CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761145Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: April 24, 2020

To: Kimberly Scott, RN, BSN, OCN, Senior Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Stacy Shord, PharmD, BCOP, Associate Director for Labeling, (DHM2)

From: Adesola Adejuwon, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

BLA: 761145

In response to DHM2 consult request dated September 8, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original BLA submission for DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use (Darzalex Faspro).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHM2 (Kimberly Scott) on April 17, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on April 24, 2020.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at (240) 402-5773 or Adesola.Adejuwon@fda.hhs.gov.

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ADESOLA F ADEJUWON
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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:	April 24, 2020
To:	Kimberly Scott, RN, BSN, OCN Senior Regulatory Project Manager **Division of Hematologic Malignancies 2 (DHM2)**
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)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	DARZALEX FASPRO (daratumumab and hyaluronidase-fihj)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761145
Applicant:	Janssen Research and Development, LLC.

1 INTRODUCTION

On July 12, 2019, Janssen Biotech, Inc. submitted for the Agency's review an original Biologic License Application (BLA) 761145 DARZALEX FASPRO (daratumumab and hyaluronidase-fihj). This original BLA proposes to support the use of subcutaneous daratumumab co-formulated with recombinant human hyaluronidase for the treatment of adult patients with multiple myeloma.

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 September 6, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DARZALEX FASPRO (daratumumab and hyaluronidase-fihj).

2 MATERIAL REVIEWED

- Draft DARZALEX FASPRO (daratumumab and hyaluronidase-fihj) PPI received on July 12, 2019, and received by DMPP and OPDP on April 16, 2020.
- Draft DARZALEX FASPRO (daratumumab and hyaluronidase-fihj) Prescribing Information (PI) received on July 12, 2019, and received by DMPP and OPDP on April 16, 2020.

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 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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04/24/2020 09:22:21 AM

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:	March 30, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761145
Product Name and Strength:	Darzalex Faspro (daratumumab and hyaluronidase-fihj) Injection, 1,800 mg and 30,000 units/15 mL
Applicant/Sponsor Name:	Janssen Research & Development, LLC
OSE RCM #:	2019-1486-2 and 2019-1490-2
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on March 20, 2020 for Darzalex Faspro. We reviewed the revised carton labeling for Darzalex Faspro (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 determined the container label was acceptable in our previous label and labeling review memo.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Iverson N. Human Factors Label and Labeling Review Memo for Darzalex Faspro (BLA 761145). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 11. RCM No.: 2019-1486-1 and 2019-1490-1.

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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:	March 11, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761145
Product Name and Strength:	Darzalex Faspro (daratumumab and hyaluronidase-fihj) Injection, 1,800 mg and 30,000 units/15 mL
Applicant/Sponsor Name:	Janssen Research & Development, LLC
OSE RCM #:	2019-1486-1 and 2019-1490-1
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 9, 2020 for Darzalex Faspro. We reviewed the revised container label and carton labeling for Darzalex Faspro (Appendix A) to determine if they were 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 container label is acceptable from a medication error perspective; however the revised carton labeling is unacceptable from a medication error perspective. The administration time is missing on principal display panel of the carton labeling, which may help mitigate administration errors.

3 RECOMMENDATIONS FOR JANSSEN RESEARCH & DEVELOPMENT, LLC

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

A. Carton Labeling

[a] Smith J. Label and Labeling Review for Darzalex Faspro (BLA 761145). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); YYYY MON DD. RCM No.: XXXX-XX.

1. In your use-related risk analysis, you have acknowledged the potential clinical consequence of administering Darazalex Faspro as an intravenous infusion, which may cause an overdose and lead to adverse events (e.g. infusion reaction). Considering this risk, we have determined that including the administration time on the principal display panel of the carton labeling should be used as a mitigation strategy to help prevent wrong route administration errors. Therefore, we recommend you revise the statement, "For Subcutaneous Use Only" to "For Subcutaneous Use Only. Administer subcutaneous injection over 3 to 5 minutes." on the principal display panel of the carton labeling.

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HUMAN FACTORS 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:	January 21, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761145
Product Name, Dosage Form, and Strength:	Darzalex Faspro (daratumumab and hyaluronidase-xxxx) Injection, 1,800 mg and 30,000 units/15 mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Research & Development, LLC.
FDA Received Date:	July 12, 2019 and November 13, 2019
OSE RCM #:	2019-1486 and 2019-1490
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

As part of the approval process for BLA 761145 Darzalex Faspro (daratumumab and hyaluronidase-xxxx) injection, 1,800 mg and 30,000 units/15 mL), this review evaluates the proposed container label, carton labeling, Patient Information, Prescribing Information (PI) Use-Related Risk Analysis, and Human Factors (HF) study results for areas that may lead to medication errors.

1.1 PRODUCT BACKGROUND

Darzalex (daratumumab) approved under BLA 761036 on November 16, 2015 is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Darzalex is currently available as 100 mg/5 mL and 400 mg/20 mL single-dose vials for intravenous infusion. The recommended dose of Darzalex is 16 mg/kg actual body weight according to a dosing schedule (see Appendix A).

The proposed product, Darzalex Faspro is a co-formulation of the currently approved Darzalex (daratumumab) and recombinant hyaluronidase. Darzalex Faspro [redacted] (b) (4) is administered as a fixed dose (1,800 mg and 30,000 units/15 mL) subcutaneously in the abdomen over 3 to 5 minutes (see Appendix A).

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

We provided written HF comments to Janssen through a Type C meeting on September 20, 2016 under IND 125541, recommending they submit a comprehensive risk analysis and plans for a HF validation study.

Subsequently, in a briefing package for a Type C meeting on June 28, 2018[a], Janssen submitted a CMC Information Amendment which included a clinical product risk assessment.

We provided additional HF comments to Janssen through a Type C meeting on December 13, 2018 under IND 125541, reiterating that they submit a comprehensive risk analysis for the proposed daratumumab/recombinant human hyaluronidase subcutaneous formulation as a part of the BLA submission.

On August 8, 2019, Janssen submitted a use-related risk analysis, product differentiation and label comprehension HF study report, which is the subject of this review.

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

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Use-Related Risk Analysis and Human Factors Study Report	C
ISMP Newsletters*	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters 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

The sections below provide our evaluation of the summary of the study design, product differentiation and label comprehension study results, PI, container label, carton labeling for the proposed Darzalex Faspro injection.

[a] DMEPA was not consulted and did not review the risk assessment at that time.

3.1 SUMMARY OF STUDY DESIGN

The study design followed a simulated use methodology with the goal to ensure the intended users can differentiate between the product presentations, by selecting the correct medication, correct dose strength, and identify the correct route of administration. The study also evaluated comprehension of the product's carton labeling, vial label, and PI to assess the user's understanding of dosing and administration procedures. The study included 16 pharmacists/ pharmacy technicians as well as 16 nurses. The study evaluated two differentiation tasks: 1) A pharmacist/pharmacy technician identifies the correct product among the two presentations of Darzalex and one presentation of Darzalex Faspro based on a prescription; and 2) a nurse verifies the medication supplied by the pharmacy by checking it against the prescription. Following the differentiation tasks, all participants completed a label comprehension questionnaire assessing the user's understanding of label and labeling for Darzalex Faspro. For any observed errors, the moderator probed for root cause and subjective feedback of the use error to determine root cause. We find the overall methodology acceptable.

3.2 ANALYSIS OF PRODUCT DIFFERENTIATION AND LABEL COMPREHENSION STUDY RESULTS

All participants completed the product differentiation tasks successfully. Table 2 describes the errors/close calls/use difficulties observed in the label comprehension study, the Sponsor's reporting of the results and proposed mitigations, and DMEPA's analyses and recommendations.

Table 2: Summary and Analyses of Study Results

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Question #7 What should you inspect the vial contents for?	Close calls =6 Two nurses (P6 and P9), one pharmacist (P20), and one pharmacy technician (P22) provided a partial answer (i.e. product color, colorless to yellow, etc.) in response to the questions. Two nurses (P21 and P 24) did not understand the question. Use error= 1 One pharmacist (P1) provided a partial answer.	*Close calls* Did not understand the question (P9) After the question was clarified answers from these participants included particulate matter (P6, P20 and P22). Question 7 was clarified to, "What should you inspect the vial contents for **prior to injection**?" The participants provided answers based on experience. Participants were able to provide the correct answer when instructions were clarified to base answers on the PI, Carton, and Vial. *Use error* One participant (P1) initially provided a partially correct answer to the question which was not clarified.	A mitigation strategy was not required as the use errors were primarily due to how the question was asked. No further changes are required to improve the saliency of the information.	We note that lack of inspection of the vial contents could result in use of product that has unacceptable product quality. Participants were able to state the correct information once the question was clarified. Our review of Section 2.4 *Preparation, Storage, and Administration* of the PI concluded that the information is available as it indicates, "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration or other foreign particles are present." Inspecting the solution prior to administration is considered best practice for all products

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				administered parenterally. We do not have any recommendations to further mitigate the risk and we find the residual risk acceptable.
Question #8 What material of syringe is this product compatible with?	Use error= 1 One nurse provided the incorrect answer (P9)	Participant replied "unsure" because they were not able to find the answer. When shown the location of the information, the participant said that the content was clear.	Current location of material compatibility in the PI is most optimal and similar to that for other injectable prescription drugs. No further changes are required to improve the saliency of the information.	Failure to use the proper syringe can result in administration of a product with degraded quality. The participant provided an incorrect answer because they were unable to find the information. However, once shown the information, they understood the content. Our review of Section 2.4 *Preparation, Storage, and Administration* of the PI concluded that compatibility information is available as it indicates, "DARZALEX Faspro is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				injection needles." Based on the root cause analysis and subjective feedback, we recommend including a sub-heading, "Preparation" to bring prominence to the preparation instructions. This may help to minimize the risk for this instruction being overlooked.
Question #9 What material of winged infusion set is this product compatible with?	Use errors= 2 One nurse (P9) provided the incorrect answer. One pharmacy technician did not provide an answer (P23).	One participant (P9) provided incorrect answer ("polypropylene barrel with polypropylene or polyethylene plunger") because they could not locate the correct information ("PVC"). When shown the location of the correct information, the participant said that the content was clear. Another participant (P23) could not find the information. When shown the location of the information, the participant said that the content was clear.	Current location of material compatibility in the PI is most optimal and similar to that for other injectable prescription drugs. No further changes are required to improve the saliency of the information.	Failure to use the correct infusion set may result in administration of a product with degraded quality. We note that participants provided incorrect answers because they were unable to find the information. However, once shown the information, they understood the content. Our review of Section 2.4 *Preparation, Storage, and Administration* of the PI concluded that compatibility information is available as it indicates, "DARZALEX Faspro is compatible with polypropylene or

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles." Based on the root cause analysis and subjective feedback, we recommend including a sub-heading, "Preparation" to bring prominence to the preparation instructions. This may help to minimize the risk for this instruction being overlooked.
Question #10 How long can the product be stored at ambient temperature after transfer to the syringe?	Close call = 1 One nurse (P2) did not understand the question. Use error=1 One nurse (P27) did not provide an answer.	*Close call* One participant (P2) responded "24 hours" and asked for further clarification of the question. Question was clarified to mean time period "after transfer to the syringe". With this clarification, participant provided correct answer ("4 hours").	Per feedback from study participants to improve flow of information in section 2.4 of the PI, storage information was relocated to precede the Administration section. This update is minor and does not	Failure to properly store the product may result in administration of a product with degraded quality. One participant was able to state the correct information once the question was clarified. The other participant was unable to find the information. However, once shown the information, they understood the content.

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		Use error Another participant (P27) left the answer blank because they could not find the answer. When shown the location of the answer, the participant said that the content was clear but suggested that information be moved to precede the Administration" steps.	require further validation.	Our review of Section 2.4 *Preparation, Storage, and Administration* of the PI concluded that information is available as it indicates, "If the syringe containing DARZALEX Faspro is not used immediately, store the DARZALEX Faspro solution for up to 4 hours at ambient temperature and ambient light." We do not have any recommendations to mitigate the risk for this use error and we find the residual risk acceptable.
Question #11 What can be done to prevent clogging?	Use errors= 4 Two nurses (P31 and N6), one pharmacist (P1), and one pharmacy technician (P23) provided an incorrect answer.	One participant (P1) provided "Equilibrate to ambient temperature". One participant (N6) responded with "Pause or slow down delivery for pain or 2nd site".	Per feedback from study participants to improve flow of information in section 2.4 of the PI, information about what to do if the needle clogged was relocated to precede the Administration section. This update	Failure to prevent clogging may result in no dose or delay in dose administration if the syringe clogs. We note that participants provided incorrect answers because they were unable to find the information. One participant stated this instruction was not where they expected it because it was buried after a sentence of a different topic. However, once

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		Another participant (P23) responded "Never redraw". One participant P31 responded "Administer over 3-5 minutes, do not freeze, or let sit for more than 4 hours". All participants (P1, N6, P23, P31) did not notice instructions to attach needle or infusion set immediately prior to injection. P23 stated that this instruction was not where they expected it; it was buried after a sentence of a different topic and was not noticed. When shown the location of the information, all participants understood the information.	is minor and does not require further validation.	shown the information, they understood the content. Per feedback from the study participants, the Applicant relocated the statement, "To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection." to precede the Administration section (in the "Preparation" section). Our review of Section 2.4 *Preparation, Storage, and Administration* of the PI conclude this information has been relocated to precede the administration section. The Applicant determined that this change can be implemented without further validation. Based on our post marketing experience with similar products, we agree with the Applicant's mitigation

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				strategy. We do not have any recommendations to further mitigate the risk and we find the residual risk acceptable.
Question #15 How should you dispose of waste material?	Use errors= 2 One pharmacist (P20) and one pharmacy technician (P23) provided an incorrect answer.	Both participants were unable to locate information on how to dispose of waste material. P20 responded with "chemo waste" and P23 responded red/blue bin" per their facility regulations. When shown the location of the information, both participants understood the information but indicated that it was not where they expected; it was at the end of the entire section with no header.	Current location of disposal instructions in the PI is most optimal. No further changes are required to improve the saliency of the information.	Failure to dispose of waste material appropriately may result in improper disposal of the product. We note that participants provided incorrect answers because they were unable to find the information. However, once shown the information, they understood the content. Our review of Section 2.4 *Preparation, Storage, and Administration* of the PI concluded that disposal information is available as it indicates, "Any waste material should be disposed in accordance with local requirements." We identified no further mitigations are recommended because there is no special handling required and this task is not unique to this product.

Tasks (include C for critical and E for essential)	Number and Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				We do not have any recommendations to mitigate the risk for these use errors and we find the residual risk acceptable.

3.3 LABELS AND LABELING

In addition to the HF label comprehension study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. Our evaluation of the proposed Darzalex Faspro PI, Patient Information, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. We note areas of labels and labeling that can be improved to minimize the risk for medication errors and the PI can be revised to improve clarity and emphasis of important information. There were some errors observed in the HF label comprehension study that can be attributed to lack of prominence of syringe and infusion set compatibility information in the PI. We have determined that further modifications are recommended to highlight the compatibility information. Based on our heuristic and expert review of the user interface and post marketing experience with known use errors of similar products, we have also determined that further modifications to the labels and labeling are suggested to bring prominence to the route of administration and administration technique. We have determined that these changes can be implemented without additional validation testing. Tables 3 and 4 below include the identified medication error issues with the submitted label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3 . Identified Issues and Recommendations for Division of Hematologic Malignancies 2 (DHM 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The route of administration is expressed with a negative statement.	Post-marketing reports indicate that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action."	Remove the statement, "**Do not administer intravenously**."
2.	We note inconsistency in the expression of the dose. In the Highlights of Prescribing Information, the recommended dose is expressed as 15 mL; however, in the Full Prescribing Information,	We recommend expressing the dose consistently throughout the Prescribing Information.	Revise the statement, "Administer 15 mL Darzalex Faspro (1,800 mg daratumumab and 30,000 units hyaluronidase) into the subcutaneous tissue of abdomen over 3 to 5 minutes according to the recommended schedule." to:

Table 3 . Identified Issues and Recommendations for Division of Hematologic Malignancies 2 (DHM 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	the recommended dose is expressed as 1,800 mg/30,000 units.		"The recommended dose of Darzalex Faspro is 1,800 units/30,000 units (1,800 daratumumab and 30,000 units hyaluronidase) administered subcutaneously in the abdomen over 3 to 5 minutes according to the recommended schedule."
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In section 2.1, , *Recommended Dose and Schedule*, the route of administration is expressed with a negative statement.	Post-marketing reports indicate that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action."	Remove the statement, "**Do not administer intravenously**."
2.	In section 2.2, *Recommended Concomitant Medications*, the dose of acetaminophen is expressed as "1000 mg" and appears with a comma.	Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".	Revise the dose of acetaminophen to include a comma, for example, to read as 1,000 instead of 1000.
3.	In section 2.2, *Recommended Concomitant Medications*, confusing symbols (e.g., "≤") are used.	The use of an error prone symbol may lead to misinterpretation and confusion.	Replace the symbol "≤"with the intended meaning.
4.	The compatibility of the syringe material and infusion winged set is important information and may be overlooked.	The first bullet in Section 2.4 *Preparation, Storage, and Administration* advises, "Darzalex Faspro is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC)	We recommend including a sub-heading, "Preparation" to bring prominence to the preparation instructions. This may help to minimize the risk for this instruction being overlooked.

Table 3 . Identified Issues and Recommendations for Division of Hematologic Malignancies 2 (DHM 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		subcutaneous infusion sets; and stainless steel transfer and injection needles." Participants provided subjective feedback in the HF label comprehension study stating that this information was overlooked.	
5.	We note that although the Prescribing Information states the compatible syringe, infusion sets, and needle materials, it does not clearly state the product should be withdrawn into a syringe from the vial.	Lack of clear preparation guidance may lead to product administration and preparation errors.	We recommend relocating the statement, "Darzalex Faspro is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles." to appear as the fourth bullet to improve the flow of information. We also recommend including the statement, "Withdraw the necessary amount into a syringe" in the fourth bullet in Section 2.4 *Preparation, Storage and Administration* to provide clear preparation guidance for healthcare professionals.
6.	The vial has a peel-off label that should be attached to the syringe after the product is withdrawn from the vial; however this information is not communicated in the PI.	The peel-off label is used as a tool to mitigate wrong administration errors as it is clearly labeled "For subcutaneous use only".	We recommend that this important information be conveyed in the PI by revising the statement in Section 2.4 *Preparation, Storage, and Administration*, (b) (4) " To as follows: " (b) (4) After the solution of Darzalex Faspro is withdrawn

Table 3 . Identified Issues and Recommendations for Division of Hematologic Malignancies 2 (DHM 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			from the vial and into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker."
7.	In section 2.4, *Preparation, Storage, and Administration,* the administration technique is expressed with a negative statement.	Post-marketing reports indicate that negative statements (e.g. do not) may have the opposite of the intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative action."	Revise the statement, "Do not inject DARZALEX Faspro at other sites of the body as no data are available." to "No data are available on performing the injection at other sites of the body."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage information lacks clarity.	Lack of clarity of the storage information may lead to product storage errors.	Revise the storage statement to appears as, "Store Darzalex Faspro vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake."
Patient Information			

Table 4. Identified Issues and Recommendations for Janssen Research & Development, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date 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

Table 4. Identified Issues and Recommendations for Janssen Research & Development, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			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.
2.	The Rx Only statement is prominent.	The Rx Only statement appears prominent on the principal display panel.	Decrease the prominence by debolding the Rx Only statement.
3.	The storage information lacks prominence.	Lack of prominence of the storage information may result in product storage errors.	If space permits, revise the storage information as follows, "**Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.**
4.	The usual dosage statement on the container label and carton labeling is inconsistent with the PI.	The dosage statement should be consistent across the labels and labeling.	Revise the statement, "Usual Dosage: See package insert for full prescribing information." to "Dosage: See Prescribing Information.".
5.	Darzalex Faspro should only be administered subcutaneously which differs from the currently approved product, Darzalex which is administered intravenously.	We are concerned about the risk of administering Darzalex Faspro via an intravenous route of administration.	Revise the statement "For Subcutaneous Use" to "For Subcutaneous Use only. Administer subcutaneous injection over 3 to 5 minutes".
Container Label			
1.	The container label the numbers, "AW_159706" located in close proximity of the lot number.	The close proximity of the numbers, "AW_159706"may cause them to be mistaken for the lot number.	If possible, relocate the numbers, "AW_159706" away from the expiration date to mitigate the

Table 4. Identified Issues and Recommendations for Janssen Research & Development, LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			risk for confusion with the lot number.
2.	The administration time is omitted from the peel-off-sticker on the container label.	The peel-off label is used as a tool to mitigate wrong administration errors as it is clearly labeled "For subcutaneous use only". Post marketing reports indicate that including the administration time may also bring prominence to this important information to ensure it is not overlooked.	Revise the peel-off sticker to include the text, " For subcutaneous use only. Administer subcutaneous injection over 3-5 minutes".
Carton Labeling			
1.	As currently presented, the proprietary name and proper name lack prominence on the principal display panel of the carton labeling.	The proprietary name and proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel. Applicants should choose a font that is easy to read, not lightweight or condensed. Lastly, the color contrast between the text and the carton labeling background color should be chosen to afford adequate legibility of the text.	Increase the prominence of the proprietary name and proper name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence.
2.	The net quantity statement does not appear on the principal display panel of the carton labeling.	Missing the net quantity statement from the principal display panel may result in confusion regarding the contents of the carton.	Revise and relocate the statement, "Single-dose vial. Discard unused portion." to "One Single-dose vial. Discard unused portion." to the principal display panel of the carton labeling.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Darzalex Faspro container label and carton labeling identified areas of vulnerability that may lead to medication errors. The HF results and subjective feedback from study participants demonstrated that further revisions were needed to the Prescribing Information to ensure clarity and prominence of the information. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to Janssen Research & Development, LLC. so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Darzalex Faspro received on August 8, 2019 from Janssen Research & Development, LLC., and Darzalex.

Table 2. Relevant Product Information for Darzalex Faspro and Darzalex

Product Name	**Darzalex Faspro**	**Darzalex**[b]
Initial Approval Date	N/A	November 16, 2015
Nonproprietary Name	daratumumab and hyaluronidase-xxxx	daratumumab
Indication	The treatment of adult patients with multiple myeloma: • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy. • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients	The treatment of adult patients with multiple myeloma: • in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy. • in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.

[b] Darzalex [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 SEP 26. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761036s024lbl.pdf.No

	who are ineligible for autologous stem cell transplant. • in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy • in combination with pomalidomide and dexamethasone (b) (4) • as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.	• in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant. • In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy. • in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. • as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
Route of Administration	Subcutaneous	Intravenous
Dosage Form	Injection	
Strength	1,800 mg and 30,000 units/15 mL)	100 mg/5 mL and 400 mg/20 mL
Dose and Frequency	The recommended dose of Darzalex Faspro is 1,800 mg/30,000 units administered subcutaneously over 3-5 minutes, according to the following dosing schedule: (b) (4)	The recommended dose of Darzalex is 16 mg/kg administered as an intravenous infusion, according to the following dosing schedule: **Combination with lenalidomide or pomalidomide (4-week cycle dosing regimens) and low dose-dexamethasone and for monotherapy** **Weeks** | **Schedule**

(b) (4)

Combination with bortezomib, melphalan and prednisone, ([VMP]6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	Weekly (total of 6 doses)
Weeks 7 to 54[a]	Every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	Every four weeks

a First dose of the every-2-week dosing schedule is given at Week 7

b First dose of the every-4-week dosing schedule is given at Week 55

Combination with Bortezomib and dexamethasone, (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	Weekly (total of 9 doses)
Weeks 10 to 24[a]	Every three weeks (total of 5 doses)
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24[a]	Every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	Every four weeks

a First dose of the every-2-week dosing schedule is given at Week 9

b First dose of the every-4-week dosing schedule is given at Week 25

Combination with bortezomib, melphalan and prednisone, ([VMP]6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	Weekly (total of 6 doses)
Weeks 7 to 54[a]	Every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	Every four weeks

a First dose of the every-2-week dosing schedule is given at Week 7

b First dose of the every-4-week dosing schedule is given at Week 55

Combination with Bortezomib and dexamethasone, (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	Weekly (total of 9 doses)
Weeks 10 to 24[a]	Every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	Every four weeks

<table>
<tr>
<td></td>
<td>
<table>
<tr><td>Week 25 onwards until disease progression[b]</td><td>Every four weeks</td></tr>
</table>
a First dose of the every-2-week dosing schedule is given at Week 10
b First dose of the every-4-week dosing schedule is given at Week 25
</td>
<td>
a First dose of the every-2-week dosing schedule is given at Week 10
b First dose of the every-4-week dosing schedule is given at Week 25
Combination with Bortezomib, Thalidomide and dexamethasone, ([VTd]; 4-week cycle dosing regimen)
<table>
<tr><th>Treatment phase</th><th>Weeks</th><th>Schedule</th></tr>
<tr><td rowspan="2">Induction</td><td>Weeks 1 to 8</td><td>Weekly (total of 8 doses)</td></tr>
<tr><td>Weeks 6 to 16[a]</td><td>Every two weeks (total of 4 doses)</td></tr>
<tr><td colspan="3">Stop for high dose chemotherapy and ASCT</td></tr>
<tr><td>Consolidation</td><td>Weeks 1 to 8[b]</td><td>Every two weeks (total of 4 doses)</td></tr>
</table>
a First dose of the every-2week dosing schedule is given at Week 9
b First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT
</td>
</tr>
<tr>
<td>How Supplied</td>
<td>1,800 mg daratumumab and 30,000 units hyaluronidase human per 15 mL sine-dose vial</td>
<td>

100 mg/5 mL single-dose vial
400 mg/20 mL single-dose vial

</td>
</tr>
<tr>
<td>Storage</td>
<td>Store DARZALEX Faspro in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light.

Do not freeze or shake. This product contains no preservative.</td>
<td>Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
Do not freeze or shake. Protect from light. This product contains no preservative.</td>
</tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 10, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, hyaluronidase. Our search identified 6 previous reviews[c,d,e,f g, h], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Garrison, N. Label and Labeling Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUNE 20. RCM No.: 2016-1980-2 and 2017-59-2.

[d] Garrison, N. Label and Labeling Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUNE 15. RCM No.: 2016-1980-1 and 2017-59-1.

[e] Garrison, N. Label and Labeling Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MARCH 13. RCM No.: 2016-1980 and 2017-59.

[f] Garrison, N. Postmarket Medication Error Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 14. RCM No.: 2018-414.

[g] Gao, T. Use-Related Risk Analysis and Label and Labeling Review for Herceptin Hylecta (BLA 761106). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 17. RCM No.: 2018-918 and 2018-927.

[h] Garrison, N. Postmarket Medication Error Review for Rituxan Hycela (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 16. RCM No.: 2018-2367.

APPENDIX C. HUMAN FACTORS STUDY

C.1 URRA

\\cdsesub1\evsprod\bla761145\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-myeloma\5354-other-stud-rep\risk-analysis\commercial-prod-use.pdf

C.2 Results

\\cdsesub1\evsprod\bla761145\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-myeloma\5354-other-stud-rep\risk-analysis\ds-tec-146617.pdf

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 12, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Any of the Words: daratumumab hyaluronidase

D.2 Results

The search retrieved 5 articles that described medication errors or actions possibly associated with label and labeling for hyaluronidase.

One article recommended using barcode technology and to check the vial label to ensure that the drug being prepared and administered is subcutaneous Herceptin Hylecta and not intravenous trastuzumab or intravenous ado-trastuzumab emtansine. Also, affix a prominent auxiliary warning that states “Administer subcutaneously in the thigh,” on syringes containing Herceptin Hylecta, or utilize the peel -off sticker provided on the vial to label the syringe.[i]

Another article recommended educating oncologist and nurses who may administer Herceptin Hylecta and Rituxan Hycela about the possibility of administering them by the wrong route. In addition, the article mentioned educating nurses about the recommended procedure for administering the large subcutaneous doses of these drugs. To prevent wrong route errors, it is important to employ barcode technology and to check the vial label to ensure that the drug being prepared and administered is the subcutaneous-only formulation. Also, syringes containing Herceptin Hylecta should be labeled with a prominent auxiliary warning that states, “Administer subcutaneously in the thigh” (which is available as a peel off sticker on the vial); syringes containing Rituxan Hycela should include a prominent

[i] Institute for Safe Medication Practices. Herceptin Hylecta must be given subcutaneously. ISMP Med Saf Alert Acute Care. 2019 MAR 28;24(6):1-3.

auxiliary warning that states, “Administer subcutaneously in the abdomen.” If pharmacy-dispensed syringes are not labeled with these warnings, please request them.[j]

Two articles discussed several reports of concern that Rituxan Hycela might be confused with the intravenous form of ri**TUX**imab, Rituxan. Due to the large volume of the subcutaneous injection (11.7 mL or 13.4 mL), practitioners may easily rationalize that Rituxan Hycela should be administered as an intravenous push dose and not a subcutaneous injection make sure oncologists and nurses who may administer either form are educated about the possibility of administering the drug by the wrong route. The article also mentioned that nurses should be educated regarding the recommended procedure for administering the large subcutaneous dose of Rituxan Hycela. The products should be stored in a way that will clearly indicate that they are different formulations. In addition, pharmacies should dispense the Rituxan Hycela syringe, using an auxiliary sticker, which states, “FOR SUBCUTANEOUS USE ONLY.”[k,l]

One article recommended using barcode scanning to verify storage and administration of Rituxan Hycela. The article also advised to ensure the syringe includes a prominent auxiliary warning that states, “Administer subcutaneously in the abdomen.[m]

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[j] Institute for Safe Medication Practices. Rituxan Hycela and Herceptin Hylecta must be given subcutaneously, despite large dose volumes. ISMP Med Saf Alert Nurse Advise ERR. 2019 APR;17(4):1-2.

[k] Institute for Safe Medication Practices. Don’t confuse the IV and subcutaneous forms of riTUXimab. ISMP Med Saf Alert Nurse Advise ERR. 2018 JUN;16(6):1-2.

[l] Institute for Safe Medication Practices. Don’t confuse the IV and subcutaneous forms of riTUXimab. ISMP Med Saf Alert Acute Care. 2017 OCT 05;22(20):1,4.

[m] Institute for Safe Medication Practices. Don’t confuse Rituxan and Rituxan Hycela. ISMP Med Saf Alert Acute Care. 2019 JAN 17;24(1):2-3.

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,[n] along with postmarket medication error data, we reviewed the following Darzalex Faspro labels and labeling submitted by Janssen Research & Development, LLC..

- Container label received on July 12, 2019
- Carton labeling received on July 12, 2019
- Patient Information and Prescribing Information (Image not shown) received on November 13, 2019, available from \\cdsesub1\evsprod\bla761145\0007\m1\us\draft-labeling-text-dara-sc.pdf

G.2 Label and Labeling Images

Container label

[n] 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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