric patients were aged 10—17 years old o Seven of the 15 pediatric patients did not have a chronic condition (i.e., general population) • HCPs (n = 15) o Registered nurses, licensed practical nurses, or pediatricians
Training	Study participants did not receive training.
Test Environment	Simulated home environment that included common household items (e.g., pens, tissues, trash can) and reasonable indoor lighting levels. Participants administered the simulated doses into a dose container.
Sequence of Study	• Simulated-use dosing scenario #1 o Simulated dose: 0.4 mL or 4.8 mL • Root cause analysis (RCA) • Simulated-use dosing scenario #2 o Simulated dose: 0.4 mL or 4.8 mL (whichever dose was not simulated in scenario #1)

	• Knowledge task assessment • RCA • Health literacy assessment

3.2 DISCUSSION OF METHODOLOGY

In order to clarify which previous Agency protocol review recommendations were implemented into the HF validation study methodology, we sent a 5/9/22 Information Request (IR) to the Applicant and requested the Applicant submit a red-lined version of the HF validation study protocol used to conduct the HF validation study that identified the changes made to the HF validation study protocol after receiving Agency feedback. In response to the Agency's 5/9/22 IR, the Applicant stated that they were not aware of the HF protocol recommendations in the 11/2/21 HF Advice Letter until the 5/9/22 IR was sent. As such, they did not implement the 11/2/21 recommendations into their HF validation study methodology. See Appendix E for additional information. Specifically, we note the following:

- Pediatric user group: We previously acknowledged the Applicant's proposal to include an adult caregiver-pediatric patient dyad. However, because adult/caregiver user data would already be collected in the caregiver arm, we recommended the HF validation study include a primarily pediatric/adolescent distinct user group that allows the pediatric/adolescent participant to call upon the caregiver/parent/guardian for assistance as they normally would in real life. As noted, the Applicant indicated they did not receive this recommendation and conducted the HF validation study with a combined patient and parent/caregiver dyad user group. Although the Applicant did not include a pediatric patient only distinct user group, we acknowledge that the Applicant incorporated methodology where the pediatric patient and caregiver completed the tasks as they would at home. For example, we note the moderator informed the dyads: "I would like you [refer to the Patient Participant] to perform as much of the process as you would be comfortable doing…I would like you [refer to Caregiver] to assist in any way you feel comfortable doing if you were observing in your home." Additionally, in instances of use errors, close calls, or use difficulties, the HF results report specifies the tasks performed by each dyad participant. As such, in this particular instance, we find the methodology does not preclude our review of the HF validation study results.
- Leading language: We recommended removing leading language from the moderator script. We also recommended that if the Applicant intended for participants to specifically refer to the labeling in order to validate the instructions for use (IFU), such scenario should occur after the initial knowledge assessment and subsequent root cause analysis. As noted, the Applicant indicated they did not receive this recommendation and did not remove all instances of leading language. Per the Applicant, in order to evaluate how participants would navigate, search, comprehend and relate to the IFU, participants were directed to use the IFU for the knowledge task assessments. For example, we note the knowledge task assessments began with the phrase "According to the instructions…", which may have prompted participants to refer to the labeling

instead of independently determining whether to refer to the IFU. In response to the Agency's 5/9/22 IR, the Applicant noted that the simulated-use scenario was conducted "without instructing participants to use the available labeling (i.e., leading language) and then participants were asked to evaluate the labeling." While we find that this methodology does not represent natural interaction with the user interface regarding whether users will independently refer to the IFU to locate information, we note the knowledge task scenario did not direct participants to the specific location of the information in the labeling. Additionally, based on the sequencing of the study, the simulated use portion of the study was not impacted by the use of any leading language. As such, in this particular instance, we find the methodology does not preclude review of the HF validation study results.

4 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations. Additionally, we provide our review of the label and labeling for areas of vulnerability that may lead to medication errors.

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
1.	For the shake bottle until mixed task, there were 7 use errors. • 1 caregiver, 3 dyads, and 3 HCPs did not shake the bottle. Five of the 7 use errors occurred during scenario #1. The subjective data and Applicant's root cause analysis (RCA) indicated the above performance can be attributed to: • Negative transfer: prior experience led participants to not refer to the instructions for use (IFU) or caused them not to expect to need to shake a room temperature product • Forgetfulness: "slipped her mind" to shake the bottle • Sequence effect – study artifact o Shook the bottle in scenario #1 and caregiver believed pediatric patient participant did the same for scenario #2 o Thought they shook the bottle before the beginning of scenario #2 • Labeling o Insufficiently prominent guidance - did not see the IFU or carton labeling instruction until after withdrawing the dose into the oral syringes o Misleading design element –HCP participant did not read the IFU because it said for "your child" • Violation of mental model - work environment o Based on their work environment, the participant expected the pharmacy to send the medication already prepared or to receive instruction from the pharmacy on how to prepare the medication. • Study artifact o Performed task quickly due to excitement o Did not restart procedure after noticing error (see "insufficiently prominent guidance" above) because they knew their child would not be ingesting the product	The subjective feedback indicated participants referred to previous experience, incorrectly believed the task had already been performed, or misinterpreted or overlooked a labeling statement. We note that 1 dyad experienced a use error that was attributed to insufficiently prominent labeling; specifically, the caregiver participant in the dyad did not see the instruction in the IFU to shake the bottle until after withdrawing the dose into the oral syringes. However, we also note the caregiver participant indicated that in a real-world situation, she would have returned the medication from the syringes into the bottle, shook the bottle, and restarted the preparation procedure. IFU Step 3 instructs users to shake the bottle before each use and includes a corresponding graphic. Additionally, the instructions to shake well are redundantly placed on the carton labeling and container label and state "Shake well before each use" which is in alignment with best labeling practices. Although HCPs are intended users of the proposed product, we find use of the terminology indicating that the proposed product is for "your child" acceptable

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	o Test anxiety Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy or hepatotoxicity (due to drawing a higher concentration with later doses). The Applicant noted the following risk mitigation strategies: clear and prominent instruction on container label and carton labeling to "Shake well before each use" and a corresponding step and graphic in the IFU. The Applicant did not propose additional mitigations in response to participant performance for this task.	because patients and caregivers are also intended users and the IFU is intended to help lay users with safe and effective use. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.
2.	For the invert the bottle with the syringe attached to press in bottle adapter (PIBA) task, there were 3 use errors and 1 use difficulty. • 1 dyad and 1 HCP participant removed the PIBA from the medication bottle (scenario #1) • 1 dyad removed the PIBA from the medication bottle (the pediatric patient participant attempted to withdraw the dose while the bottle was upright and then the caregiver indicated the PIBA should be removed - scenario #1) • 1 HCP participant inverted the bottle and pushed a syringe full of air into the bottle before drawing her first oral syringe of medication. This caused the medication to squirt out of the PIBA and onto the table (scenario #2). The subjective data and Applicant's RCA indicated the above performance can be attributed to: • Violation of mental model – o Previous experience pouring oral medication into a cup o Did not understand the purpose of the PIBA o Did not believe they could withdraw medication with the PIBA in place	The subjective feedback indicated confusion regarding the purpose of the PIBA; however, we acknowledge that these participants (2 dyads and 1 HCP) did not refer to the IFU. We also note that a HCP participant referred to the first 1st bullet under IFU Step 6 ("slowly pull the syringe plunger down…) before inserting the oral syringe into the PIBA (i.e., Step 5). Figure A in the Important Information section of the IFU includes a graphic that instructs users not the remove the PIBA. Additionally, IFU Step 5 instructs users to turn the bottle and oral syringe upside down and includes a corresponding graphic. We also note that IFU Step 6 instructs users to "pull" the plunger down (i.e., "slowly pull the syringe plunger

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	Identified Issue	DMEPA's Analysis and Findings
	○ Removed the PIBA because they couldn't get the oral syringe deep enough into the bottle ○ Noted similarity with Worcestershire sauce condiment bottle and chose to remove the PIBA to save time; did not refer to the IFU • Misunderstood the terminology in IFU Step 6 - thought she had to draw the syringe past the marking before inserting it into the PIBA; however, Step 6 intends for the user to pull the syringe past the marking <u>after</u> it has been inserted into the PIBA. Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy, trauma due to drug product spill or leak, or hepatotoxicity. Additionally, if the PIBA is removed there is risk of delay in therapy, drug product spill or leak, or patient receiving more or less product than intended. The Applicant noted the following risk mitigation strategies: • IFU Figure A includes the instruction "Do not remove the adapter" • The PIBA is preinstalled, has a tight fit, and is designed to easily connect with the oral syringe • IFU Step 5 has instructions and a graphic (Figure E) indicating to push the plunger down before the syringe is connected to the PIBA. The Applicant did not propose additional mitigations in response to participant performance for this task.	down… and "pull past the amount needed") and includes a corresponding graphic. Although, there was no subjective feedback which pointed to confusion or deficiencies related to the IFU regarding PIBA removal, we find the IFU can be improved to reiterate that the PIBA should not be removed. We provide a recommendation in the Identified Issues and Recommendations Table to address this concern. We have determined that this change adds clarity to an already existing step and can be implemented without additional HF validation testing to be submitted for review.
3.	For the Pull plunger past target dose and inspect syringe content for air bubbles – purge task, there were 23 use errors. • 6 caregivers, 7 dyads, and 2 HCPs did not purge all the air bubbles in the oral syringe(s) in one dosing scenario	We acknowledge the Applicant categorized this task as non-critical; however, based on the potential harm that may occur if this task is omitted or not performed correctly (i.e.,

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	• 1 caregiver and 3 dyads did not purge all the bubbles in the oral syringe(s) in both dosing scenarios The subjective data and Applicant's RCA indicated the above performance can be attributed to: • Participant indicated that when air bubbles occur, she leaves the air bubbles because she'd rather administer less medicine than more medicine • Would offset air bubbles by overdrawing slightly • Noticed the air bubbles but did not think the air bubbles would be detrimental to patient or to delivering an effective dose of medication • IFU labeling o Believed it was unclear how the bottle should be positioned when removing air bubbles and that it made more sense to put the bottle down to remove the air from the syringe. Of note, this participant performed the task correctly with the first syringe in the 4.8 mL dose scenario but not with the second syringe. o Insufficiently prominent guidance ▪ Stopped referencing the IFU at Step 6 ▪ Only looked at the front panel because she thought that is where important information would be located o Did not think the instructions were clear regarding how purge any air bubbles that were present after filling the oral syringe/measuring 3 mL (thought that the oral syringe could not be pulled past 3 mL and you would need to repeat the task if you pulled just past the dose and purged any air bubbles that were present) • Didn't see the air bubbles in the oral syringe(s) • Focused more on finding the marking for the correct dose than on the presence of air bubbles	ineffective therapy), we consider this task critical. The subjective feedback indicated the IFU did not provide sufficient guidance or was unclear. One participant indicated the instructions for inverting the bottle were unclear. However, we note this participant correctly oriented the bottle and purged the air bubbles when measuring 3 mL in the 1st oral syringe but did not do so when measuring 1.8 mL in the 2nd oral syringe. One participant indicated the instructions for measuring a 3 mL dose were unclear. Additionally, some participants referred to previous experience or had an incorrect mental model. IFU Step 6 instructs users to pull the oral syringe past the prescribed dose and check for air bubbles and includes a corresponding graphic. We also note IFU Step 7 instructs users to remove the air bubbles (if present) and states that air bubbles must be removed to ensure the dose is correct; Step 7 also includes a corresponding graphic that shows the bottle should be inverted. As such, although some use errors pointed to the IFU labeling, we find the labeling is optimized to the extent feasible. Our

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	Identified Issue	DMEPA's Analysis and Findings

	• Inattentiveness/distraction
	• Caregiver didn't want to over-correct the pediatric patient who was unaware of how to remove air bubbles
	• Violation of existing mental model
	  o Negative transfer:
	  ▪ Experience with other medications impacted use
	  ▪ Based on previous experience with other medications, determined using the instructions was not helpful because it contains more disclaimers than information
	  ▪ Used to measuring medication into a cup and not having to worry about the presence of air bubbles
	  ▪ Intentionally overdrew the amount of medication to account for the air bubble was present, instead of trying to purge the air bubble
	  o Believed that no air would be drawn into the syringe if she had the plunger fully depressed before placing it in the PIBA.
	  o Removed the air bubble to a point that she felt the dose was appropriate after attempting to remove the bubble a couple of times
	• Error resulting from altered system state due to a previous error (removed the PIBA)
	
	Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy.
	
	The Applicant noted that the following risk mitigation strategies:
	• IFU Step 7 includes instructions on how to purge an air bubble to draw the correct dose
		review of the oral syringe finds that there is adequate space between the 3 mL graduation mark and the end of syringe barrel to allow users to perform the air bubble removal tasks as instructed in the IFU (i.e., pull the oral syringe past the prescribed dose and check for air bubbles).
		
		Additionally, we reviewed IFUs for approved products with a similar user interface (i.e., oral product supplied with an oral syringe), and we find the tasks of pulling plunger past target dose and inspecting syringe content for air bubbles are not unique tasks for this liquid oral product. As such, based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.

<table>
<tr><th colspan="3">Table 3. Identified Issues and DMEPA's Analysis and Findings
Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA</th></tr>
<tr><th></th><th>Identified Issue</th><th>DMEPA's Analysis and Findings</th></tr>
<tr><td></td><td>• IFU Step 6 includes a bullet point stating, "Check for air bubbles and proceed to Step 7 for instructions on how to remove air bubbles" , which encourages the user to find instructions on air bubble removal more easily.

The Applicant did not propose additional mitigations in response to participant performance for this task. Additionally, the Applicant noted that adding an instruction to pull a specified volume (e.g., 0.5 mL) beyond the dose may cause confusion (as was observed during Formative study #1).</td><td></td></tr>
<tr><td>4.</td><td>For the push syringe plunger to desired dose task, there were 14 use errors and 1 use difficulty. The use errors and use difficulty primarily occurred in scenario #1, with the exception of 1 dyad who experienced a use error in both scenarios.

• Use errors – 0.4 mL dose
<table>
<tr><th>Participant</th><th>Dose measured</th><th>Type of dosing error</th></tr>
<tr><td>1 caregiver</td><td>0.3 mL</td><td>25% underdose</td></tr>
<tr><td>1 dyad
(pediatric patient performed the task)</td><td>0.6 mL</td><td>50% overdose</td></tr>
<tr><td>1 dyad
(caregiver performed the task)</td><td>0.6 mL</td><td>50% overdose</td></tr>
<tr><td>1 dyad
(pediatric patient performed the task)</td><td>0.6 mL</td><td>50% overdose</td></tr>
<tr><td>1 caregiver Note: 3.2 mL was measured in one oral syringe</td><td>3.2 mL</td><td>800% overdose</td></tr>
</table></td><td>We acknowledge the Applicant identifies clinically significant dosing errors as a dose at least 200% lower or higher than the intended dose. However, we disagree based on our discussion with the clinical review team. The clinical review team clarified that an underdose or overdose over 10% of the intended dose (e.g., 50% overdose, 25% underdose) increases the risk of subtherapeutic clinical response or toxicity. The clinical team noted that a toxic overdose would likely manifest as cytopenia which would be discovered early. The clinical team also noted that an underdose or overdose of up to 10% of the intended dose is less concerning and less likely to lead to clinical harm.

We carefully reviewed each use error and use difficulty, the subjective feedback, and the</td></tr>
</table>

Table 3. Identified Issues and DMEPA's Analysis and Findings
Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA

	Identified Issue	DMEPA's Analysis and Findings

(drew past the 3 mL graduation line)		
1 dyad (pediatric patient performed the task)	4 mL	1000% overdose

- Use errors – 4.8 mL dose

Participant	Dose measured	Type of dosing error
1 caregiver	4.7 mL	3% underdose
1 caregiver	4.7 mL	3% underdose
3 HCPs	4.9 mL	2% overdose
1 caregiver	5 mL	4% overdose
1 dyad (caregiver and pediatric patient performed the tasks together and the caregiver adjusted the volume of the 1st oral syringe [2.4 mL])	5.1 mL	6% overdose
1 dyad (pediatric patient performed the task)	5.3 mL	10% overdose

  - Several participants drew over or under the 1.8 mL or 3 mL graduation markings when targeting 1.8 mL or 3 mL. This led to several incorrect doses being 0.1 or 0.2 mL under or over the intended dose of 4.8 mL.

- Use difficulty – 0.4 mL dose

Applicant's mitigations. We note the subjective feedback indicated misreading the prescription or misinterpreting the oral syringe graduations or mental model on how to address air bubbles in general contributed to use errors with this task. We also note that some participants did not read the IFU or only partially read the IFU. Additionally, we note that the larger magnitude dosing errors occurred in the 0.4 mL dosing scenario and that per the Applicant, doses of the proposed product will typically be above 1 mL; therefore, the likelihood of an error involving overlooking the decimal point is minimized.

IFU Step 7 instructs users to remove air bubbles and adjust to the prescribed dose and includes a corresponding graphic. This IFU step also informs users that air bubbles must be removed to ensure the correct dose. See row #3 for additional discussion regarding air bubble removal. Additionally, the Prescribing Information indicates that doses less than 1 mL are only indicated in instances of dose modification in patients with a BSA of 0.9 m^2 or less.

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	Identified Issue	DMEPA's Analysis and Findings
	o 1 dyad filled two oral syringes to 0.4 mL and squirted them into the bottle cap (due to air bubbles); repeated the process successfully on the third attempt (pediatric patient performed task) The subjective data and Applicant's RCA indicated the above performance can be attributed to: • 0.4 mL dose scenario - 25% underdose (0.3 mL) o Insufficient IFU guidance regarding how much over to draw to purge the air bubble: stated that in the future he would draw to 0.6 mL to remove the air bubbles and ensure he measured the correct dose. The participant believed they had adjusted dose to 0.4 mL. • 0.4 mL dose scenario - 50% overdose (0.6 mL) o Participants were attempting to account for air bubbles o Insufficiently prominent guidance ▪ Did not read past IFU Step 6 and overlooked IFU Step 7 ▪ Referred to the information on the front of the IFU o Negative transfer ▪ Did not refer to IFU because they would not use it at home • 0.4 mL dose scenario - 800% overdose (3.2 mL) o Misread the dose on the pharmacy label and intended to decipher where the 4 mL was on the oral syringe (instead of 0.4 mL). o Was more focused on the "number 4", not the decimal point and were not paying attention. • 0.4 mL dose scenario - 1000% overdose (4 mL) o Caregiver in dyad told the pediatric patient to fill the 1st oral syringe to 3 mL and the 2nd oral syringe to 1 mL. o Misunderstood terminology on the mock pharmacy label ▪ Thought they were to measure 4 mL instead of 0.4 mL	Our review of the oral syringe finds that the graduation markings are adequately labeled, and the purple plunger provides sufficient contrast between the medication and oral syringe. We also note the Applicant indicated that oral syringe plunger force specification is acceptable for the ergonomic needs of the intended user population. Additionally, we note that there are other marketed products that are co-packaged with two or more oral syringes that are of similar shape and size as the proposed 3 mL oral syringe and also have similar labeling or dosing. Overall, based on our review of the user interface, subjective feedback, and RCA, and the Applicant's mitigations, we did not identify areas of improvement and have no recommendations at this time.

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	o Focused on the bigger dose markings (e.g., 1 mL, 2 mL, etc.) on the oral syringe and not the smaller dose increment markings. o Did not refer to the IFU o Believed they needed to use both oral syringes • 0.4 mL dose scenario – use difficulty o Physical design – oral syringe moved more than expected • 4.8 mL dose scenario – underdose and overdose errors o Violation of existing mental model ▪ Negative transfer based on experience with other products (e.g., insulin vial, Tylenol) • For example, 1 caregiver noted similarity between the proposed product and removing air from an insulin injection. The caregiver noted it was more important to get the air out of insulin [injection] than an oral medication. ▪ Believed they did not need to be precise o Syringe design ▪ Misleading design element – believed filling the entire oral syringe would result in 3 mL (i.e., filling syringe past the 3 mL graduation. However, they overdrew by 0.2 mL. ▪ Graduation markings too small for caregiver with vision problems who did not have their glasses ▪ Difficult to adjust the plunger due to being stiff o Did not refer to IFU labeling o Inattentiveness – pediatric patient did not inspect oral syringe to confirm an accurate amount or graduation line reading Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy if the dose is less than 75% of the intended dose or hepatoxicity	

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	due to overdose (ranging from minor to catastrophic depending upon the magnitude of the overdose). The Applicant noted 12 of the 14 use errors would not have clinical significance if they occurred in a real-world scenario because the doses were within the range consistent with a safe and efficacious dose. Additionally, the Applicant acknowledged that 2 use errors with the 0.4 mL dose would have resulted in significant overdose. The Applicant noted they considered mitigations, (b) (4) The Applicant also noted the following risk mitigations: • IFU Step 6 instructs users to "Fill Syringe… past your prescribed dose" and includes a corresponding graphic (i.e., Figure F) • IFU Step 7 instructs users to "Remove air bubbles and adjust to prescribed dose" and includes a corresponding graphic (i.e., Figure G) • Oral syringe is provided with 0.1 mL graduations and 3 mL is prominently marked • The plunger color (purple) of the oral syringe contrasts with white suspension • The proposed product will be dispensed from a limited number of outpatient pharmacies that regularly train patients and caregivers • The syringe plunger force is specified to meet the ergonomic needs of the intended user population • Misinterpretation of the dose by a factor of 10 using the current 3 mL oral syringe is unlikely or would occur in very rare cases • Doses in clinical practice will typically be above 1 mL as a dose below 1 mL is only required for children with a body surface area (BSA) <0.9 m^2 and who are on concomitant strong CYP inhibitors or with moderate hepatic impairment.	

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	• See the Applicant's mitigations in row #3 regarding the Pull plunger past target dose and inspect syringe content for air bubbles – purge task. The Applicant did not propose additional mitigations in response to participant performance for this task.	
5.	For the upright bottle and remove syringe task, there were 5 use errors. • 1 caregiver did not upright the bottle when removing the oral syringe during both dosing scenarios (2 use errors). Per the Applicant, a small amount of liquid spilled out of the PIBA in both instances. • 1 caregiver and 1 HCP did not upright the bottle when removing the first oral syringe during scenario #2 only. • 1 caregiver held the bottle horizontally when removing the second oral syringe during scenario #2 only. The subjective data and Applicant's RCA indicated the above performance can be attributed to: • User lapse • Did so without thinking and that it's a natural reaction to remove the oral syringe while the bottle is inverted • Inattentiveness o focused more on trying to calculate the syringe doses and get the correct amount of medication • Negative transfer o prior knowledge of pediatric oral medication administration • Participant forgetfulness • Mental model	The subjective feedback indicated forgetfulness, inattentiveness, and negative transfer contributed to the use errors. We did not identify any subjective feedback indicating labeling confusion for this task. Furthermore, we note in a 7/25/22 response to Information Request, the Applicant indicated accidental exposure due to drug product spill or leak might result in minor irritation that does not require medical intervention. IFU Step 8 instructs users to turn the bottle upright prior to removing the oral syringe and includes a corresponding graphic. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	o was not concerned about medication spilling when the bottle is inverted Based on the URRA, if this task is omitted or not performed correctly there is risk of trauma (i.e., accidental exposure) due to drug product spill or leak. The Applicant noted the following risk mitigations: IFU Step 8 instructs users to upright bottle and PIBA minimizes risk of drug spillage. The Applicant did not propose additional mitigations in response to participant performance for this task.	
6.	For the close the bottle task, there was 1 use error in which 1 HCP was unable to fully close the bottle due to pulling the cap components apart when opening the bottle during scenario #1 (i.e., pulled the outer bottle cap off from the inner child-resistant cap liner). The subjective data and Applicant's RCA indicated the above performance can be attributed to: • Was confused by the bottle cap and indicated that IFU Step 4 did not provide the information needed to successfully open the bottle • Violation of existing mental model – familiar with removing press and turn caps Based on the URRA, if this task is omitted or not performed correctly, there is risk of ineffective therapy or infection. The Applicant noted the following risk mitigations: • IFU includes instructions regarding how to open the bottle • the product requirement limits the torque needed to operate the cap • (b) (4) • the PIBA minimizes the risk of spilling the medication	The subjective feedback indicated the participant did not find adequate instructions for removing the bottle cap in IFU Step 4 . IFU Step 4 instructs users to remove the bottle cap and includes a corresponding graphic, and IFU Step 10 instructs users to recap the bottle and includes a corresponding graphic. Per the Applicant, (b) (4) However, we find the graphic in IFU Step 4 can be improved to depict how the cap should be removed. As such, we provide a recommendation in the Identified Issues and Recommendations Table to address this concern. We have determined that this change which further emphasizes an existing use step

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	The Applicant did not propose additional mitigations in response to participant performance for this task.	can be implemented without additional HF validation testing to be submitted for review.
7.	For the administer entire dose to patient task, there was 1 use difficulty and 1 close call. • 1 dyad dropped the oral syringe (pediatric patient participant performed task) • 1 HCP initially measured two oral syringes to 0.4 mL for a total of 0.8 mL (0.4 mL dose scenario); however, they caught their mistake before depressing the plunger and only administered one oral syringe. The subjective data and Applicant's RCA indicated the above performance can be attributed to: • Physical design – oral syringe is "tiny" and "easily slips [in hands]" • Sequence effect – the HCP participant indicated that she had used two syringes for the first scenario in her counterbalance and was doing the same for the current dosing scenario. • Test anxiety Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy, infection, hepatotoxicity and bruising/tissue damage (if the oral syringe is pressed forcibly against the cheek). The Applicant noted the following risk mitigations: IFU contains instructions regarding how to properly administer the medication and the 3 mL oral syringe has 0.1 mL graduations. The Applicant did not propose additional mitigations in response to participant performance for this task.	The subjective feedback indicated the physical design (i.e., size) of the oral syringe contributed to the pediatric patient participant's use difficulty for this task. We note the Applicant attributed the HCP participant's close call to sequence effect and study test anxiety; however, we identified subjective feedback that suggests the presence of two oral syringes also contributed to the close call. For example, the HCP participant stated, "Because there were two in there, I thought 'Oh I should do both'…". We also note that this participant confirmed the dose and realized she only needed to administer one of the syringes she measured. IFU Step 9 instructs users on administering the dose and includes a corresponding graphic. Additionally, the beginning of the IFU states indicates the product is supplied with "2 reusable 3 mL oral dosing syringes" and IFU Step 1 states "If the dose is more than the marking on the syringe, split the dose between syringes as prescribed". We note that there are other

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
		marketed products that are co-packaged with two or more oral syringes that are of similar shape and size as the proposed 3 mL oral syringe. Additionally, we note the Applicant indicates that the oral syringe is a Class 1, 510(k) exempt oral dosing device and available for commercial use is available off-the-shelf in the US market. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.
8.	For the knowledge assessment question regarding inspecting the product for damage *(According to the instructions, what should you do if the medicine has been tampered with?)*, there was 1 use error in which a caregiver was unable to find the information on tampering in IFU Step 1. The subjective data and Applicant's RCA indicated the above performance can be attributed to: • Insufficiently prominent guidance - expected to see a warning label and expected the information to be higher up in the IFU Based on the URRA, if this task is omitted or not performed correctly, there is risk of ineffective therapy and trauma due to accidental exposure or exposure to sharp edges/corners.	The subjective feedback indicated the participant expected to see a warning labeling on the product and expected the IFU information to be more prominent. We also note that the participant was able to quickly locate the information in the IFU when asked the question again during the RCA. The IFU statement "DO NOT use if the IMBRUVICA carton seal appears to be tampered with" appears next to caution symbol at the end of IFU Step 1. We note the Applicant implemented a post-validation revision to the carton to inform users not to use the product if

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	The Applicant implemented a post-validation revision in response to participant performance for this knowledge assessment question. Specifically, the Applicant added the statement "Do not use if the carton seal is broken or missing" to the carton labeling. The Applicant did not validation the revision.	the carton seal is broken or missing. We find this post-validation revision acceptable because it reiterates important information already included in the IFU labeling and is located on the user interface where the user needs to draw their attention to. We also find it can be implemented without submission of additional HF validation data. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.
9.	For the knowledge assessment question regarding checking the expiration date *(HCPs and Caregivers: According to the instructions, what should you do if the medication is expired?/Dyad: According to the instructions, where can you find the expiration date?)*, there were 11 use errors. • 8 dyads and 1 HCP failed to give the correct answer of the expiration date being found on the carton and bottle and provided the information on the discard date instead (Note: pediatric patients primarily provided the response for the dyads) • 2 caregivers were unable to locate the information about the expiration date in IFU Step 1 and said expired medication should be disposed of. The subjective data and Applicant's RCA indicated the above performance can be attributed to:	We note the Applicant reported the results of the two knowledge assessment questions collectively to assess the manufacturer's expiration date. However, we also note the questions differ because the HCP/caregiver question asks participants what action should be taken if the medication is expired; whereas the dyad question asks participants where the expiration date is located. The subjective feedback indicated participants expected to see expiration information in the same location as disposal information or referred to the discard date information.

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	• Insufficiently prominent guidance - thought the expiration information would appear with the disposal information or referred to IFU Step 2 (including the figure) which includes discard date information Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy or infection. The Applicant implemented post-validation mitigations in response to participant performance for this knowledge assessment question. Specifically, the Applicant proposes to (b) (4) in the discard date and disposal instructions section of the IFU. The Applicant determined the post-validation revisions do not require validation because they are duplication of an existing warning and are intended to improve noticeability and comprehension but are not expected to increase residual risk.	However, we acknowledge that the proposed product should not be used if the discard date exceeds the expiration date. As such, we find that referring to the discard date as the expiration date is an acceptable response to the knowledge assessment question for this task. IFU Step 1 instructs users to check the expiration date and not to use the product if the expiration date has passed. We note the Applicant implemented post-validation revisions to the IFU to (b) (4) in the discard date section and disposal instructions section of the IFU. However, we find it is unclear if the post-validation revisions may introduce confusion if end users do not understand when to refer to the expiration date versus the discard date. In addition, we find the discard date is more crucial in determining if the drug product should be administered or not. As such, we provide a recommendation below in the Identified Issues and Recommendations Table for the Applicant to address this concern. Because this revision is reverting to the original language used in the IFU in the HF study, we have determined this change can be implemented without additional HF validation testing to be submitted for review.

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
10.	For the knowledge assessment question regarding cleaning and storage *(According to the instructions, what temperature should the medication be stored at?)*, there was 1 use error in which a caregiver correctly stated that the medication should be stored at or below 77°F, but did not include "Do Not Freeze" as a part of her answer. The subjective data and Applicant's RCA indicated the above performance can be attributed to: • Order of information - considered the information about not freezing the medication to be dismissible because they believed that it was evident that room temperature or refrigerated (which appeared first) excluded freezing. Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy or infection. The Applicant noted that the current risk mitigation strategies in the IFU were effective, and no design flaws were uncovered. The Applicant did not propose additional mitigations in response to participant performance for this knowledge assessment question.	The subjective feedback indicated study artifact may have contributed to the use error due to the phrasing of this knowledge assessment question. For example, the participant stated it "did not register" to include "do not freeze" as part of her response. The (b) (4) page of the IFU includes the "How to store Imbruvica oral suspension" section which includes the statement, "DO NOT freeze" in addition to other storage information. We note similar storage information appears on the carton labeling and container label. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.
11.	For the knowledge assessment question regarding cleaning and storage *(According to the instructions, how should the medication bottle be stored?)*, there was 1 use error in which a dyad did not locate the information and failed to state that the medication should be stored away from children. The subjective data and Applicant's RCA indicated the above performance can be attributed to:	The subjective feedback indicated the dyad was unable to locate the information in the IFU and that study artifact may have contributed to the use error due to the phrasing of the knowledge assessment question. For example the pediatric participant responded that the medication should be stored upright.

Table 3. Identified Issues and DMEPA's Analysis and Findings Legend: adult caregiver-pediatric patient dyad = dyad, healthcare professional = HCP, use-related risk analysis = URRA		
	Identified Issue	DMEPA's Analysis and Findings
	• Violation of existing mental model – believed the information was common sense and didn't think to specifically state the information Based on the URRA, if this task is omitted or not performed correctly there is risk of ineffective therapy or infection. The Applicant did not propose additional mitigations in response to participant performance for this knowledge assessment question.	The (b) (4) page of the IFU states "Store IMBRUVICA and all medications out of sight and reach of children". We note similar information appears on the carton labeling and container label. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.

4.1 ANALYSIS OF NON-CRITICAL TASK ERRORS

The HF validation study showed use errors and use difficulties with the non-critical tasks listed below. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis, and Applicant's proposed risk mitigation strategy we determined the residual risk is acceptable. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following non-critical tasks:

- Open the bottle
- Expel air from syringe
    - Based on the URRA, if the user does not expel air from the syringe prior to drawing up the dose, there is risk that an air bubble in the syringe could lead to a pressure differential and result in dosing errors. We note in a subsequent step users are instructed to remove an air bubble.
- Wipe PIBA with a tissue
- Cleaning and storage of the oral syringe (assessed via the following knowledge assessment questions)
    - According to the instructions, can you use the syringe to administer medicine if the syringe is wet? For instance after washing the syringe with water.
    - According to the instructions, how should the syringe be dried?

4.2 LABELS AND LABELING

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

Table 4. Identified Issues and Recommendations for Division of Hematologic Malignancies 1 (DHM 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The Dosage and Administration section contains an error-prone symbol (i.e., <).	Use of error-prone symbols to describe dosage information may lead to misinterpretation and medication error (e.g., mistaken as opposite of intended).[c]	We recommend replacing the "<" symbol with its intended meaning (i.e., less than).
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2 contains several instances of error-prone symbols (i.e., >, <, and ≥).	Use of error-prone symbols to describe dosage information may lead to misinterpretation and medication error (e.g., mistaken as opposite of intended).[c]	We recommend replacing the ">", "<", and "≥"symbols with their intended meanings (i.e., greater than, less than, and greater than or equal to).
2.	The title of Table 1 does not specify that the body surface area ranges and corresponding doses provided in Table 1 applies to patients 1 to less than 12 years of age only.	Confusion regarding dosing might result in wrong dose errors.	We recommend revising the title of Table 1 to specify the applicable patient population. For example, consider the following title: "Recommended dosage based on body surface area (BSA) for patients 1 to less than 12 years of age using either IMBRUVICA

[c] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2021 [cited 2022 JUN 6]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 4. Identified Issues and Recommendations for Division of Hematologic Malignancies 1 (DHM 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			capsules/tablets or oral suspension".
3.	The numerical values in the dose and volume columns in Table 1 and Table 3 are not followed by units of measure.	Lack of units of measure may contribute to confusion and wrong dose errors.	We recommend revising the dose and volume columns in Table 1 and Table 3 to ensure that each numerical value is followed by the unit of measure to mitigate the risk of wrong dose errors. For example, revise "1.2" to "1.2 mL".
4.	Tables 1 and 3 contain trailing zeroes (e.g., 1.0, 4.0).	To avoid ten-fold misinterpretation, trailing zeroes should be eliminated from dose expressions.[c]	We recommend removing all instances of trailing zeroes in Tables 1 and 3.
5.	In Table 3, the 160 mg/m^2 dosage modification information and 80 mg/m^2 dosage modification information can be improved to further differentiate the dosage modification schemes.	We are concerned that users may overlook the headers, "Recommended dose to achieve…", and identify the wrong dose based on the patient's body surface area (BSA).	We recommend increasing the thickness of the border that separates the 160 mg/m^2 dosage information and 80 mg/m^2 dosage information in Table 3.

Table 5. Identified Issues and Recommendations for Pharmacyclics LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Instructions for Use			
1.	The IFU can be improved to reiterate that the press in bottle adapter	Removal of the PIBA might result in delay in therapy, drug product spill or leak, or patient receiving more or less	Include the statement "Do not remove the adapter" in IFU Step 4. To align with other important

Table 5. Identified Issues and Recommendations for Pharmacyclics LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(PIBA) should not be removed.	product than intended, according to your use-related risk analysis (URRA).	statements, increase prominence by notating with a red triangle.
2.	Step 4 can be improved to provide additional information on how to remove the cap. For example, the graphic in IFU Step 4 (i.e., Figure D) does not depict the actions needed to remove the cap from the bottle (i.e., press down and twist the cap). Additionally, Step 4 does not indicate the direction users should twist the cap (e.g., clockwise vs. counterclockwise).	In the human factors (HF) validation study, 1 participant incorrectly pulled the cap components apart when opening the bottle and indicated that IFU Step 4 did not provide the information needed to remove the cap. Difficulty removing the cap might result in delay in therapy according to your URRA.	Revise Figure D in IFU Step 4 to depict the press and turn actions needed to remove the cap. Additionally, revise the statement, "Press down and twist the cap to remove it from the bottle…" to include the direction in which users must twist the cap for removal.
3.	Your IFU can be improved to minimize confusion regarding when to dispose of the product after it has been dispensed to the end user. We acknowledge that you implemented the following post-validation revisions to your IFU to address incorrect responses provided to knowledge-based assessment question related to the expiration date and discard date:	We note the revisions were not validated in an HF study. Without HF validation study data to support these changes, we are concerned that confusion between the expiration date and discard date might result in deteriorated drug errors if end users dispose of the product on the manufacturer's expiration date instead of 60 days after first opening.	Remove the (b) (4) section. Specifically, delete the following statement from both sections: - (b) (4)

Table 5. Identified Issues and Recommendations for Pharmacyclics LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	- Addition of the (b) (4) section of the IFU.		
Carton Labeling			
1.	The location of the 2D data matrix barcode product identifier can be improved.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.[d] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The DSCSA guidance recommends that the human-readable portion	Relocate the 2-D matrix barcode to appear in close proximity to the human-readable portion of the product identifier on the carton labeling.

[d] The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 5. Identified Issues and Recommendations for Pharmacyclics LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		be located near the 2D data matrix barcode.	
Container Label and Carton labeling			
1.	The expiration date format is not defined.	Lack of clarity regarding the expiration date might contribute to confusion and deteriorated drug medication errors.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

5 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation study identified use errors with critical tasks; however, based on our review and based on input from the clinical review team, we find the residual risks are acceptable or can be further mitigated via additional labels and labeling revisions for these use errors. Thus, in this specific instance, we find the simulated use HF validation study results are acceptable provided our recommendations are implemented.

Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations that we advise are implemented during this review cycle of NDA 217003. These changes can be implemented without submitting additional HF validation testing for Agency review. 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.

5.1 RECOMMENDATIONS FOR PHARMACYCLICS LLC

Our review of the results of your human factors (HF) validation study to support your proposed ibrutinib 70 mg/mL oral suspension product identified areas of vulnerability in your labels and labeling that may lead to medication errors. We provide recommendations in Table 5, and we recommend that you implement these recommendations and submit the revised labels and labeling. We have determined that in this instance, you may implement these revisions without submitting additional HF validation data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Imbruvica that Pharmacyclics LLC submitted on February 24, 2022.

Table 6. Relevant Product Information for Imbruvica	
Initial Approval Date	- NDA 217003 is not approved - NDA 205552 Imbruvica capsules was approved on 11/13/2013 - NDA 210563 Imbruvica tablets was approved on 2/16/2018
Active Ingredient	ibrutinib
Indication	*Current* - the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. - the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). - the treatment of adult patients with CLL/SLL with 17p deletion - the treatment of adult patients with Waldenström's macroglobulinemia (WM). - treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. - the treatment of chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy. *Proposed revision to cGVHD indication* - the treatment of adult and pediatric patients aged 1 year and older with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.
Route of Administration	Oral
Dosage Form	- Proposed: oral suspension - Current: capsules, tablets
Strength	- Proposed: 70 mg/mL - Current: 70 mg and 140 mg capsules; 140 mg, 280 mg, 420 mg, and 560 mg tablets
Dose and Frequency	<u>Chronic Graft versus Host Disease</u> The recommended dosage of IMBRUVICA for patients aged 12 years and older with cGVHD is 420 mg orally once daily, and for patients 1 to < 12 years of age with cGVHD is 240 mg/m^2 orally once daily (up to a dose of 420 mg), until cGVHD progression, recurrence of an underlying

malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, IMBRUVICA should be discontinued considering the medical assessment of the individual patient. Recommended dosage based on body surface area (BSA) using either IMBRUVICA capsules/tablets or oral suspension:

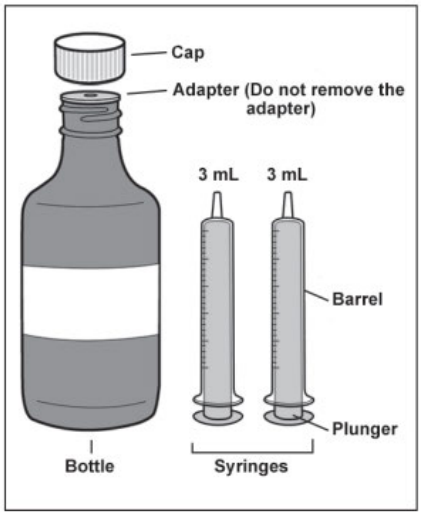
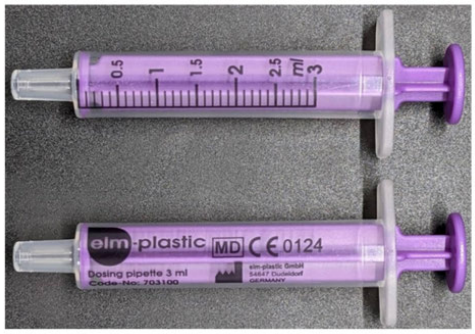
	Recommended dose to achieve 240 mg/m^2	
BSA (m^2) Range	Dose (mg) of IMBRUVICA Capsules/Tablets to Administer	Volume (mL) of IMBRUVICA Oral Suspension (70 mg/mL) to Administer
> 0.3 - 0.4	-	1.2
> 0.4 - 0.5	-	1.5
> 0.5 - 0.6	-	1.9
> 0.6 - 0.7	(b) (4)	2.2
> 0.7 - 0.8	210	2.6
> 0.8 - 0.9	210	2.9
> 0.9 - 1.0	210	3.3
> 1.0 - 1.1	280	3.6
> 1.1 - 1.2	280	4.0
> 1.2 - 1.3	280	4.3
> 1.3 - 1.4	350	4.6
> 1.4 - 1.5	350	5.0
> 1.5 - 1.6	350	5.3
> 1.6	420	6.0

Recommended dose modifications based on BSA using either IMBRUVICA capsules/tablets or oral suspension:

	Recommended dose to achieve 160 mg/m^2		Recommended dose to achieve 80 mg/m^2	
BSA (m^2) Range	Dose (mg) of IMBRUVICA Capsules/Tablets to Administer	Volume (mL) of IMBRUVICA Oral Suspension (70 mg/mL) to Administer	Dose (mg) of IMBRUVICA Capsules/Tablets to Administer	Volume (mL) of IMBRUVICA Oral Suspension (70 mg/mL) to Administer
> 0.3 - 0.4	-	0.8	-	0.4
> 0.4 - 0.5	-	1.0	-	0.5
> 0.5 - 0.6	-	1.3	-	0.6
> 0.6 - 0.7	-	1.5	-	0.7
> 0.7 - 0.8	140	1.7	70	0.9
> 0.8 - 0.9	140	1.9	70	1.0
> 0.9 - 1.0	140	2.2	70	1.1
> 1.0 - 1.1	140	2.4	70	1.2
> 1.1 - 1.2	210	2.6	-	1.3
> 1.2 - 1.3	210	2.9	-	1.4
> 1.3 - 1.4	210	3.1	-	1.5
> 1.4 - 1.5	210	3.3	140	1.7
> 1.5 - 1.6	280	3.5	140	1.8
> 1.6	280	4.0	140	2.0

How Supplied

The IMBRUVICA (ibrutinib) oral suspension is a white to off-white suspension supplied as 108 mL in a 150 mL amber glass bottle with a

	pre-inserted bottle adapter and a child resistant closure. Each mL contains 70 mg of ibrutinib. The oral suspension bottle is provided in a carton with two 3 mL reusable oral dosing syringes: NDC 57962-007-12
Storage	Store the oral suspension bottle at 2°C to 25°C (36°F to 77°F). Do not freeze. Discard any unused IMBRUVICA oral suspension remaining (b) (4) 60 days after first opening the bottle.
Container Closure	 
Intended Users	HCPs, caregivers, pediatric patients
Intended Use Environments	Home, clinical

APPENDIX B. PREVIOUS REVIEWS

B.1.1 Methods

On April 21, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, IND 147315, NDA 217003, and ibrutinib.

B.1.2 Results

Our search identified 2 previous reviews[e,f] ,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 accessible in EDR via:
\\CDSESUB1\evsprod\nda217003\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-graft-versus-host-disease\5354-other-stud-rep\hf-validation-report\human-factors-report.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On 5/9/2022, we issued an Information Request (IR) to request the Applicant submit a red-lined version of the HF validation study protocol used to conduct the HF validation study and if applicable, identify and provide justification for previous Agency recommendations that were not implemented. On 5/12/2022, the Applicant did provide an acceptable response on that can be accessed in EDR via:
    - \\CDSESUB1\evsprod\nda217003\0003\m1\us\111-information-amendment\agency-response-2022-may-9.pdf

[e] Getahun, S. HF Validation Study Protocol Review for ibrutinib (IND 147315). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 18. RCM No.: 2021-408.

[f] Whaley, E. Review of Response to HF Advice for ibrutinib (IND 147315). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 OCT 07. RCM No.: 2021-408-1.

- On 6/28/2022, the Agency issued an IR to request the Applicant describe the root causes of bubble formation of the suspension when in the oral syringe, the steps implemented to minimize bubble formation, and how the labeling supports the findings. On 7/7/2022, the Applicant did provide an acceptable response on that can be accessed in EDR via:
    - \\CDSESUB1\evsprod\nda217003\0011\m1\us\111-information-amendment\us-agency-responses-cmc.pdf

- On 7/22/2022, we issued an IR to request the Applicant describe the clinical impact of a drug product spill or leak with Imbruvica oral suspension. On 7/25/2022, the Applicant did provide an acceptable response on that can be accessed in EDR via:
    - \\CDSESUB1\evsprod\nda217003\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\chronic-graft-versus-host-disease-cgvhd\5354-other-stud-rep\human-factors-response\agency-response-qa-2022-jul-22.pdf

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,[g] along with postmarket medication error experience with similar products, we reviewed the following Imbruvica labels and labeling submitted by Pharmacyclics LLC.

- Container label(s) received on 2/24/2022
- Carton labeling received on 2/24/2022
- Instructions for Use received on 2/24/2022, available from \\CDSESUB1\evsprod\nda217003\0001\m1\us\114-labeling\draft\labeling\pifu-ibrutinib-patient.pdf
- Prescribing Information (Image not shown) received on 5/24/2022, available from \\CDSESUB1\evsprod\nda217003\0005\m1\us\114-labeling\draft\labeling\uspi-ibrutinib-redline.pdf

F.2 Label and Labeling Images

Container label

(b) (4)

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

1 Page(s) 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
08/08/2022 10:17:25 AM

LOLITA G WHITE on behalf of COLLEEN L LITTLE
08/08/2022 02:51:12 PM

LOLITA G WHITE
08/08/2022 02:51:27 PM

DANIELLE M HARRIS
08/09/2022 10:19:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 7/14/22 **Date consulted:** 5/31/22

From: Katherine Kratz, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
DPMH

Lynne P. Yao, MD, OND, Division Director
DPMH

To: Office of Oncologic Diseases/Division of Hematologic Malignancies 1 (DHM1)

Drug: Imbruvica® (ibrutinib) 70 mg/mL oral suspension

NDA: 217003

Applicant: Pharmacyclics LLC and Janssen Research & Development, LLC

Subject: Pregnancy and Lactation Labeling

Proposed Indication:

- Treatment of adult and pediatric patients ages 1 year and older with: Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Materials Reviewed:

- DPMH consult request dated May 31, 2022, DARRTS Reference ID 4991544
- Applicant's background package and proposed labeling for NDA 217003
- United States Prescribing Information (USPI) for Imbruvica® capsules (NDA 205552)
- United States Prescribing Information (USPI) for Imbruvica® tablets (NDA 210563)

- DPMH review of Imcivree (setmelanotide) injection (contains benzyl alcohol), NDA 213793, September 30, 2020, Jacqueline Yancy, PhD, DARRTS Reference ID 4678725
- DPMH review of Ferrlecit (ferric gluconate complex in sucrose injection) for intravenous use (contains benzyl alcohol), NDA 020955/S-019, October 19, 2020, Jeannie Limpert, M.D., DARRTS Reference ID 4686589

Consult Question:
"Since the oral suspension contains benzyl alcohol, can DPMH review the language in the USPI to ensure it is in compliance?"

INTRODUCTION AND BACKGROUND
On February 24, 2022, the applicant (Pharmacyclics LLC and Janssen Research & Development, LLC) submitted a 505(b)(1) New Drug Application (NDA) for Imbruvica® (ibrutinib) in a multi-dose, oral suspension formulation at 70 mg/mL to treat cGVHD in patients unable to swallow solid dosage forms. The oral suspension contains benzyl alcohol (b) (4) mg/mL as a (b) (4) There are currently no approved therapies for children < 12 years of age with cGVHD in the relapsed/refractory setting.

This submission focuses on the efficacy and safety of ibrutinib in the pediatric cGVHD population (≥ 1 to < 22 years of age). The proposed dosage and administration of the oral suspension is 420 mg orally daily (6 mL of a 70 mg/mL solution) for children ≥ 12 years old and 240 mg/m^2 orally up to a dose of 420 mg daily orally daily in children 1 to < 12 years old. Pediatric patients who receive ibrutinib oral suspension 420 mg orally daily would ingest (b) (4) mg of benzyl alcohol daily. Although the submission focuses on a pediatric indication and dosing, it is possible that adults who cannot swallow the approved formulations of ibrutinib (tablet and capsule) would elect to use the oral suspension. The maximum dose of ibrutinib that an adult may receive is 560 mg daily for treatment of mantle cell and marginal zone lymphomas. The adult who takes ibrutinib oral suspension 560 mg daily would ingest (b) (4) mg of benzyl alcohol daily.

DHM1 consulted the DPMH Maternal Health Team on May 31, 2022, to review the language related to benzyl alcohol in the Pregnancy and Lactation subsections of the USPI and to attend labeling meetings.

Relevant Regulatory History

- Imbruvica® was approved by the FDA under NDA 205552 (capsule dosage form) for one or more of the following indications in adult patients (the year of approval appears in parentheses next to the indication):
    - mantle cell lymphoma (MCL) in those who have received at least 1 prior therapy (2013);
    - chronic lymphocytic leukemia (CLL, 2014)/small lymphocytic lymphoma (SLL, 2016);
    - CLL/SLL with 17p deletion (del 17p, 2016), Waldenström macroglobulinemia (WM, 2015);
    - marginal zone lymphoma (MZL) in those who require systemic therapy and have received at least 1 prior anti CD20-based therapy (2017); and

    - adult cGVHD after failure of 1 or more lines of systemic therapy (2017)
- 2018: Approval of NDA 210536 for Imbruvica® tablet
- 2021: Approval in Japan for the treatment of adult and adolescent patients ≥ 12 years of age with cGVHD after hematopoietic stem cell transplantation after failure of steroid treatment

Drug Characteristics[1]

Drug class	Bruton's tyrosine kinase (BTK) inhibitor
Mechanism of action	Bonds to cysteine residue in the BTK active site
Molecular weight	440.50
Half-life	4-6 hours
% protein bound	97.3% *in vitro*
Bioavailability	2.9%

Current State of the Labeling[1]

- The labeling for Imbruvica® capsules (NDA 205552) and Imbruvica® tablets (NDA 210536) is in the Physician Labeling Rule (PLR) format, and in the Pregnancy and Lactation Labeling Rule (PLLR) format.
- There is no boxed warning for embryofetal toxicity; however, the following appears under WARNINGS AND PRECAUTIONS:
    - "Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman... Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. (b) (4)
- There is no contraindication for pregnancy or lactation.
- Serious adverse reactions
    - Hemorrhage
    - Infections
    - Cytopenias
    - Cardiac arrythmias, cardiac failure, sudden death
    - Hypertension
    - Second primary malignancies
    - Tumor lysis syndrome
    - Embryo-fetal toxicity as detailed above
- Subsection 8.1 Pregnancy
    - Human data are not present in labeling.
    - Animal data are present in labeling.
        - *"Risk Summary*
          IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical

[1] Imbruvica®, NDA 210563, USPI, Drugs@FDA, accessed 6/3/2022.

doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Data)*. Advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

- Data

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss.

The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively."

- Subsection 8.2 Lactation

"*Risk Summary*

There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose."

- Section 8.3 Females and Males of Reproductive Potential
  - Pregnancy testing is recommended prior to initiating Imbruvica therapy.

    "Verify the pregnancy status in females of reproductive potential prior to initiating IMBRUVICA."
  - Avoidance of pregnancy and contraception are recommended during treatment and for up to 1 month after stopping treatment.

"*Females*
Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose.

Males
Advise men with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose."

- Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  - Carcinogenesis: "'Ibrutinib was not carcinogenic in a 6-month rasH2 mouse study at oral doses up to 2000 mg/kg/day resulting in exposures approximately 23 (males) to 37 (females) times higher than the exposure in humans at a dose of 560 mg daily."
  - Mutagenesis: Animal data are present in labeling.
    "Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in mice at doses up to 2000 mg/kg."
  - Impairment of Fertility: Animal data are present in labeling.
    "Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg)."
- There are no specified drug-drug interactions with hormonal contraceptives.

REVIEW

Ibrutinib

Applicant's Review:

PREGNANCY, LACTATION, and FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

With this NDA submission, the applicant did not provide any additional nonclinical data, a review of their pharmacovigilance database, or a literature search related to ibrutinib and pregnancy, lactation, or reproductive outcomes. The applicant proposes to use the same language in subsections 8.1, Pregnancy, 8.2, Lactation, and 8.3, Females and Males of Reproductive Potential for the proposed product as was used in the approved USPI for Imbruvica® capsules (NDA 205552) and Imbruvica® tablets (NDA 210563) and that was outlined in the previous section of this document.

DPMH Review:

PREGNANCY, LACTATION, and FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

DPMH searched reference sites, including Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*,[2] Micromedex,[3] ReproTox,[4] TERIS,[5] *Hale's Medications and Mothers' Milk*,[6] and the Drugs and Lactation Database (LactMed),[7] for information related to ibrutinib in pregnancy, lactation, and reproduction. Information was found in Briggs, Micromedex, ReproTox, and TERIS as noted below:

- Briggs (Briggs cites the Product information. Imbruvica. Pharmacyclics, 2019 for information below):
  - Pregnancy: There are no reports on the use of ibrutinib in human pregnancy. "The animal data suggest moderate risk, but the absence of human pregnancy experience prevents a better assessment of the embryo-fetal risk." Animal reproduction studies conducted in rats and rabbits at exposures 14-20 times the patient exposure demonstrated visceral (heart and major vessels) malformations and increased post-implantation loss in rats. At doses that were about 6 times the exposure in patients, decreased fetal weights were seen. In pregnant rabbits, skeletal variations (fused sternebrae) and pregnancy loss were seen with doses approximately 2-3 times higher than in patients.
  - Placental transfer: "It is not known if ibrutinib crosses the placenta. The molecular weight and the elimination half-life suggest that ibrutinib will cross; however, the high plasma protein binding may limit the embryo-fetal exposure."
  - Breastfeeding: "There are no reports describing the use of ibrutinib during human lactation. The molecular weight and the elimination half-life suggest that excretion into milk will occur; however, the high plasma protein binding may limit exposure."

- Micromedex:
  - "Pregnancy rating: Fetal risk cannot be ruled out.
  - Crosses Placenta: Unknown.
  - Lactation Rating: Infant risk cannot be ruled out."

- ReproTox:
  - "Ibrutinib interfered with embryofetal development in rats and rabbits at maternally toxic dose levels. We did not locate human data."

- TERIS:
  - "Although unknown, the risk associated with maternal ibrutinib treatment during early pregnancy may be substantial because ibrutinib inhibits tyrosine kinases, which play an important role in embryogenesis. Major congenital abnormalities:

[2] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.
[3] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 6/8/2022.
[4] ReproTox Website: www.Reprotox.org. REPROTOX was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 6/8/2022.
[5] TERIS database, Truven Health Analytics, Micromedex Solutions.
[6] Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www halesmeds.com
[7] Drugs and Lactation Database (LactMed).

No epidemiological studies of congenital anomalies among infants born to women who were treated with ibrutinib during pregnancy have been reported."

DPMH also searched PubMed and Embase using the following search terms:

1) "ibrutinib" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss"
2) "ibrutinib" AND "breastfeeding" or "lactation"
3) "ibrutinib" AND "fertility," "infertility," "contraception," and "oral contraceptives"

The only clinical research study that was found in PubMed was by de Jong J, et al.[8] and entitled *Ibrutinib does not have clinically relevant interactions with oral contraceptives or substrates of CYP3A.* This phase I study was conducted in Poland and Spain and evaluated the effect of ibrutinib on the pharmacokinetics of an oral contraceptive (OC) containing 30 µg of ethinyl estradiol (EE) and 150 µg levonorgestrel (LN). Twenty-two female subjects with B-cell malignancies were enrolled and received a single dose of OC on study day 1 to assess the systemic baseline level of the OC. On study day 8, subjects started ibrutinib 560 mg daily for at least 2 weeks. The steady state of ibrutinib was reached on study day 22, and subjects received a single dose of OC on study day 22 to evaluate the systemic level of the OC during daily dosing of ibrutinib. Results demonstrated that the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) for EE + ibrutinib was 33% higher than EE alone. No changes in the C_{max} and AUC were noted for LN. The study concluded that coadministration of ibrutinib and an OC did not lead to a decreased exposure to EE or LN, suggesting that OCs should remain effective when used during ibrutinib therapy.

The literature search conducted in Embase did not yield any additional clinical studies.

Reviewer comment: The only clinical study found in the literature search suggests that oral contraceptives are effective when taken concomitantly with ibrutinib; therefore, this reviewer does not recommend a change to the current language in subsection 8.3, Females and Males of Reproductive Potential, where contraception is recommended while taking ibrutinib and for 1 month following treatment. The reference site and literature searches did not yield new data related to the effects of ibrutinib on pregnancy and lactation outcomes. This reviewer does not recommend any changes to the current language pertaining to ibrutinib in subsections 8.1, Pregnancy, and 8.2, Lactation, in the USPI for Imbruvica®.

Oral benzyl alcohol
PREGNANCY, LACTATION, and FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

In the human body, benzyl alcohol is oxidized to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. Very high concentrations of benzyl alcohol can result in toxic effects including respiratory failure, vasodilation, hypotension, convulsions, and paralysis.

[8] de Jong J, Mitselos A, Jurczak W, Cordoba R, Panizo C, Wrobel T, Dlugosz-Danecka M, Jiao J, Sukbuntherng J, Ouellet D, Hellemans P. Ibrutinib does not have clinically relevant interactions with oral contraceptives or substrates of CYP3A and CYP2B6. Pharmacol Res Perspect. 2020 Oct;8(5):e00649. doi: 10.1002/prp2.649. PMID: 32945596; PMCID: PMC7506988

Intravascular benzyl alcohol has been shown to cause severe metabolic acidosis, encephalopathy, respiratory distress, gasping respirations, and death ("the gasping syndrome") in low birth weight, premature infants at doses of 99-234 mg/kg/day.[9] In 1982, the Centers for Disease Control and Prevention (CDC) reported sixteen neonatal deaths thought to be caused by the benzyl alcohol preservative in intravascular solutions. Review of the medical records of the affected infants estimated that the daily intake of benzyl alcohol ranged from 99-405 mg/kg/day.[10] Based on these reports, the FDA recommended that intravascular flush solutions containing benzyl alcohol not be used in newborn infants.

The amount of intravascular or oral benzyl alcohol that can lead to toxicity in a developing fetus exposed during pregnancy is unknown. Whether benzyl alcohol in breastmilk leads to toxicity in a newborn is unknown.

Applicant's Review:
With this NDA submission, the applicant did not provide nonclinical data, a review of a pharmacovigilance database, or a literature search related to oral benzyl alcohol and pregnancy, lactation, or reproductive outcomes. The applicant reviewed the FDA Inactive Ingredient Database (IID) and the applicant's background package states that the IID has a "MDE [maximum daily exposure] of 100 mg for benzyl alcohol used in oral suspensions and the European Scientific Committee for Food (SCF) included benzyl alcohol in the group of ADI [acceptable daily intake] of 0 to 5 mg/kg body weight for benzoic acid and benzoates which was reevaluated to be 4 mg/kg. Based on the highest dose of Ibrutinib Oral Suspension of 6.0 mL (420 mg of ibrutinib) per day, the maximum amount of benzyl alcohol delivered to a pediatric patient is (b) (4) mg or (b) (4) mg/kg/day, which is well below the MDE limit and ADI."[11]

DPMH Review:
DPMH performed a search in in the FDA IID and confirmed that the MDE for benzyl alcohol in oral suspension is 100 mg.

DPMH searched reference sites, including Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*,[2] Micromedex,[3] ReproTox,[4] Hale's *Medications and Mothers' Milk*,[5] the Drugs and Lactation Database (LactMed),[6] for data related to benzyl alcohol in pregnancy, lactation, and reproduction. Information was found in Briggs, Micromedex, and ReproTox as follows:

- Briggs: No data on oral formulations of benzyl alcohol; information below pertains to topical and injectable benzyl alcohol:
    - "Pregnancy recommendation: Limited Human Data—Probably Compatible (Topical) Contraindicated (Injectable)
    - Breastfeeding recommendation: No Human Data—Probably Compatible (Topical) Contraindicated (Injectable)"

[9] Gershanik, J et al. The Gasping Syndrome and Benzyl Alcohol Poisoning. NEJM. 1982; 307:1384-1388.
[10] Centers for Disease Control (CDC). Neonatal deaths associated with use of benzyl alcohol--United States. MMWR Morb Mortal Wkly Rep. 1982 Jun 11;31(22):290-1. PMID: 6810084.
[11] NDA 217003, Sequence Number 0001, Applicant 2.3.P Quality Overall Summary – Drug Product, p. 20.

- Micromedex:
    - "Teratogenicity/Effects in Pregnancy: Fetal risk cannot be ruled out. Crosses placenta: unknown.
    - Breastfeeding: Infant risk cannot be ruled out."

- ReproTox:
    - "Benzyl alcohol has been used as a preservative in bacteriostatic medical solutions. Its use in neonates (particularly premature babies) was associated with neurologic abnormalities and death.[12, 13, 14] It is no longer used under such circumstances. In pregnant mice dosed by gavage with 750 mg/kg/day on gestation days 7-14, there were lower mean litter and pup weights associated with maternal toxicity[15,16] We have not located reports on possible reproductive or lactation effects of benzyl alcohol."

Finally, DPMH searched PubMed and Embase for articles related to benzyl alcohol in pregnancy, lactation, and reproduction. The following search terms were used:

1) "benzyl alcohol" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss"
2) "benzyl alcohol" AND "breastfeeding" or "lactation"
3) "benzyl alcohol" AND "fertility," "infertility," "contraception," and "oral contraceptives"

Using the search terms above, no clinical research articles were found in PubMed and Embase.

The reader is referred to the Pharmacology/Toxicology review by Shwu-Luan Lee, Ph.D., and the Clinical Pharmacology review by Ankit Shah, Ph.D. for additional information related benzyl alcohol in the proposed oral product.

Reviewer comment:
The current USPI for ibrutinib states that the drug can cause fetal harm and women are advised to avoid pregnancy while taking ibrutinib and for 1 month after stopping treatment. Despite this warning, it is possible for an adult female of reproductive potential to take the proposed oral suspension up to a maximum dose of 560 mg daily and become pregnant and/or breastfeed while taking it. The 560 mg dose of the oral suspension will contain (b) (4) *mg of benzyl alcohol. This* (b) (4)

[12] Hiller JL et al: Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. Pediatrics 77:500-6, 1986.
[13] Menon PA et al: Benzyl alcohol toxicity in a neonatal intensive care unit. Incidence, symptomatology, and mortality. Am J Perinatol 1:288-92, 1984.
[14] Anderson CW et al: Benzyl alcohol poisoning in a premature newborn infant. Am J Obstet Gynecol 148:344-6, 1984.
[15] Hazelden KP. 1983. Screening of priority chemicals for potential reproductive hazard. NIOSH, Public Health Service, U.S. Department of Health, Education and Welfare, Cincinnati, OH. Contract No. 20-81-6005. 135 p. As cited in U.S. EPA. 1989. Health and environmental effects document for benzyl alcohol. EPA/600/8-90/033. National Technical Reports Library, accession number PB91213694. Available at https://ntrl.ntis.gov
[16] Hardin BD, Schuler RL, Burg JR, et al. 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. Terat Carcin Mut 7: 29-48. As cited in U.S. EPA. 1989. Health and environmental effects document for benzyl alcohol. EPA/600/8-90/033. National Technical Reports Library, accession number PB91213694. Available at https://ntrl ntis.gov

mg daily dose in an oral suspension falls below the maximum daily exposure (MDE) published in the FDA Inactive Ingredient Database (IID) for oral suspensions. Other than the information from the IID, DPMH did not identify any clinical data to inform the labeling related to the effects of oral benzyl alcohol on pregnancy, lactation, or reproductive outcomes. Given that the proposed oral suspension contains a small amount of benzyl alcohol, which is lower than the MDE in the IID and will be rapidly metabolized, and that there are no clinical reports of adverse events related to benzyl alcohol as a (b) (4) *in oral suspensions, this reviewer does not recommend including language about benzyl alcohol in subsections 8.1, Pregnancy, 8.2, Lactation, and 8.3, Females and Males of Reproductive Potential, in the labeling for ibrutinib.*

DISCUSSION AND CONCLUSIONS

There are no clinical studies evaluating the effects of oral benzyl alcohol on pregnancy, lactation, and reproductive outcomes. Given that the amount of benzyl alcohol in the proposed oral solution is small and that it will be rapidly metabolized, it is unlikely that benzyl alcohol will cause harm to the fetus in pregnancy, the child who is breastfeeding, or the female or male of reproductive potential.

Pregnancy

DPMH does not recommend any changes to Subsection 8.1, Pregnancy. Subsection 8.1 will include the "Risk Summary" and "Animal Data" as they appears currently in the approved USPI for Imbruvica® tablets and capsules. No information related to the oral suspension containing benzyl alcohol will be included in subsection 8.1 as benzyl alcohol exposure in the fetus is unlikely due to the small amount in each dose and the rapid metabolism of benzyl alcohol. Furthermore, the main message of subsection 8.1 needs to be that ibrutinib itself can cause fetal harm when used in pregnant patients, and DPMH is concerned that adding information about benzyl alcohol will detract from the main message.

Lactation

DPMH does not recommend any changes to Subsection 8.2, Lactation. Subsection 8.2 will include the "Risk Summary" as it appears currently in the approved USPI for Imbruvica® tablets and capsules. No information related to the oral suspension containing benzyl alcohol will be included in subsection 8.2 as benzyl alcohol exposure in the breastfed child is unlikely due to rapid metabolism.

Females and Males of Reproductive Potential

DPMH does not recommend any changes to Subsection 8.3, Females and Males of Reproductive Potential. Subsection 8.3 will remain unchanged from the approved USPI for Imbruvica® tablets and capsules as there are no new data related to Imbruvica® since approval, the amount of benzyl alcohol in the oral suspension is small, and the metabolism of benzyl alcohol is rapid and unlikely to have effects on males or females of reproductive potential.

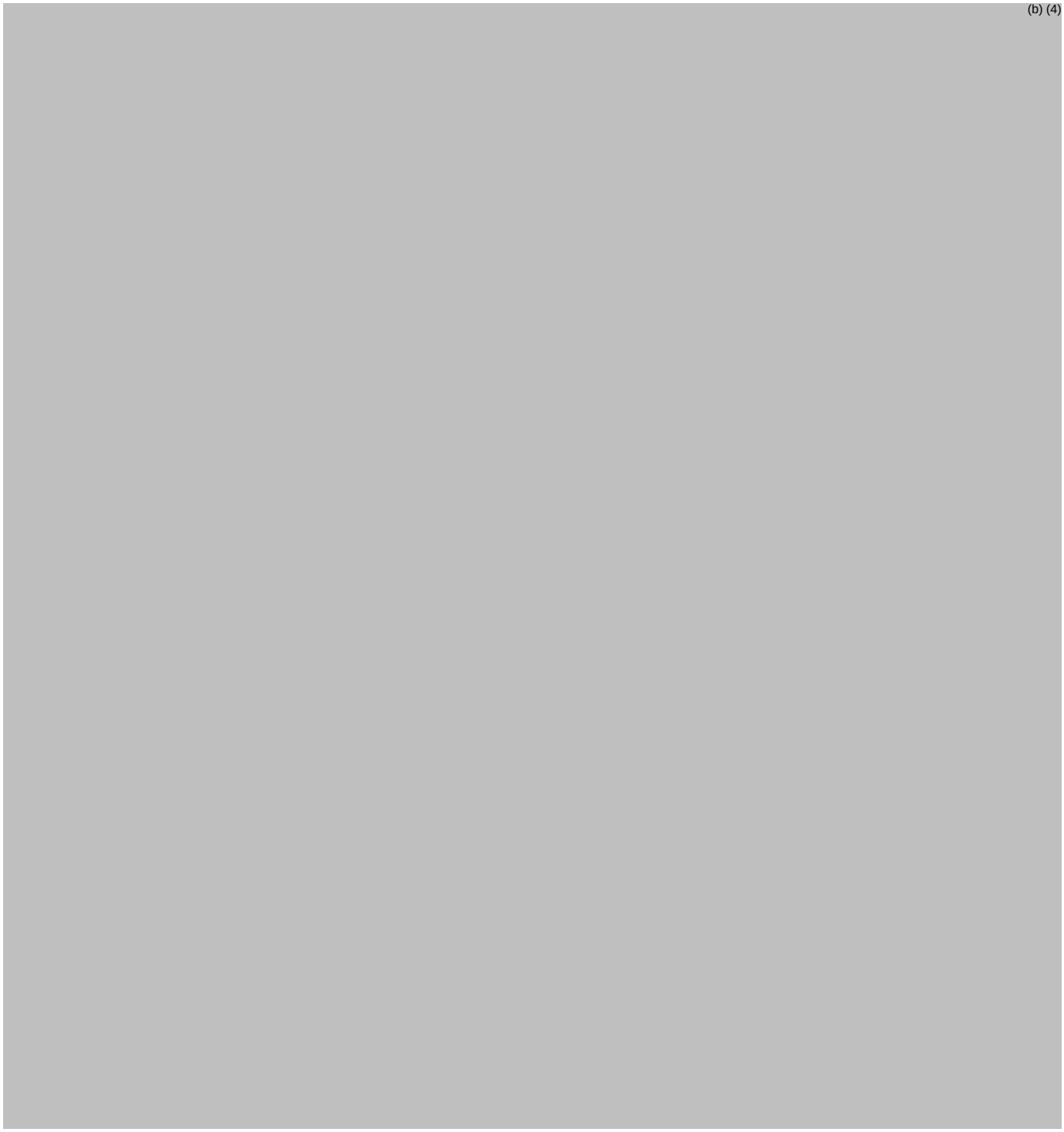
There are no published safety concerns related to oral benzyl alcohol use during pregnancy, lactation, or reproduction and the amount used in this suspension falls within the recommended amounts in the IID. Therefore, DPMH does not recommend any post-marketing pregnancy safety studies or a clinical lactation study at this time for this new oral suspension product of ibrutinib.

LABELING RECOMMENDATIONS

DPMH does not recommend any labeling changes to subsections 8.1, 8.2, 8.3, and 17 of labeling. DPMH discussed our labeling recommendations with the Division on July 12, 2022. DPMH recommendations are below and reflect the discussions with DHM1. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)



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MIRIAM C DINATALE
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LYNNE P YAO
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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: 7/26/22

To: Rosa J. Lee-Alonzo, PharmD, RAC, Senior Regulatory Health Project Manager, Division of Hematologic Malignancies I (DHM1)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for
IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use
IMBRUVICA® (ibrutinib) oral suspension

NDA: NDA 205552/Supplement 36, 37
NDA 217003

In response to DHM1's consult request dated March 11, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for IMBRUVICA® (ibrutinib) oral suspension, a new pediatric formulation. The supplements (S-036 and S-037) pertain to a new pediatric patient population and a labeling change with clinical data.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DHM1 (Rosa J. Lee-Alonzo) on July 15, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on July 25, 2022.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DHM1 (Rosa J. Lee-Alonzo) on July 20, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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JENNIFER W CHEN
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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:	July 25, 2022
To:	Bernetta Lane, PharmD Senior Regulatory Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	IMBRUVICA (ibrutinib)
Dosage Form and Route:	capsules and tablets, for oral use
Application Type/Number:	NDA 205552/S-038 NDA 210563/S-014
Applicant:	Pharmacyclics, LLC

1 INTRODUCTION

On February 24, 2022, Pharmacyclics LLC., submitted for the Agency's review a Prior Approval Supplement-Efficacy, to their original New Drug Application (NDA 205552/S-038) for IMBRUVICA (ibrutinib) capsules, for oral use, and on April 1, 2022, submitted for the Agency's review a Prior Approval Supplement-Efficacy, to their original New Drug Application (NDA 210563/S-014) for IMBRUVICA (ibrutinib) tablets, for oral use, respectively. The purpose of the submissions is to provide pediatric data to support updates of the existing indication in Chronic versus Host Disease (cGVHD) to the following: "IMBRUVICA is a kinase inhibitor indicated for the treatment of adult and pediatric patients aged one year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy" and to providing the supporting updated labeling.

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 Hematologic Malignancies II (DHM2) on June 6, 2022 and July 25, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IMBRUVICA (ibrutinib) capsules and tablets, for oral use.

2 MATERIAL REVIEWED

- Draft IMBRUVICA (ibrutinib) PPI received on February 24, 2022, and April 1, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2022.
- Draft IMBRUVICA (ibrutinib) Prescribing Information (PI) received on February 24, 2022, and April 1, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2022.
- Approved IMBRUVICA (ibrutinib) labeling dated May 11, 2022.

3 REVIEW METHODS

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is 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 PPI is 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 PPI.

Please let us know if you have any questions.

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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:	July 25, 2022
To:	Rosa Lee-Alonzo, PharmD, RAC Senior Regulatory Project Manager **Division of Hematologic Malignancies I (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name) and	IMBRUVICA (ibrutinib)
Dosage Form and Route:	capsules and oral suspension, for oral use
Application Type/Number:	• NDA 205552/S-036 • NDA 205552/S-037 • NDA 217003
Applicant:	Pharmacyclics, LLC

1 INTRODUCTION

On February 24, 2022 Pharmacyclics, LLC, submitted for the Agency's review two Prior Approval Supplements-Efficacy, to their original New Drug Application (NDA 205552/S-036 and S-037) for IMBRUVICA (ibrutinib) capsules, for oral use. The purpose of the S-036 submission is to propose the addition of a pediatric chronic graft versus host disease indication based on pediatric study data, and the purpose of S-037 is to propose updates to the PI regarding chronic graft versus host disease in adult patients. On February 24, 2022, the Applicant also submitted for the Agency's review an original New Drug Application (NDA 217003) for IMBRUVICA (ibrutinib) oral suspension, for oral use, which provides for an additional formulation (oral suspension).

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 Hematologic Malignancies I (DHM1) on March 11, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for IMBRUVICA (ibrutinib) capsules and oral solution, for oral use.

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 IMBRUVICA (ibrutinib) PPI and IFU received on February 24, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on July 21, 2022.
- Draft IMBRUVICA (ibrutinib) Prescribing Information (PI) received on February 24, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 21, 2022.
- Approved IMBRUVICA (ibrutinib) labeling dated May 11, 2022.

3 REVIEW METHODS

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI 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 PPI 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 PPI and IFU.

Please let us know if you have any questions.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
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M E M O R A N D U M

From: Ndidi Nwokorie, MD, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic & Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Hematologic Malignancies I (DHM1)
Office of Oncologic Diseases (OOD)

Subject: Pediatric Labeling Review

Drug: ibrutinib

Proprietary Name: IMBRUVICA

Application Number: NDA 217003

Applicant: Pharmacyclics

Indications: Treatment of adult patients with

- Mantle cell lymphoma (MCL)
- Chronic lymphocytic leukemia (CLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Proposed Indications: Treatment of pediatric patients 1 year and older with

- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Dosage Form & Strength:	Capsules:	70 mg and 140 mg
	Tablets:	140 mg, 280 mg, 420 mg, and 560 mg
	Oral Suspension:	70 mg/ml

Route of Administration: Oral

Consult Request:
DHM1 consulted DPMH to review the language in the U.S. Prescribing Information (USPI) for IMBRUVICA to ensure regulatory compliance regarding the pediatric safety of the benzyl alcohol (BA) content in this product. This memorandum describes the scientific rationale for excluding language describing the potential toxicity of BA in pediatric patients under 1 year of age in IMBRUVICA labeling.

I. Background

A. Benzyl Alcohol Toxicity in the Pediatric Population

Published reports of benzyl alcohol (BA) toxicity resulting in the clinical pattern of multi-organ dysfunction coined the "gasping syndrome" were first described in the 1980's. Details of this safety signal and subsequent FDA response have been the subject of a recent DPMH review.[1] DPMH's review concluded the following:

- Reports of BA toxicity have been well-described in the literature as a fatal adverse reaction almost exclusively occurring in very low birth weight (less than 1500 g)[2], early preterm (less than 34 weeks gestational age) neonates who received BA-containing flush solutions[2,3] in neonatal intensive care unit settings. This neonatal subpopulation appears to be uniquely susceptible to fatal BA toxicity due to their hepatic and renal immaturity.

- The "gasping syndrome" is a theoretical risk in late preterm (34 to less than 37 weeks gestational age) and term neonates greater than 2,500 g.

- The risk has not been substantiated in the literature in pediatric patients outside of the neonatal setting.

DPMH has not identified any published unconfounded cases of BA toxicity outside of the neonatal period. The literature describes a single case outside of the neonatal period of a 5-year-old girl who was inadvertently given 180 mg/kg/day over 36 hours of BA while receiving continuous IV diazepam infusion for her underlying encephalitis-induced coma and status epilepticus. She developed hypotension, hypernatremia and severe metabolic acidosis and later died.[4] This case, however, was confounded by the patients underlying medical condition and concomitant continuous IV infusion of diazepam. DPMH has not identified any evidence describing BA toxicity with IV administration in neonates or any other pediatric age groups at doses less than 99 mg/kg/day[3] or any evidence of BA toxicity in any pediatric age groups with other routes of administration (i.e., oral, topical, intramuscular). One explanation for the lack of reports may be increased awareness and near avoidance of IV use of BA containing products in clinical practice.[4]

B. Templated BA Toxicity Labeling Language

Given that a safe threshold for BA exposure is not known, in 2009, DPMH developed templated labeling language with the Labeling Policy Team (LPT) for products containing benzyl alcohol either as an active ingredient or as an excipient to caution prescribers about the "gasping syndrome." Though the published reports described BA toxicity at doses ranging from 99 mg/kg/day to 234 mg/kg/day[1], the level of systemic exposure (Cmax, Tmax, AUC) of BA

[1] Primary Review-Joint DPMH and Division of Cardiology and Nephrology entered into DARRTS on 2-16-2019 under NDA206814 s-008
[2] Brown WJ, Buist NRM, Gepson HT, et al. Fatal Benzyl Alcohol Poisoning in a Neonatal Intensive Care Unit. Lancet 1: 1250, 1982.
[3] Gershanik J, Boecler B, Ensley H, et al. The Gasping Syndrome and Benzyl Alcohol Poisoning. New England Journal of Medicine 307(22): 1384-1388, 1982
[4] DPMH Memorandum entered into DARRTS.6.11.2021

associated with the observed toxicity in neonates was unknown, and there continues to be a lack of data to inform what level of BA exposure at doses less than 99 mg/kg/day would be considered safe in the neonatal population. The templated labeling language describes the known clinical manifestations at reported doses to inform prescribers about the potential for this adverse reaction to occur, how to identify the clinical manifestations, and what steps should be taken to mitigate the risk and serious outcomes. DPMH is currently working with the LPT to update this templated language to focus on VLBW, early preterm neonates as the pediatric subpopulation in whom BA toxicity has almost exclusively been described and is, therefore, most at risk.

II. BA content of IMBRUVICA:

IMBRUVICA oral suspension contains (b) (4) mg/mL of benzyl alcohol. IMBRUVICA tablets and capsules do not contain benzyl alcohol. Each mL of oral suspension contains 70 mg of IMBRUVICA. IMBRUVICA is dosed at 240 mg/m^2 orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. The average body surface area (BSA) for a one-year-old is ~ 0.49 m^2. Therefore, the daily dose for an average (50th %ile) one-year old would be 117.6 mg or 1.7 ml. [(240 x 0.49) ÷70] The expected daily exposure of BA from IMBRUVICA corresponding to a dose of 117.6 mg would then be approximately (b) (4) mg. ((b) (4) mg/mL x 1.7 mL). The expected daily intake of BA for a one-year-old weighing 10 kg (50th %ile for weight) would be (b) (4) mg/kg/day. At this exposure, even if the oral dose was 100% bioavailable, the amount of BA received by the child will be below the lowest dose of 99 mg/kg/day implicated in the 'gasping syndrome' observed in neonates after IV administration. This observation would be true if IMBRUVICA was to be administered to patients less than 1 year of age. The expected daily intake of BA in this subpopulation would not exceed 2 mg/kg/day, which is far below doses reported to be associated with the "gasping syndrome"

Projected Maximum Daily Intake (MDI) of BA for the average Infant by weight

Age	50th ile by Wt* in kg	BSA for Wt**	Dose of Imbruvica	MDI of BA	BA Dose (mg/kg/day)
Newborn	3.5	0.24	57.6 mg	(b) (4)	(b) (4)
3 months	6.0	0.34	81.6 mg		
6 months	8.0	0.42	100.8 mg		
9 months	9.0	0.46	110.4 mg		
12 months	10.0	0.49	117.6 mg		

Source: Table created by Reviewer

* National Center for Health Statistics

** Children's Cancer and Leukaemia Group - www.cclg.org.uk

Patients in the neonatal period are the most vulnerable to BA toxicity but would not be expected to receive IMBRUVICA for treatment of cGVHD. The diagnosis of cGVHD is made 100 days after transplantation.[5] A neonate requiring a bone marrow transplant will need to wait approximately 100 days for the diagnosis to be made followed by failure of one or more

[5] CDTL Review of NDA 205552_S17_entered into_DARRTS-7-12-2017

therapies for graft vs host disease prior to initiation of IMBRUVICA treatment. By this time, the patient will no longer be in the neonatal period. Even if a neonate received IMBRUVICA off-label, DPMH anticipates that the amount of BA delivered orally and subsequently absorbed would be so minimal compared to published reports of doses associated with BA toxicity that the risk of BA toxicity would be negligible.

III. Conclusion

Inclusion of BA templated language in IMBRUVICA labeling is not justified based on the amount of BA contained in the product and the anticipated pediatric population likely to receive the product. Early preterm VLBW neonates are the pediatric subpopulation most at risk for BA toxicity but are unlikely to receive IMBRUVICA. In general, BA toxicity is a theoretical concern outside of the neonatal period. Use of IMBRUVICA at the recommended dosage will result in the oral administration of approximately (b) (4) mg/kg/day of BA to patients down to 1 year of age. And if used off-label in patients less than 1 year of age, the oral administration amount would not exceed 2 mg/kg/day. There are no published reports of toxicity occurring from this amount of BA administration in pediatric patients of any age. Although a safe threshold of BA exposure is not known, administration of (b) (4) mg/kg/day of BA is nearly 60-fold less than the IV doses implicated in causing the gasping syndrome in the literature.

DPMH Recommended Labeling

This DPMH labeling review of IMBRUVICA focuses primarily on subsection 8.4. IMBRUVICA labeling includes templated language regarding BA toxicity in subsection 8.4. DPMH proposed the following labeling recommendations. Underlined text represents our proposed additions and strikethroughs represent our proposed deletions to the Applicant's proposed labeling.

Applicant's Proposed Labeling

(b) (4)

(b) (4)

[redacted]

DPMH reviewed the Applicant's draft labeling and participated in the team meetings held during June 2022 through July 2022. The final labeling and approval letter will reflect DPMH's input. The final labeling will be agreed upon with the Applicant.

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