

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761112Orig1s000

OTHER REVIEW(S)

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

Date of This Memorandum: December 21, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761112
Product Name and Strength: Cablivi
(caplacizumab)
10 mg per vial
Applicant/Sponsor Name: Ablynx NV
FDA Received Date: December 14, 2018
OSE RCM #: 2018-1338-1 and 2018-1803-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels (diluent syringe and drug vial) and carton labeling for Cablivi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised drug vial label, diluent syringe label and carton labeling are unacceptable from a medication error perspective. The format for the expiration date is not defined on the labels and labeling and may lead to confusion and the risk for deteriorated drug medication errors. The machine-readable product identifier is not indicated on the carton labeling. In addition, the National Drug Code (NDC) number is provided in the Prescribing Information (b) (4)

^a Garrison N. Label and Labeling Review for Cablivi (BLA 761112). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 21. RCM No.: 2018-1338 and 2018-1803.

3 RECOMMENDATIONS FOR ABLYNX NV

We recommend the following be implemented prior to approval of this BLA:

A. (b) (4) Carton Labeling

1. 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. We recommend 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 hyphen or a space be used to separate the portions of the expiration date.

B. Carton Labeling

1. Please clarify where the machine-readable product identifier will be located as it is not indicated on the carton labeling as described in the September 2018, FDA draft guidance on product identifiers in the Drug Supply Chain Security Act.¹

[1] The draft guidance is available from: 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

2. We recommend revising the statement, (b) (4) to "See prescribing information for dosage and administration."

C. Container Label (drug vial)

1. (b) (4)
2. (b) (4)

D. Container Label (diluent syringe)

1. (b) (4)

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

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

/s/

NICOLE B GARRISON
12/21/2018

HINA S MEHTA
12/21/2018

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

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

Date of This Review:	November 21, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761112
Product Name and Strength:	Cablivi (caplacizumab) 10 mg per vial
Product Type:	Combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ablynx NV
Submission Date:	April 4, 2018, June 6, 2018, August 2, 2018
OSE RCM #:	2018-1338 and 2018-1803
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPPS
DMEPA Team Leader:	Hina Mehta, PharmD
Senior Human Factors Specialist:	Shannon Hoste, MS
DMEPA Deputy Director:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review is in response to a request from the Division of Hematology Products (DHP) to review the human factors (HF) validation study results and labels and labeling, submitted as part of the 351(a) submission for Cablivi (caplacizumab) (BLA 761112), to address any areas of vulnerability that may lead to medication errors.

1.1 PRODUCT DESCRIPTION

Cablivi (caplacizumab) is a combination product (e.g. caplacizumab with vial adapter) intended for treatment of (b) (4)

The Cablivi user interface consists of a kit containing a carton box with lyophilized caplacizumab in a single-dose glass vial together with a sterile diluent pre-filled syringe, vial adapter, sterile hypodermic needle, and two alcohol swabs. The Cablivi kit is intended for administration by patients, caregivers and healthcare providers (HCPs) in the home or healthcare setting. Currently, the standard of treatment for acquired TTP is daily plasma exchange (PE) in conjunction with immunosuppressive therapy (e.g. corticosteroids, rituximab).

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

We previously reviewed the Sponsor's proposed human factors (HF) validation study protocol under IND 107609; as part of our review, we noted that the proposed (b) (4)

recommended that the Sponsor revise the HF study protocol to include untrained patient and caregiver participants (b) (4)

We recommended that the protocol be revised to address our concerns and to ensure that the methodology is acceptable.^a

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review
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^a Rychlik, I. Human Factors Protocol Review for Caplacizumab Convenience Kit IND 107609. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 16. RCM No.: 2016-2434.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Requests Issued During the Review	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the human factors (HF) validation study results, prescribing information (PI), Instructions for Use (IFU), container labels, and carton labeling are as follows:

3.1 HUMAN FACTORS VALIDATION STUDY METHODOLOGY

We previously reviewed the HF validation study protocol and note that our recommendations were implemented.^b We note that the HF validation study included 45 participants (15 patients/caregivers with injection experience, 15 injection naïve patients/caregivers, and 15 healthcare providers). All healthcare provider participants were untrained, and half of the patients/caregivers were untrained. Each study participant performed simulated use testing by preparing and delivering 1 dose of placebo into an injection pad. Following the simulated use test, all study participants answered a series of knowledge-based questions. A final interview was conducted to discuss any usability issues and to determine root causes for use errors.

3.2 HUMAN FACTORS VALIDATION STUDY RESULTS

Table 2 describes the study results, Sponsor's analyses of the results, and DMEPA's analyses and recommendations.

^b Rychlik, I. Human Factors Protocol Review for Caplacizumab Convenience Kit IND 107609. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 16. RCM No.: 2016-2434.

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor’s Root Cause Analysis	Sponsor’s Discussion of Mitigation Strategies	DMEPA’s Analysis and Recommendation
Insert vial adapter	Two (2) injection experienced patients/caregivers, one (1) injection naïve patient/caregiver, and three (3) healthcare providers mounted the adapter onto the vial and then immediately removed its cover. However, the IFU instructs users to keep the cover in place until it is removed in a later step.	Upon probing, one participant mentioned that it made more sense to remove the vial adapter cover off right away, rather than install it, put it down, do something else, and then return to it later. Another participant indicated that she was concerned about breaking the syringe cap off, then setting the syringe down to remove the vial adapter, because she would not want the syringe to become contaminated before attaching the syringe and the vial together.	The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as result of the design validation testing.	<p>Our review of the IFU finds that Step 3 advises the user to place the adapter over the vial, while keeping the adapter in its plastic packaging. The submitted root information suggest the difficulties with this step were related to intentional deviation from the instructions because it made more sense to the participant or the participant was concerned with next step in the process (preparing the syringe).</p> <p>We find Step 3 of the IFU can be better presented although the Sponsor proposes no mitigation. Specifically, bolding statement, “Place the adapter over the vial, while keeping the adapter in its plastic packaging.” We will provide recommendations in Section 4.2 of the review to address our concern.</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study

Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor’s Root Cause Analysis	Sponsor’s Discussion of Mitigation Strategies	DMEPA’s Analysis and Recommendation
Swirl to dissolve	<p>Two (2) untrained injection naive patient participants skipped this step.</p> <p>Two (2) healthcare providers and one (1) injection experienced participant shook the vial vigorously after expelling the fluid into it.</p> <p>One (1) healthcare provider pushed the plunger up and down a couple of times, mixing the medicine back and forth between the vial and the syringe</p>	<p>The two (2) untrained injection naive patients skipped the step because “it didn’t register” or “I was trying to accelerate things.” They didn’t notice the step in the IFU and proceeded straight to pulling solution into the syringe.</p> <p>Two (2) healthcare providers and one (1) injection experienced participant shook the vial vigorously after expelling the fluid into it. The healthcare providers said, “shaking a solution is our method of reconstituting all medication.” Both relied on their work habits and did not notice the IFU’s instruction to gently swirl.</p> <p>One (1) healthcare provider, mentioned that this was the method she uses in her practice when reconstituting medication.</p>	<p>The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as result of the design validation testing.</p>	<p>Our review of the IFU finds that Step 6 advises the user to gently swirl the vial with the attached syringe until the powder is dissolved in the vial. Do not shake the vial. In addition, a coordinating image displays vial adapter with an arrow circled around the vial.</p> <p>The submitted root cause information suggested that omission of this step was related to previous experience for healthcare workers. The submitted root causes for patients suggested the step was skipped because they were trying to accelerate things or did not see the step.</p> <p>The Sponsor submitted data demonstrating no change in the product quality attributes after shaking, thus the risk associated with shaking the solution is low. In addition, we find the IFU mitigates this use error adequately, and no further mitigation of this error is required.</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor’s Root Cause Analysis	Sponsor’s Discussion of Mitigation Strategies	DMEPA’s Analysis and Recommendation
Pull solution into syringe	<p><u>Use Error</u></p> <p>One (1) untrained naïve caregiver expelled fluid into the vial, mixed the solution, and then immediately detached the syringe from the vial (leaving the solution in the vial). After attaching the needle, she prepared to follow the step in the IFU instructing her to remove the air from the syringe. She then realized her error, and self-corrected by removing the needle, reattaching the vial, and withdrawing the fluid. However, she did not “bottom out” the plunger before withdrawing only a small amount of fluid in the syringe.</p>	<p><u>Use Error</u></p> <p>The untrained naïve caregiver mentioned that she stopped pulling the plunger when it reached its end-of-travel, and that the earlier mistake made her want to “hurry up and get the process done.”</p>	<p>The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as result of the design validation testing.</p>	<p>Our review of the IFU finds that Step 7 advises the user to slowly press the syringe plunger fully down. Keep the syringe on the vial and turn the vial, adapter and syringe upside down. Slowly pull the plunger to withdraw all the solution from the vial into the syringe. The submitted root cause suggest the participant was not following the IFU because after attaching the needle she prepared to follow the next step in the IFU. The participant self-corrected and attempted to remove the solution from the vial but did not fully press the plunger as they wanted to hurry up and complete the process. Other participants assumed the plunger had “bottomed out”, had a mental model of the plunger being able to suck the medicine into the vial regardless of the angle, or thought she withdrew the contents of the vial because the solution stopped dripping.</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study

Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor’s Root Cause Analysis	Sponsor’s Discussion of Mitigation Strategies	DMEPA’s Analysis and Recommendation
	<p><u>Use Difficulties</u></p> <p>One (1) trained caregiver did not “bottom out” the plunger before withdrawing it from the vial.</p> <p>One (1) experienced, untrained patient did not initially invert the syringe/vial assembly before pulling on the plunger. Holding it horizontally, she pulled on the plunger, only managing to get a small amount into the syringe. After detaching and seeing the small amount, she reattached the syringe and referred to the IFU in more detail. She noticed that she had to invert the syringe/vial assembly in order for the syringe to be filled.</p>	<p><u>Use Difficulties</u></p> <p>One (1) trained caregiver assumed the plunger had reached its end of travel.</p> <p>One (1) experienced, untrained patient had a mental model of the plunger being able to suck the medicine into the vial regardless of the angle.</p>		<p>We determine Step 7 of the IFU provides clear text on how to pull the plunger fully down. In addition, a coordinating image displays the solution being withdrawn from the vial. We find the IFU mitigates this use error adequately, and no further mitigation of this error is required.</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendation
	One (1) trained patient did not withdraw all of the solution of the vial.	One (1) trained patient mentioned that she did not pay attention while withdrawing the solution and she thought it was all withdrawn. She thought she remembered pulling all of it "because it stopped dripping from the vial."		
Prime/ remove air	<p><u>Use Errors</u> Five (5) patients/caregivers did not remove air from the syringe before injecting.</p> <p>Two (2) healthcare providers did not remove air from the syringe before injection.</p>	<p>The five (5) patients/caregivers indicated having "a lot to keep track of" at that point in the process, and with the needle exposed and the injection about to happen, their attention was on the syringe and not on the IFU. The participants were able to read and demonstrate comprehension of the step in the IFU.</p> <p>One (1) of the healthcare providers indicated that in her practice, a subcutaneous injection with a small amount of medication would be given without priming, because she was taught that a small amount of air will not cause any harm to a patient. Another healthcare</p>	The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as result of the design validation testing.	Our review of the IFU finds that Step 11 advises the user to remove any air bubbles by tapping the side of the syringe with your finger until they rise to the tip. Then, slowly push the plunger up until a small amount of liquid drips from the needle. In addition, a coordinating image displays a syringe with a small amount of liquid at the tip of the needle. The submitted root causes from the patients and caregivers suggest the task was not completed because of the high cognitive load and they choose to focus on the syringe since the needle was exposed and not the IFU. All were able to read and demonstrate comprehension of the

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study

Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor’s Root Cause Analysis	Sponsor’s Discussion of Mitigation Strategies	DMEPA’s Analysis and Recommendation
	<p><u>Close call</u> One (1) trained patient initially forgot to expel the air. He inserted the needle into the injection pad and saw the bubble and realized he missed a step. He self-corrected and withdrew the needle, expelled the air, and then continued with the injection.</p>	<p>provider (1) indicated that in her practice, they are taught to expel air when drawing solution into the vial (i.e., expelling it before detaching the syringe from the vial).</p> <p><u>Close call</u> One (1) trained patient stated he forgot the step but when he saw the bubble he realized the mistake.</p>		<p>step in the IFU. One of the participants mentioned that she does not prime her injections at home and was not in the habit of removing air from the syringe.</p> <p>The submitted root causes from the healthcare providers suggest that they do not prime subcutaneous injections in their practice or were taught to expel air when drawing solution into a vial.</p> <p>We find Step 11 of the IFU can be better presented although the Sponsor proposes no mitigation. Specifically, including an image that demonstrates the action of tapping the side of the syringe. We also recommend including an “up arrow” to further clarify that the plunger should be pushed up to expel a small amount of liquid.</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendation
				We will provide recommendations in Section 4.2 of the review to address our concern.
Attach the needle to the syringe	One (1) injection experienced trained caregiver and one (1) injection naïve trained patient struggled to attach the needle to the syringe by trying to push the needle on to the syringe instead of twisting the needle. Both participants assumed the needle and syringe would "click" together. They referred to the IFU and self-corrected. The injection naïve patient removed the needle from the syringe when performing the step of expelling air from the syringe. When some fluid inside of the syringe was expelled, the participant paused and stated that she	The investigator asked the injection naïve patient (1) what she would have done if this had occurred at home. The patient stated she would continue as if she has received a new kit and was able to attach the needle correctly after referring to Figures U and V in the IFU, which illustrate attachment of the needle and syringe. Upon probing, the patient stated she was not paying attention to the instructions the first time she tried to attach the needle, and that she was going by her memory from training.	The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as result of the design validation testing.	Our review of the IFU finds that Step 9 advises the user to attach the needle with needle cap to the syringe by turning clockwise until it cannot twist any further. The text also refers users to Figure Q, which illustrates the action of locking the syringe into the needle by turning it clockwise. The submitted root causes from the caregiver and patient suggest they assumed how the needle and syringe would attach without referring to the IFU. The patient also relied upon her memory from training when completing this step and did not pay attention to the instructions. When the patient and caregiver referred to the IFU they were able to self-correct and complete the step correctly.

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendation
	believed she had "done something wrong."			We determine Step 9 of the IFU provides clear text on how to attach the needle to the syringe. In addition, a coordinating image displays the needle being attaching syringe. We find the IFU mitigates this use error adequately, and no further mitigation of this error is required.
Choose site	<p><u>Use Errors</u></p> <p>Two (2) injection experienced patients/caregivers and one (1) injection naïve patient/caregiver chose the chose the upper arm as the injection site.</p> <p>One (1) healthcare provider chose the thigh as the injection site.</p>	<p><u>Use Errors</u></p> <p>The two (2) injection experienced patients/caregivers usually use the upper arm as their injection site and felt that this assumption caused them not to pay much attention to the part of the IFU that indicates intended injection location. All were able to read and demonstrate comprehension of the step in the IFU.</p> <p>One (1) healthcare provider chose the thigh as the injection site because she would normally give subcutaneous injections into the thigh or stomach and hadn't paid</p>	The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as result of the design validation testing.	<p>Our review of the IFU finds that Step 11 advises users to gently use one hand to pinch the skin that has been cleaned between the thumb and the forefinger, making a fold. In addition, a coordinating image in Step 11 demonstrates the user pinching the skin on the abdomen.</p> <p>The submitted root causes suggest user selected incorrect injection sites based on previous injection experience. All were able to read and demonstrate comprehension of the step in the IFU.</p> <p>We find the image for Figure W in the IFU can be better presented although</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendation
	<p><u>Close call</u></p> <p>One (1) healthcare provider initially chose the arm as the site for injection.</p>	<p>much attention to the step in the IFU indicating the location.</p> <p><u>Close call</u></p> <p>After the investigator made note of her choice, and instructed her to use the abdomen, the healthcare provider (1) self-corrected and stated that she remember that "the abdomen was where the injection would normally take place." She continued with the process and injected into the mannequin's abdomen.</p>		<p>the Sponsor proposes no mitigation. Specifically, identifying the area surrounding the navel. We also note the Figure ^{(b) (4)}</p> <p>We will provide recommendations in Section 4.2 of the review to address our concern.</p>
Inject: complete, correct orientation	<p>One (1) healthcare provider did not give the full injection. The participant had made an earlier error and not expelled the air from the syringe before attempting to inject. When she pressed the plunger, she expelled the air into the</p>	<p>When probed, the healthcare provider (1) stated that she did not know what happened and could not give a definite answer. She believed she had hit the end of the plunger on the syringe as soon as she felt resistance.</p>	<p>The observed use-related errors were in line with the expectations and were considered acceptable true residual risks. Therefore, no new designed modifications were introduced as</p>	<p>Our review of the IFU finds that Step 11 advises users to push down the plunger of the syringe until all the solution is injected into your skin. In addition, to the coordinating step, Figure ^{(b) (4)} demonstrates the syringe injected into the skin with the plunger pressed all the way down.</p> <p>The submitted root cause did not provide information as the participant</p>

Table 2: Analyses of Critical Tasks Use Errors and Close Calls for Cablivi HF Validation Study				
Critical Task Description	Number and Description of Failures, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendation
	<p>injection pad, and as soon as she felt the resistance from the solution in the needle, she stopped, pulled the needle out and discarded it with the fluid still inside.</p> <p>One (1) healthcare provider did not press the plunger all the way down.</p>	<p>The second healthcare provider (1) stated she was pushing with her index finger out of habit and when she felt resistance she decided it was complete. She did inject the majority of the solution, leaving less than 20% in the syringe.</p>	<p>result of the design validation testing.</p>	<p>could not provide a reason why the error occurred.</p> <p>We determine Step 11 of the IFU provides clear text on how to injection the dose. In addition, a coordinating image displays a syringe injected into the skin. We find the IFU mitigates this use error adequately, and no further mitigation of this error is required.</p>

3.3 ANALYSIS OF ESSENTIAL/NON-CRITICAL TASKS

We observed use errors/close calls/use difficulties with the following essential task:

Checking for expiration date

We note that Four (4) healthcare providers, one (1) injection naive caregiver/patient, and two (2), injection experienced caregivers and patients did not check the expiration date prior proceeding with the injection process. However, these failures are not unique to the use of this product. We note that these failures commonly occur across all product types. We evaluated the subjective feedback from the participants that made these use errors. Several participants attributed these errors failures to expecting medication that they just received from the pharmacy to not be expired or the odds of holding on to a medication for a long period of time would be low. We note that checking the expiration date is a standard practice for all products.

Activate needle shield

We note that 7 participants did not activate the needle shield prior to disposal. However, these failures are not unique to the use of this product as this can occur with any product that requires manual activation of the needle shield. We evaluated the subjective feedback from the participants that made these use errors. Several participants attributed the failures to having a high cognitive load at that point in the process and were focusing on the discarding the syringe and not on the IFU. Other participants attributed failures to not being familiar with that type of needle shield or they typically recap the needle on the syringe. We note that manual activation of the needle shield is a standard practice for devices that are equipped with them.

Disposing of the syringe

One participant disposed of the syringe in the regular trash instead of a sharps container. Another participant activated the needle shield, detached the needle from the syringe, and disposed of both the syringe and the needle in the sharps container. However, these failures are not unique to the use of this product and can occur with any injectable product. We evaluated the subjective feedback from the participants that made these use errors. Both participants attributed the failure to their previous experience with injectable products. We note that discarding a syringe and needle in a sharps container is standard practice for all injectable products.

We evaluated the IFU, which provides clear text on checking the expiration date, activating the needle shield, and disposal of the needle and syringe. In addition, the IFU provides an image that illustrates where to find the expiration date on the carton and how to activate the needle shield. We find the IFU mitigates this use error adequately, and no further mitigation of this error is required.

3.4 LABEL AND LABELING

Our review of the proposed Prescribing Information (PI) labeling, Instructions for Use (IFU) labeling, container label and carton labeling identified areas which may be improved to decrease risk of medication error. Additionally, we note the (b) (4) carton labeling use the package type term, (b) (4) IFU uses the package type term, "single-dose". We defer to the Office of Pharmaceutical Quality (OPQ) for determination of the appropriate package type and to maintain consistency of terms on labels and labeling. We also note that OPQ is determining the strength of the product to reflect the amount contained in the vial and the amount that can be extracted after reconstitution.

Highlights of Prescribing Information

1. The dosage information in the Dosage and Administration section can be revised for clarity.

Prescribing Information

1. Section (b) (4)
(b) (4)
2. (b) (4)
3. The storage information in Section 16 *How Supplied/Storage and Handling* can be revised for clarity to bring prominence to important information.

(b) (4) Instructions for Use (IFU)

1. The instruction for retaining the vial adapter in the packaging lacks prominence and can be revised to mitigate the risk of preparation errors.
2. The instruction for removing air bubbles lacks clarity and contains an image that is incongruent with the accompanying text, which may lead to administration errors.
3. The image used to illustrate administration of the product lacks clarity on area surrounding the navel for administration and can be revised to mitigate the risk of administration errors.

Container label and carton labeling (all)

1. The container label and carton labeling use package type terms inconsistent with Patients and Caregivers IFU and with the draft guidance.^c

^c See Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, which, when finalized, will represent FDA's current thinking on the topic. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

Container label (syringe)

1. [REDACTED] (b) (4)

Container label (vial)

1. [REDACTED] (b) (4)
2. [REDACTED]

Carton labeling

1. [REDACTED] (b) (4)
2. The NDC is denoted by a placeholder and not in accordance with 21 CFR 207.33 and 21 CFR 201.2.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur.

4 CONCLUSION & RECOMMENDATIONS

The HF validation study results identified use errors on critical tasks and noncritical/essential tasks. The root cause analysis and subjective feedback submitted by the Sponsor did not suggest that the user interface contributed to the use errors encountered by participants. Our evaluation of the proposed the Prescribing Information, IFU, container label, and carton labeling identified areas to improve clarity of the labeling as it relates to storage, preparation and administration of the product. We provide recommendations in section 4.1 for the Division and 4.2 for the Sponsor and recommend their implementation prior to approval of this BLA 761112.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

1. In Dosage and Administration section, revise the following statements to increase clarity.

- a. "Subsequent treatment during plasma exchange: [REDACTED] (b) (4) to "Subsequent treatment during plasma exchange: 10 mg subcutaneous injection once daily following plasma exchange."

- b. Treatment after the plasma exchange period: [REDACTED] (b) (4) to "Treatment after the plasma exchange period: 10 mg subcutaneous injection once daily for 30 days."

B. Prescribing Information

1.

(b) (4)

2.

4. Section 16 *How Supplied/Storage and Handling*

1. Revise the first sentence in the storage statement to “Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.”

C. (b) (4) Instructions for Use (IFU)

1. In Step 3, bold the statement, “Place the adapter over the vial, while keeping the adapter in its packaging.” to bring prominence to this important information.
2. (b) (4) The text states to remove air bubbles by tapping the side of the syringe with your finger until they rise to the toward the tip; however, (b) (4) Please revise the image used in Figure (b) (4) We recommend including an additional image that demonstrates the action of tapping the side of the syringe to provide congruency with the text and the image. We also recommend including an “up arrow” to further clarify that the plunger should be pushed up to expel a small amount of liquid. We recommend this to mitigate the risk of preparation errors.
3. Revise the image in Figure (b) (4) to identify the area surrounding the navel where the subcutaneous injection should be administered. We recommend this revision to mitigate the risk of injection site administration errors.

4.2 RECOMMENDATIONS FOR ABLYNX NV

We refer to your human factors (HF) validation study report submitted on April 4, 2018, in support of BLA 761112. Based on our evaluation we have the following recommendations and we recommend that these are implemented prior to approval of this BLA 761112.

A. All Container Label and Carton Labeling

1. As currently presented, (b) (4) carton labeling use the package type term, (b) (4); however, the (b) (4) IFU uses the package type term, "single-dose". Revise the (b) (4) carton labeling to "single-dose" to be consistent throughout the labeling.
2. As currently presented the (b) (4) carton labeling use the (b) (4) however, the (b) (4) Prescribing Information uses the dosage form, "For Injection". Revise the (b) (4) carton labeling to "For Injection" to be consistent throughout the labeling.

B. Container label (syringe)

1. (b) (4)
2. (b) (4)

C. Container label (vial)

1. (b) (4)
2. (b) (4)
3. (b) (4)

4.

D. Carton labeling

1. Revise the statement from [REDACTED] (b) (4) to read as follows: "Must be reconstituted with diluent provided" and relocate to appear below the route of administration on the principal display panel. We recommend bolding this statement to bring prominence to this important information.
2. As currently presented the NDC is denoted by a placeholder. We request that you submit the NDC in accordance with 21 CFR 207.33 on the carton labeling.
3. Revise and relocate the contents statement including the net quantity statement to the Principal Display Panel and ensure that the appropriate package type term and USP nomenclature are included in the contents statement as follows:

Each carton contains:

One 10 mg Cablivi single-dose vial

One 1 mL Sterile Water for Injection, USP prefilled syringe, diluent for Cablivi

One sterile vial adapter

One sterile needle hypodermic needle (30 gauge)

Two individually packed alcohol swabs

4. Revise and bold the storage information from [REDACTED] (b) (4) to "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Unopened vials may be stored at room temperature up to 30°C (86°F) for a single period of up to 2 months. Write the date removed from the refrigerator: ___/___/___."
5. Revise and relocate to the PDP the statements [REDACTED] (b) (4) to "Single-dose only. Discard unused portions."
6. The font size of the route of administration statement, "For intravenous and subcutaneous [REDACTED] (b) (4) and the Rx only statement are equal in prominence. We recommend increasing the prominence of the statement, "For

intravenous and subcutaneous [REDACTED] (b) (4) to bring further attention to the route of administration to mitigate the risk of product administration errors.

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 6, 2018, we searched DMEPA's previous reviews using the terms, Caplacizumab. Our search identified 1 previous review^d, and we note that our previous recommendations were implemented.

^d Rychlik, I. Human Factors Protocol Review for Caplacizumab Convenience Kit IND 107609. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 16. RCM No.: 2016-2434.

APPENDIX C. HUMAN FACTORS STUDY

Link to the human factors validation study results document:

[\\cdsesub1\evsprod\bla761112\0000\m3\32-body-data\32p-drug-prod\cablivi-powder-patheon\32p2-pharm-dev\pharmaceutical-development-32p22-attachment3.pdf](#)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Cablivi labels and labeling submitted by Ablynx NV on June 6, 2018 and August 2, 2018.

- Container labels submitted on June 6, 2018
- Carton labeling submitted on June 6, 2018
- Prescribing Information and Instructions For Use (Image not shown) submitted on June 6, 2018 and August 2, 2018

G.2 Label and Labeling Images



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^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NICOLE B GARRISON
11/21/2018

HINA S MEHTA
11/21/2018

SHANNON M HOSTE
11/21/2018

MISHALE P MISTRY
11/26/2018

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

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

Memorandum

Date: November 1, 2018

To: Beatrice Kallungal, Senior Regulatory Project Manager, Division of Hematology Products (DHP)
Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for CABLIVI® (Caplacizumab) for injection, for intravenous or subcutaneous use

BLA: 761112

In response to DHP's consult request dated October 17, 2018, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Cablivi.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Beatrice Kallungal) on October 18, 2018, and are provided below.

IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 6, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
11/01/2018

**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: November 1, 2018

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): CABLIVI (caplacizumab)

Dosage Form and Route: for injection, for intravenous and subcutaneous use

Application Type/Number: BLA 761112

Applicant: Ablynx, Inc.

1 INTRODUCTION

On June 6, 2018, Ablynx, Inc. submitted for the Agency's review a rolling Biologics License Application (BLA) 761112 for CABLIVI (caplacizumab) for injection. The proposed indication for CABLIVI (caplacizumab) for injection is for (b) (4)

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 Hematology Products (DHP) on October 16, 2018 and October 17, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for CABLIVI (caplacizumab) for injection.

2 MATERIAL REVIEWED

- Draft CABLIVI (caplacizumab) for injection IFU received on June 6, 2018, and received by DMPP and OPDP on October 18, 2018.
- Draft CABLIVI (caplacizumab) for injection Prescribing Information (PI) received on June 6, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 18, 2018.

3 REVIEW METHODS

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

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

In our collaborative review of the IFU we:

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

4 CONCLUSIONS

The IFU 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 IFU 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 IFU.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
11/01/2018

ROBERT L NGUYEN
11/01/2018

LASHAWN M GRIFFITHS
11/01/2018

CLINICAL INSPECTION SUMMARY

Date	October 24, 2018
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrew Dmytrijuk, M.D., Medical Officer Kathy Robie Suh, M.D., Ph.D., CDTL Ann Farrell, M.D., Director Beatrice Kallungal, M.Sc., Senior Regulatory Project Manager Division of Hematology Products
BLA	761112
Applicant	Ablynx NV
Drug	caplacizumab
NME	Yes
Therapeutic Classification/Status	humanized bivalent nanobody inhibitor
Proposed Indication	(b) (4)
Consultation Request Date	July 19, 2018 (Priority Review)
Summary Goal Date	December 1,, 2018
Action Goal Date	February 6, 2019
PDUFA Date	February 6, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Flora Peyvandi and Marie Scully) were selected for inspection in support of BLA 761112. The study data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.

The preliminary regulatory classification of Drs. Peyvandi and Scully is No Action Indicated.

2. BACKGROUND

Plasma exchange therapy is the standard of care treatment for acquired thrombotic thrombocytopenic purpura (TTP). It replenishes ADAMTS13, partially normalizing vWF processing, and removes pathogenic auto antibodies when present. Immunosuppressive treatment, most commonly corticosteroids, is started together with plasma exchange therapy.

Sponsor states that there are no approved pharmacologic treatments for TTP, and proposes caplacizumab as treatment for microvascular thrombosis inherent in TTP. Caplacizumab is a humanized bivalent nanobody which is produced in *E. coli* and consists of two identical humanized anti-vWF building blocks, genetically linked by a 3-alanine linker.

Caplacizumab (ALX-0081) inhibits the interaction between von Willebrand factor (vWF) and platelets by targeting the A1 domain of vWF. Caplacizumab selectively prevents thrombus formation in high-shear blood vessels, and blocks ultra-large (UL) vWF-mediated platelet interactions.

Study Protocol ALX0681-2.1/10 (TITAN):

Study Protocol ALX0681-2.1/10 (TITAN Study) was a Phase 2, single-blind, randomized, placebo-controlled trial to study the efficacy and safety of anti-von Willebrand factor nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura. The primary objective of the study was the reduction of time-to-response. The primary study endpoint was reduction of time-to-response, defined by the achievement of platelet count response, confirmed at 48 hours after the initial reporting of this response. This defined “confirmed platelet response” had to be confirmed at 48 hours after the initial reporting of platelet recovery at least 150,000/ μ L, by a de novo measure of platelets at least 150,000/ μ L and lactate dehydrogenase (LDH) less than twice the upper limit of normal (ULN).

There were 32 participating active sites (out of 56 approved sites) in 11 countries. A total of 75 adult subjects were randomized (36 patients randomized to caplacizumab [ALX-0081] and 39 patients randomized to placebo). The date of first patient enrolment was on January 7, 2011, and the last patient follow-up date was completed on March 14, 2014.

Study ALX0681-C301 (HERCULES):

Study ALX0681-C-301(HERCULES Study) was a Phase 3, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of caplacizumab when administered in addition to standard of care treatment in subjects with an acute episode of acquired TTP. The primary objective of this study was to evaluate efficacy of caplacizumab in restoring normal platelet counts as a measure of prevention of further microvascular thrombosis. The primary study endpoint for this study was time to platelet count response defined as initial platelet count $150 \times 10^9/L$ or greater, with subsequent stop of daily plasma exchange within five days.

This multicenter study enrolled subjects in 55 study centers in 15 countries. The primary efficacy population consisted of 145 subjects (72 subjects randomized to caplacizumab and 73 subjects randomized to placebo). The first subject enrolled on November 19, 2015. The last patient completed the primary evaluation period on August 16, 2017.

3. RESULTS (by site):

Name of Clinical Investigator Address	Protocol #/ Site # # Subjects enrolled	Inspection Dates	Classification
Dr. Flora Peyvandi Centro Emofilia e Trombosi Angelo Bianchi Bonomi Via della Pace, 9 Milano 20122, Italy	Study ALX0681-2.1/10 (TITAN) Site #602 10 subjects	October 15 - 19, 2018	Preliminary: NAI
Dr. Marie Scully Haematology Research Unit Department of Haematology University College London Hospitals 51 Chenies Mews, First Floor London WC1E 6HX, England	Study ALX0681-2.1/10 (TITAN) Site #901 7 subjects Study ALX0681-C301 (HERCULES) Site #044-001 15 subjects	October 15 - 19, 2018	Preliminary: NAI*

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator**1. Flora Peyvandi, M.D.**

Eleven subjects were screened and 10 subjects were enrolled. All subjects received treatment. Eight study subjects completed the study (Subject (b) (6) withdrew from the study due to a bleed. Subject (b) (6) was lost to follow-up).

For this inspection, a complete review of all regulatory documentation at the study site was performed, as well as the source records for all the subjects screened and enrolled at the site prior to the database lock. A 100% review of informed consent forms was completed. The source records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records. The study was initially monitored by (b) (4), and later monitored by (b) (4).

Source documents for all the 11 study subjects, whose records were reviewed, were verified against the case report forms and sNDA subject line listings, in part, for primary efficacy endpoints, adverse events and serious adverse event reporting. Source documents for the raw data

used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Marie Scully, M.D.

For Study ALX0681-2.1/10, seven subjects were screened, and enrolled. Four subjects completed the treatment phase of this study (Subject (b) (6) discontinued due to a pulmonary embolism. Subjects (b) (6) discontinued due to sponsor terminating the study).

For Study ALX0681-C301, 18 subjects were screened, and 15 subjects were enrolled. Twelve subjects completed the treatment phase of this study (Subjects (b) (6) discontinued due to adverse events).

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents in Study ALX0681-2.1/10 and Study ALX0681-C301, for the all the screened subjects whose records were reviewed, were verified against the case report forms and sNDA subject line listings, in part, for patient inform consent documentation, primary study endpoint assessment, adverse event and serious adverse event reporting. A comprehensive audit of the inclusion and exclusion criteria for patient enrollment was evaluated at this site inspection. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.

Branch Chief, Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation

Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
10/24/2018

KASSA AYALEW
10/25/2018



Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	February 6, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Jacek Cieslak, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761112
Applicant:	Ablynx NV
Submission Date:	April 4, 2018
Product:	Cablivi (caplacizumab-yhdp)
Dosage form(s):	for injection
Strength and Container-Closure:	11 mg/vial single-dose vials
Background and Summary Description:	The Applicant submitted a biologics license application for Agency review.
Recommendations:	The prescribing information and instructions for use (submitted on February 4, 2019) and container labels and carton labeling (submitted on January 31, 2019) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B). The prescribing information, instructions for use, container labels, and carton labeling were reviewed and found to comply with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100, 21 CFR 208.20(a)(7), 21 CFR 208.20(a)(7)).

The prescribing information and instructions for use (submitted on February 4, 2019) and container labels and carton labeling (submitted on January 31, 2019) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Instructions for Use

(submitted on June 6, 2018 <\\cdsesub1\evsprod\bla761112\0003\m1\us\114-labeling\draft\labeling\draft-labeling-text.pdf>)

Container Labels (submitted on June 6, 2018)



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Package Label⁵ Evaluation

Regulations, Guidance, and USP	Acceptable
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Manufacturer name, address, and license number 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: Revise the license manufacturer information to include the US license number as follows: Manufactured by: Ablynx N.V. Zwijnaarde, Belgium U.S. License No. xxxx <i>The Applicant revised as requested</i>	
Clarify if you intend to list (b) (4) as the distributor. Distributor information may be included but must be listed as "Distributed by: Distributor name and address".	

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Applicant's response: The distributor will be Genzyme Corporation and the name and address have been included accordingly. Acceptable.

<p><u>Lot number or other lot identification</u> 21 CFR 610.61</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Preservative</u> 21 CFR 610.61</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Number of containers</u> 21 CFR 610.61</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Comment/Recommendation: Ensure that the appropriate package type term and USP nomenclature are included in the contents statement. Revise the following portion of the contents statement to read as follows: <div style="background-color: #cccccc; width: 50%; height: 20px; margin: 5px 0;"></div> <i>The Applicant revised the package type term and applied USP nomenclature as requested</i></p> <p>Revise the dosage form from <div style="background-color: #cccccc; width: 50px; height: 15px; display: inline-block;"></div> to the appropriate dosage form for this product "for injection". <i>The Applicant revised as requested</i></p>	
<p><u>Strength/volume</u> 21 CFR 610.61, 21 CFR 201.10, 21 CFR 201.100</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Storage temperature/requirements</u> 21 CFR 610.61 Recommended labeling practices: USP General Chapters: <7> Labeling</p> <p>Comment/Recommendation: Revise the storage statement as follows for clarity: "Store refrigerated...freeze. Unopened vials may be stored at room temperature up to 30°C (86°F) for a single period of up to 2 months. Write the date removed from the refrigerator: ___/___/___." <i>The Applicant revised as requested</i></p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Handling: "Do Not Shake", "Do not Freeze" or equivalent</u> (21 CFR 610.61)</p> <p>Comment/Recommendation: See comment below to include important handling information, the statement "Do Not Shake"</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes

	<input checked="" type="checkbox"/> N/A
Route of administration 21CFR 610.61, 21 CFR 201.5, 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: Revise the route of administration statement as follows: "For Intravenous or Subcutaneous Use" <i>The Applicant revised as requested</i>	
Known sensitizing substances 21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: Revise the inactive ingredient list to appear in alphabetical order per USP <1091> Labeling of Inactive Ingredients with the qualitative list of inactive ingredients followed by their quantitative information (x mg). Revise the inactive ingredient list as follows: Each single-dose vial delivers 11 mg caplacizumab-xxxx, anhydrous citric acid (xx mg), polysorbate-80 (xx mg), sucrose (xx mg), and trisodium citrate dihydrate (xx mg) <i>The Applicant revised as requested</i>	
Source of the product 21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Minimum potency of product 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: Since no US standard of potency has been prescribed, the words "No U.S. standard of potency" per 21 CFR 610.61(r). <i>The Applicant revised as requested</i>	
Rx only 21CFR 610.61 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Divided manufacturing 21 CFR 610.63	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Distributor 21 CFR 610.64	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: <i>see comment above</i>	
Bar code 21 CFR 610.67 21 CFR 201.25	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68, 21 CFR 201.26	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A

<p><u>Preparation instructions</u> 21 CFR 201.5</p> <p>Comment/Recommendation: Instructions for reconstituting the product and the resultant concentration (XX mg/mL) should be included on the carton. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted. Information on the expiry and post-reconstitution storage should also be included. Relocate the preparation instructions to appear beneath the storage statement to coincide with order of use. revise the preparation instruction as follows: "Reconstitute using the provided syringe containing 1 mL Sterile Water for Injection, USP to yield a 11 mg/mL single-dose solution. Gently swirl, do not shake. The reconstituted solution can be kept for up to 4 hours in the refrigerator at 2°C to 8°C (36°F to 46°F)." <i>The Applicant revised as requested</i></p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Package type term</u> <i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements</i></p> <p>Comment/Recommendation: Revise to the appropriate package type term as follows: "Single-dose vial. Discard unused portion." <i>The Applicant revised as requested</i></p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Spanish-language (Drugs)</u> 21 CFR 201.16</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><u>Sulfites; required warning statements</u> 21 CFR 201.22</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><u>Net quantity</u> 21 CFR 201.51</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><u>Usual dosage statement</u> 21 CFR 201.55</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes

21 CFR 201.100	<input type="checkbox"/> N/A
<u>Dispensing container</u> 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

Prescribing Information and Patient Labeling Evaluation

Regulations	Acceptable
PRESCRIBING INFORMATION	
Highlights of prescribing information	
<u>PRODUCT TITLE</u> 21 CFR 201.57(a)(2)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<u>DOSAGE AND ADMINISTRATION</u> <i>Recommended labeling practices: USP nomenclature for diluents and intravenous solutions</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<u>DOSAGE FORMS AND STRENGTHS</u> 21 CFR 201.57(a)(8)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Comment/Recommendation: We added the dosage form per 21 CFR 201.57(a)(8) <i>The Applicant revised as requested</i></p> <p>Revise to the appropriate package type term. The appropriate package-type term for this product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. <i>The Applicant revised as requested</i></p>	
Full Prescribing Information	
<u>2 DOSAGE AND ADMINISTRATION</u> 21 CFR 201.57(c)(3)(iv)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Comment/Recommendation: We added instructions for reconstituting the product, the resultant concentration (XX mg/mL). "Reconstitute CABLIVI before intravenous or subcutaneous administration using the provided syringe containing 1 mL Sterile Water for Injection, USP to yield a 11 mg/mL single-dose solution." <i>Applicant's response: The applicant proposes to delete this statement, as it is not possible for the HCP to check the concentration of the solution.</i> OBP labeling response: According to 21 CFR 201.57(c)(3)(iv), this section of labeling must</p>	

contain specific direction on dilution, preparation including the strength of the final dosage solution, when prepared according to instructions, in terms of milligram of active ingredient per milliliter of reconstituted solution.

The applicant revised as requested.

We relocated

(b) (4)

The Applicant relocated as requested

(b) (4)

3 DOSAGE FORMS AND STRENGTHS

21 CFR 201.57(c)(4)

No
 Yes
 N/A

Comment/Recommendation: We added identifying characteristic of the dosage form per 21 CFR 201.57(c)(4)

The Applicant revised as requested

11 DESCRIPTION

(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

No
 Yes
 N/A

Comment/Recommendation: We deleted (b) (4) from this first paragraph since this paragraph discusses drug substance.

The Applicant revised as requested

We added the pharmacological or therapeutic class of the drug per 21 CFR 201.57(c)(12)

The Applicant revised as requested

We added the dosage form per 21 CFR 201.57(c)(12)

The Applicant revised as requested

We listed the inactive ingredients in alphabetical order (see USP General Chapters <1091> Labeling of inactive ingredients.

The Applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING

21 CFR 201.57(c)(17)

No
 Yes
 N/A

Comment/Recommendation: we added the dosage form and identifying characteristics of the dosage form per 21 CFR 201.57(c)(17).

The Applicant revised as requested

Ensure that the NDC number for the vial is listed
The Applicant revised as requested

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]

[REDACTED] The HOW SUPPLIED/STORAGE AND HANDLING section may include summary statement with a cross-reference to this information in DOSAGE AND ADMINISTRATION section, e.g., "Store reconstituted solutions of DRUG-X at Y temperature [*see Dosage and Administration (2.x)*]."
The Applicant revised as requested

MANUFACTURER INFORMATION

21 CFR 610.61, 21 CFR 610.64

- No
- Yes
- N/A

Comment/Recommendation: We added a placeholder for the US license number which must be included per 21 CFR 610.61(b)
The Applicant revised as requested

INSTRUCTIONS FOR USE

TITLE (NAMES AND DOSAGE FORM)

- No
- Yes
- N/A

Comment/Recommendation: We revised the dosage form from [REDACTED] (b) (4) to the appropriate dosage form for this product "for injection".
The Applicant revised as requested

STORAGE AND HANDLING

- No
- Yes
- N/A

Comment/Recommendation: We added "unopened" for clarification: "Unopened Cablivi vial may also be stored at room temperature (up to 30°C or 86°F) for up to two months"
The Applicant revised as requested

We revised to USP nomenclature: 1 mL Sterile Water for Injection, USP
The Applicant revised as requested

INGREDIENTS

- No
- Yes
- N/A

MANUFACTURER INFORMATION

21 CFR 610.61, 21 CFR 610.64

- No
- Yes
- N/A

Comment/Recommendation: We added a placeholder for the US license number which must be included per 21 CFR 610.61(b) and included the qualifying phrase for the license manufacturer statement
The Applicant revised as requested



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 2/06/2019 09:49:22AM
GUID: 50814c7000007a3d59329f660d8ddf02



Jacek
Cieslak

Digitally signed by Jacek Cieslak
Date: 2/06/2019 10:01:19AM
GUID: 508da6da000265ae26d11a28833fbeba

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

Date of This Memorandum: February 1, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761112
Product Name and Strength: Cablivi
(caplacizumab)
for Injection
11 mg per vial
Applicant/Sponsor Name: Ablynx NV
FDA Received Date: January 31, 2019
OSE RCM #: 2018-1338-2 and 2018-1803-2
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels (diluent syringe and drug vial) and carton labeling for Cablivi (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We note the strength of the product was revised based on the recommendation by the Office of Product Quality (OPQ) to more accurately represent the deliverable amount of product and extractable volume after reconstitution. The strength of Cablivi is now 11 mg per vial.^b

^a Garrison N. Label and Labeling Review for CABLIVI (BLA 761112). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 21. RCM No.: 2018-1338-1 and 2018-1803-1.

^b Division of Hematology Products Late-Cycle Meeting Minutes. Silver Spring (MD): FDA, CDER, OND, DHP (US); 2018 December 7.

2 CONCLUSION

The revised container labels (diluent syringe and drug vial) and carton labeling for Cablivi are acceptable from a medication error perspective. We have no further recommendations at this time.

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

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

/s/

NICOLE B GARRISON
02/01/2019 12:26:23 PM

HINA S MEHTA
02/01/2019 10:47:47 PM