CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213586Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	April 28, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 213586
Product Name, Dosage Form, and Strength:	Uzedy[a] (risperidone) extended-release injectable suspension, 50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, and 250mg/0.7 mL
Applicant/Sponsor Name:	Teva Neuroscience (Teva)
TTT ID #:	2022-2733-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container (syringe) labels and carton labeling received on April 24, 2023 for Uzedy. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Uzedy (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 labels and labeling review.[b]

[a] This proposed proprietary name was found conditionally acceptable in the following DMEPA 1 Review: Holmes, L. Proprietary Name Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Jan 05. PNR ID No. 2022-1044724823.

[b] Holmes, L. Labels and Labeling Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Apr 03. TTT ID No.: 2022-2733.

2 CONCLUSION

Teva implemented all of our recommendations for the carton labeling.[c] However, Teva is (b) (4)

Additionally, in response to a follow-up question regarding the timeline for introducing the revised syringe labels, Teva stated, (b) (4) (b) (4) (b) (4) Teva agreed.[e] We have no additional recommendations regarding the carton labeling or syringe labels.

[c] We also note that responses from Teva to previous labels/labeling recommendations as stated in the following DMEPA 1 memorandum were implemented by Teva: Lee, S. Review of Revised Label and Labeling for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Apr 07. RCM No.: 2021-1234-1.

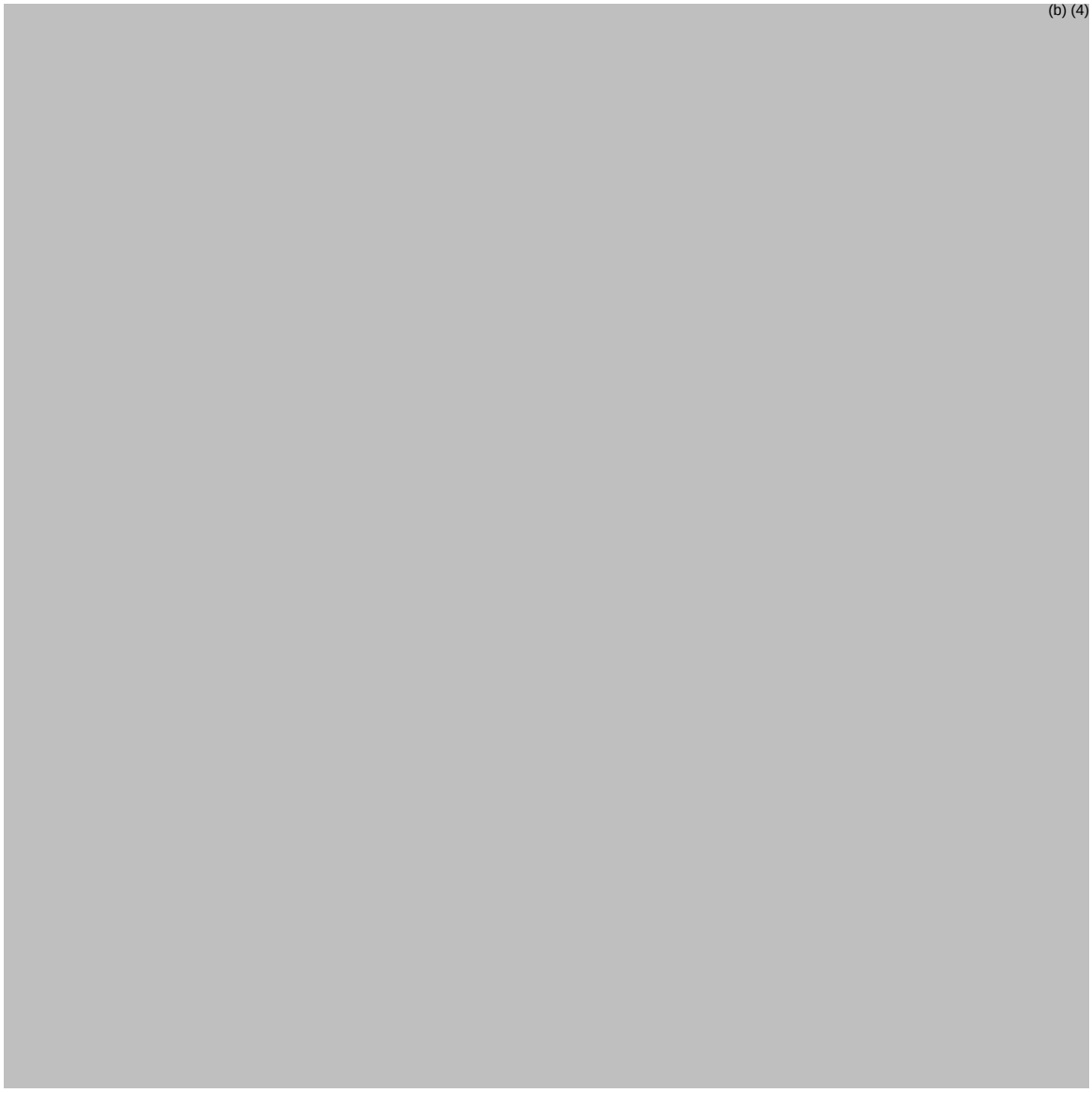
[d] See Appendix A for the full email communication from Teva.

[e] Sikka, S. Response to Information Request "[EXTERNAL] RE: NDA 213586 - FDA carton/container (b) (4) Message from Angela Randall. Silver Spring (MD): FDA, CDER, OND, DP (US); 2023 Apr 28.

APPENDIX A. IMAGES OF THE CARTON LABELING RECEIVED ON APRIL 24, 2023 AND THE EMAIL COMMUNICATION RECEIVED FROM TEVA ON APRIL 21, 2023

Container (syringe) Labels

(b) (4)



(b) (4)

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/s/

LORETTA HOLMES
04/28/2023 02:47:15 PM

MADHURI R PATEL
04/28/2023 02:58:25 PM

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

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

Memorandum

Date: April 19, 2023

To: Simran Parihar, Regulatory Project Manager, Division of Psychiatry (DP)

Roberta Rasetti, Clinical Reviewer, DP

Kimberly Updegraff, Associate Director for Labeling, DP

From: Aline Moukhtara, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for UZEDY™ (risperidone) extended-release injectable suspension, for subcutaneous use

NDA: 213586

Background:
In response to DP's consult request dated December 21, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for UZEDY™ (risperidone) extended-release injectable suspension, for subcutaneous use (Uzedy).

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on March 29, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Aline Moukhtara at 301-796-2841 or Aline.Moukhtara@fda.hhs.gov.

46 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

ALINE M MOUKHTARA
04/19/2023 02:40:42 PM

LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	April 3, 2023
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 213586
Product Name, Dosage Form, and Strength:	Uzedy[a] (risperidone) extended-release injectable suspension, 50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, and 250mg/0.7 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Teva Neuroscience (Teva)
FDA Received Date:	October 28, 2022 and March 13, 2023
TTT ID #:	2022-2733
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

[a] This proposed proprietary name was found conditionally acceptable in the following DMEPA 1 Review: Holmes, L. Proprietary Name Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Jan 05. PNR ID No. 2022-1044724823.

1 REASON FOR REVIEW

As part of the approval process for Uzedy (risperidone) extended-release injectable suspension, the Division of Psychiatry (DP) requested that we review the proposed Uzedy Prescribing Information (PI), syringe labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 213586 is a 505(b)(2) NDA and the listed drug product is Risperdal (risperidone) tablets, NDA 020272. The application was initially submitted on June 17, 2021. A Complete Response Letter (CRL) was issued on April 15, 2022 for clinical reasons. In response, the Applicant submitted a class 2 resubmission of the application on October 28, 2022.

2 MATERIALS 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
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Prescribing Information (PI), syringe labels, and carton labeling, identified areas where the syringe labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Teva Neuroscience. Our evaluation of the PI did not identify areas of vulnerability that may lead to medication errors.

We note that a Human Factors Validation Study was completed for this product. The study results were reviewed under separate cover.[b]

[b] Lee, S. Human Factors Validation Study Report Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Mar 10. RCM No.: 2021-1234.

4 RECOMMENDATIONS FOR TEVA NEUROSCIENCE

Table 2. Identified Issues and Recommendations for Teva Neuroscience (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Syringe Labels and Carton Labeling			
1.	The established name "risperidone" is on the Agency's list of established names that are recommended to use the tall man lettering format.	The established name does not appear in tall man lettering format.	Revise the established name "risperidone" to read "risperiDONE" on the syringe labels and carton labeling. You may choose to refer to our guidance titled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
Carton Labeling			
1.	The "Usual Dosage" statement is not consistent with Section 2.1 of the PI which states "Recommended Dosage".	The "Usual Dosage" statement should be consistent with the PI.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read: "Recommended Dosage: See Prescribing Information".
2.	The Kit Contents information is not clear. It reads as follows: " (b) (4) (b) (4)	Lack of clarity may lead to confusion.	Revise the Kit Contents information to read: "One UZEDY (risperidone) extended-release injectable suspension prefilled syringe **and one** 21 gauge, 5/8-inch needle" or use similar verbiage. ((b) (4) (b) (4)
3.	The following statements are on the carton labeling: (b) (4) (b) (4)	The first statement is duplicative and, therefore, unnecessary. The second statement is confusing because the contents of the (b) (4)	Delete the statements: (b) (4) (b) (4)

Table 2. Identified Issues and Recommendations for Teva Neuroscience (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4)	

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Uzedy that Teva Neuroscience submitted on October 28, 2022.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Uzedy</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>risperidone</td></tr>
<tr><td>Indication</td><td>Treatment of schizophrenia in adults</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Extended-release injectable suspension</td></tr>
<tr><td>Strengths</td><td>50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL,
125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, and 250mg/0.7 mL</td></tr>
<tr><td>Dose and Frequency</td><td>To start Uzedy, switch from oral daily risperidone. Initiate Uzedy, as either a once monthly injection or a once every two month injection, the day after the last dose of oral therapy. See Table 1 to determine how to switch from oral risperidone to Uzedy once monthly (50 mg, 75 mg, 100 mg, or 125 mg) or once every 2 months (100 mg, 150 mg, 200 mg, or 250 mg) given via abdominal or upper arm subcutaneous injection. Neither a loading dose nor supplemental oral risperidone doses are recommended when switching. For patients who have never taken risperidone, establish tolerability with (b) (4) oral risperidone prior to initiating Uzedy.
Table 1: Dosage Recommendations for Switching from Daily Oral Risperidone to Uzedy
<table>
<tr><th>Prior Therapy</th><th>UZEDY Dosage Once Monthly</th><th>UZEDY Dosage Once Every Two Months</th></tr>
<tr><td>2 mg of oral risperidone per day</td><td>50 mg</td><td>100 mg</td></tr>
<tr><td>3 mg of oral risperidone per day</td><td>75 mg</td><td>150 mg</td></tr>
<tr><td>4 mg of oral risperidone per day</td><td>100 mg</td><td>200 mg</td></tr>
<tr><td>5 mg of oral risperidone per day</td><td>125 mg</td><td>250 mg</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Cartons containing one single-dose prefilled syringe and one 21 gauge, 5/8-inch needle</td></tr>
<tr><td>Storage</td><td>Store in refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. May be stored in unopened original packaging at room temperature, 68°F to 77°F (20°C to 25°C), for up to 90 days. If unopened, may be returned to refrigerated storage within 90 days. Once the carton is opened, administer Uzedy or discard.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 28, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 213586 and Uzedy. Our search identified three previous reviews and we confirmed that our previous recommendations were implemented.

- Lee, S. Human Factors Study Report Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Mar 10. OSE RCM No.: 2021-1234.

- Holmes, L. Labels and Labeling Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Mar 31. OSE RCM No.: 2021-1233.

- Lee, S. Revised Label and Labeling Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Apr 07. OSE RCM No.: 2021-1234-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Uzedy labels and labeling submitted by Teva Neuroscience.

- Syringe Labels received on October 28, 2022, available at: \\Cdsesub1\evsprod\NDA213586\0041\m1\us
- Syringe Tag received on October 28, 2022, available at: \\Cdsesub1\evsprod\NDA213586\0041\m1\us
- Carton labeling received on March 13, 2023 available at: \\Cdsesub1\evsprod\NDA213586\0046\m1\us
- Prescribing Information (image not shown) received on October 28, 2022, available at: \\CDSESUB1\EVSPROD\nda213586\0041\m1\us\draft-labeling-text-clean.pdf

F.2 Labels and Labeling Images (not to scale)

Syringe Labels

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

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LORETTA HOLMES
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MADHURI R PATEL
04/03/2023 11:12:35 PM

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

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

Memorandum

Date: April 19, 2022

To: Roberta Rasetti, MD, Clinical Reviewer
Division of Psychiatry (DP)

Mona Kalsi, PharmD, Regulatory Project Manager, (DP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Risperidone extended-release injectable suspension

NDA: 213586

This memo is in response to DP's labeling consult request dated July 8, 2021.

Reference is made to a Complete Response letter that was issued on April 17, 2022.

Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
04/19/2022 12:19:48 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	April 07, 2022
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 213586
Product Name and Strengths:	Uzedy (risperidone) extended-release injectable suspension, 50 mg/0.1 mL, 75 mg/0.2 mL, 100 mg/0.3 mL, 125 mg/0.4 mL, 150 mg/0.4 mL, 200 mg/0.6 mL, 250 mg/0.7 mL
Applicant Name:	Teva Neuroscience, Inc. (Teva)
OSE RCM #:	2021-1234-1
DMEPA 1 Safety Evaluator:	Seung Hoon Lee, BS
DMEPA 1 Associate Director of Human Factors:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU) and carton label on March 21, 2022 for Uzedy (risperidone). The Division of Psychiatry (DP) requested that we review the revised IFU and carton label for Uzedy (risperidone) (Appendix A) to determine if it is acceptable from a medication error perspective. The labeling revisions are in response to recommendations that we made during a previous human factors results review[1].

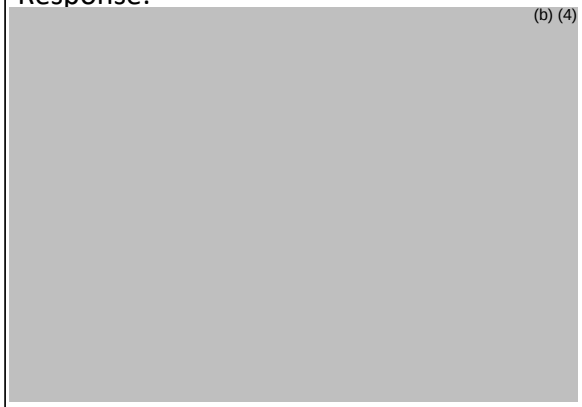
[1] Lee, S. Human Factors Results Review for Uzedy (risperidone) (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 10. RCM No.: 2021-1234.

2 RESPONSES FOR TEVA NEUROSCIENCE, INC.

Please see our responses to your information request response submitted on March 21, 2022 under NDA 213586, related to your revised instructions for use (IFU) and carton label for Uzedy (risperidone).

FDA Identified Issues and Recommendations for Human Factors Validation Study Results for Teva		
Original FDA Human Factors Validation Study Results Recommendation Information Request (IR) dated March 15, 2022	Applicant's IR response dated March 21, 2022	FDA Response to Applicant
IFU #1: The IFU does not include a warning statement that the product should not be frozen. We are concerned if the user freezes the product, there is a risk of injecting degraded or expired drug. The human factors (HF) validation study identified subjective feedback that indicated that the participant misinterpreted the statement "TRADENAME is solid at refrigerated (b) (4) temperature" to mean the product can be frozen. We recommend revising the IFU to include a warning statement that the product should not be frozen.	IFU #1: Applicant response to Agency (Seeking Agency confirmation): Response: Teva does not agree that a warning statement should be included to say the product should not be frozen. Teva believes this statement will create confusion as this product freezes/reaches solid state at 2-8°C; therefore, it would not be accurate to say "Do not freeze". Further, stability results already provided in the NDA in Section 3.2.P.8.1 (see Table 11 and Conclusion) demonstrate that the product tolerates freezing and temperature cycling.	IFU #1: We acknowledge your response and agree with your approach.
IFU #2: Step 5 does not include information to let the user know that if the task of flicking with a downward whipping motion to move the bubble to the cap of the prefilled syringe is omitted or not performed correctly this could result in a decreased amount of drug administration with consequent potential risk of symptom exacerbation. The task to "flick with downward whipping motion to move the bubble to the cap of the syringe" may be overlooked because the instruction does not	IFU #2: Applicant response to Agency (Seeking Agency confirmation): Response: Teva's position is that the current language in Step 5 addresses this concern already with the statement that "Failure to move the bubble to the cap of the syringe could result in incomplete dosage." Healthcare providers should have an understanding already that incomplete dosage could potentially result in reduced efficacy of the	IFU #2: We acknowledge your response and agree with your approach.

include the reason why this task is important. We recommend revising the IFU to include information to let the user know that if the task of flicking with a downward whipping motion to move the bubble to the cap of the prefilled syringe is omitted or not performed correctly that this could result in a decreased amount of drug administration with consequent potential risk of symptom exacerbation.	product. This is consistent with language in other approved products.	
IFU #3: Step 5 does not include information to let the user know how much force to use when flicking the prefilled syringe. We are concerned if this task is omitted or not performed correctly there is risk of underdose. The HF validation study identified subjective feedback that the participant was uncertain about the amount of force to use when flicking the syringe and was concerned with using too much force so they chose to flick the PFS using only the range of motion in his wrist. We recommend revising Step 5 to clearly emphasize on how much force to use when flicking the prefilled syringe.	IFU #3: Applicant response to Agency (Seeking Agency confirmation): Response: Teva proposes changes in Step 5 of the Instructions for Use that are intended to reinforce the forceful downward whipping motion and that this motion is to be performed with your full arm. The intent is to eliminate potential misunderstanding of this motion being in the wrist. Three locations have been revised (changes shown in bold), including 1) the second heading of Step 5 states “Flick Syringe Forcefully Three Times to Move the Bubble to the Cap”; 2). The first bullet under the second heading states “Flick with a forceful downward whipping motion of your full arm to move the bubble to the cap of the syringe”; and 3) The caption above the	IFU #3: We acknowledge your response and agree with your approach.

	second image states “Flick downwards forcefully with your full arm”.	
Carton #1: Carton labeling does not include information to let the user know that the IFU is embedded in the Prescribing Information (PI). We are concerned if the user does not locate the IFU, there is risk of incorrect use of the prefilled syringe. The HF validation study results identified subjective feedback that indicated that the participant did not locate IFU because they thought that the PI only included prescribing information and did not think it would include instructions. We recommend revising carton labeling to include information to let the user know that the IFU is embedded in the PI.	Carton #1: Applicant response to Agency (Seeking Agency confirmation): Response: (b) (4) 	Carton #1: We acknowledge your response and agree with your approach.
Carton #2: Carton labeling does not include an important information statement to let the user know that the product is viscous. We are concerned if the user is not informed on the viscosity of the product, there is risk of not delivering the full dose. The HF validation study results identified subjective feedback that indicated that the viscosity of the medication made the injection difficult. We recommend revising carton labeling to include an important information statement about the viscosity of the product.	Carton #2: Applicant response to Agency (Seeking Agency confirmation): Response: Teva is proposing changes to the inside panel of the carton to address this comment. Below the images on the inside panel, the following new statement will be added: (b) (4) 	Carton #2: We acknowledge your response and agree with your approach.

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/s/

SEUNG H LEE
04/07/2022 02:21:59 PM

JASON A FLINT
04/08/2022 11:05:31 AM

LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	March 31, 2022
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 213586
Product Name and Strength:	Uzedy[a] (risperidone) extended-release injectable suspension, 50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, and 250 mg/0.70 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Teva Neuroscience
FDA Received Date:	January 24, 2022, and March 21, 2022
OSE RCM #:	2021-1233
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

[a] The proposed name Uzedy was found conditionally acceptable in the following DMEPA review: Howard, C. Proprietary Name Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 Jan 11. PNR ID No. 2021- 1044724246.

1 REASON FOR REVIEW

As part of the approval process for Uzedy (risperidone) extended-release injectable suspension, the Division of Psychiatry (DP) requested that we review the proposed Uzedy syringe labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 213586 is a 505(b)(2) NDA. The listed drug is Risperdal (risperidone) tablets, NDA 020272.

2 MATERIALS 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 (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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 CONCLUSION AND RECOMMENDATIONS

We note that the DMEPA 1 Human Factors (HF) team evaluated the HF validation study results under separate cover and provided recommendations.[b] Teva submitted revised labels and labeling on March 21, 2022, in response to those recommendations. For this review, we reviewed the syringe labels submitted on January 24, 2022 as well as the revised carton labeling, revised 250 mg syringe label, and revised Prescribing Information submitted on March 21, 2022.

We find that the proposed syringe labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Teva Neuroscience.

[b] Lee, S. Human Factors Study Report Review for Uzedy (NDA 213586). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Mar 10. RCM No.: 2021-1234.

4 RECOMMENDATIONS FOR TEVA NEUROSCIENCE

Table 2. Identified Issues and Recommendations for Teva Neuroscience (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comment for All Syringe Labels and Carton Labeling			
1.	The primary statement of strength (e.g., (b) (4)) does not indicate the (b) (4)	The primary statement of strength is incomplete.	Revise the primary statement of strength from (b) (4) to read XX mg/XX mL (e.g., revise (b) (4) to read 50 mg/0.14 mL). With implementation of this revision, the secondary statement of strength below it (i.e., (b) (4)) is unnecessary and should be deleted. (b) (4)
Syringe Labels			
1.	The "Rx Only" statement is not on the labels	The "Rx Only" statement is required on the label.	Add the "Rx Only" statement.
2.	The expiration date format is not specified.	A clear expiration date format will minimize confusion and risk for deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, please specify 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 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-

Table 2. Identified Issues and Recommendations for Teva Neuroscience (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
3.	The route of administration is not on the labels.	The route of administration should be on the labels.	Add the route of administration to the labels.
Carton Labeling			
1.	There is no statement of dosage on the carton labeling.	The statement of dosage should be on the carton labeling.	Add a statement of dosage (e.g., "Recommended Dosage: See Prescribing Information") or use similar verbiage.
2.	It is not clear whether there is a human-readable and machine-readable (2D data matrix barcode) product identifier on the carton labeling.	Human-readable and machine-readable (2D data matrix barcode) product identifiers are used for identification and tracing purposes.	Please clarify whether a 2D data matrix barcode is on the carton labeling. If not present, we recommend that you review the Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021) to determine if the product identifier requirements apply to your product's labels. The guidance is available at: https://www.fda.gov/media/116304/download.
3.	The expiration date format is not specified.	A clear expiration date format will minimize confusion and risk for deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, please specify 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

Table 2. Identified Issues and Recommendations for Teva Neuroscience (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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 slash or a hyphen be used to separate the portions of the expiration date.
4.	The proprietary name, established name, and dosage form are on a side panel but the strength is missing (see example below). (b) (4)	The strength is product identifying information and should be present.	Add the strength (e.g., 50 mg/0.14 mL) to the side panel.
5.	The product is intended for administration by a healthcare professional.	The statement "For administration by a healthcare professional" is not on the carton labeling.	Add the statement "For administration by a healthcare professional" (or use similar verbiage) to the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Uzedy that Teva Neuroscience submitted on March 21, 2022.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Uzedy</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>risperidone</td></tr>
<tr><td>Indication</td><td>Treatment of schizophrenia</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Extended-release injectable suspension</td></tr>
<tr><td>Strengths</td><td>50 mg/0.1 mL, 75 mg/0.2 mL, 100 mg/0.3 mL, 125 mg/0.4 mL, 150 mg/0.4 mL, 200 mg/0.6 mL, 250 mg/0.7 mL</td></tr>
<tr><td>Dose and Frequency</td><td>To start Uzedy, switch from oral daily risperidone. Initiate Uzedy, as either a once monthly injection or a once every two month injection, the day after the last dose of oral therapy.

See Table 1 to determine how to switch from oral risperidone to Uzedy once monthly (50 mg, 75 mg, 100 mg, or 125 mg) or once every 2 months (100 mg, 150 mg, 200 mg, or 250 mg) given via abdominal or upper arm subcutaneous injection. Neither a loading dose nor supplemental oral doses are recommended when switching. For patients who have never taken risperidone, establish tolerability with (b) (4) oral risperidone prior to initiating Uzedy.

Table 1: Dosage Recommendations for Switching from Daily Oral Risperidone to Uzedy
<table>
<tr><th>Prior Therapy</th><th>UZEDY Dosage Once Monthly</th><th>UZEDY Dosage Once Every Two Months</th></tr>
<tr><td>2 mg of oral risperidone per day</td><td>50 mg</td><td>100 mg</td></tr>
<tr><td>3 mg of oral risperidone per day</td><td>75 mg</td><td>150 mg</td></tr>
<tr><td>4 mg of oral risperidone per day</td><td>100 mg</td><td>200 mg</td></tr>
<tr><td>5 mg of oral risperidone per day</td><td>125 mg</td><td>250 mg</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Kits containing a single-dose prefilled syringe, packaged in a carton with one 21-gauge, 5/8-inch needle</td></tr>
<tr><td>Storage</td><td>Store in refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Uzedy may be stored in unopened original packaging at room temperature, 68°F to 77°F (20°C to 25°C), for up to 90 days. If unopened, Uzedy may be returned to refrigerated storage within 90 days. Once the carton is opened, administer Uzedy or discard.</td></tr>
</table>

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Uzedy labels and labeling submitted by Teva Neuroscience.

- Syringe labels received on January 24, 2022, available at \\CDSESUB1\evsprod\NDA213586\0025\m1\us
- Revised 250 mg syringe label received on March 21, 2022, available at \\CDSESUB1\evsprod\nda213586\0035\m1\us\
- Carton labeling received on March 21, 2022, available at \\CDSESUB1\evsprod\nda213586\0035\m1\us\
- Prescribing Information (image not shown) received on March 21, 2022, available at \\CDSESUB1\evsprod\nda213586\0035\m1\us\

F.2 Label and Labeling Images (not to scale)

Syringe Labels

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

9 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

LORETTA HOLMES
03/31/2022 06:11:40 PM

SEVAN H KOLEJIAN
03/31/2022 10:47:28 PM

Clinical Inspection Summary

Date	03/17/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director/(Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jasmeet (Mona) Kalsi, Regulatory Project Manager Roberta Rasetti, M.D., Medical Officer Pamela Horn, M.D., Team Leader Division of Psychiatry Office of Neuroscience
NDA #	213586
Applicant	Teva Pharmaceuticals
Drug	Risperidone extended-release injectable suspension for subcutaneous use
NME	No
Proposed Indication	Treatment of schizophrenia
Consultation Request Date	8/5/2021
Summary Goal Date	1/18/2022, extended to 2/25/2022, 3/9/2022
Priority/Standard Review	Standard
Action Goal Date	4/17/2022
PDUFA Date	4/17/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bari, Castro, Gamez, Lapeyra, and [redacted] (b) (4) CRO) were inspected in support of this NDA, covering the pivotal efficacy study, TV46000-CNS-30072 (Study 30072), and the long-term safety study, TV46000-CNS-30078 (Study 30078). The inspections identified protocol deviations related to investigational product (IP) dosing errors, lack of documentation of IP administration, duplicate subject enrollment at different clinical sites, and potential unblinding at one clinical site. No discrepancies in primary efficacy endpoint data were identified.

However, based on these inspections and related information requests, the extent of the IP dosing errors cannot be determined. Additionally, the extent of the lack of IP dose documentation, which precludes IP dose verification, is not known. Therefore, we recommend that an independent third party audit or post-study monitoring by the sponsor/CRO be conducted for *all sites* and *all subjects* to determine the extent of IP dosing errors and lack of IP dose documentation.

The CRO, (b) (4) was responsible for clinical monitoring for these two studies. The clinical site monitoring performed by (b) (4) was inadequate. Clinical site monitoring included blinded monitoring visits, however, unblinded monitoring visits to verify IP dose administration were not planned. Approximately one year after Study 30072 was initiated, IP dose errors were inadvertently identified at one clinical site during a blinded monitoring visit. Due to these dosing errors, unblinded monitoring visits were conducted for approximately 32% (19/59) of sites while Study 30072 was ongoing. Approximately one year after the unblinded monitoring visits were completed, when Study 30072 was close to completion, (b) (4) informed the sponsor of the results of these monitoring visits. Subsequently, unblinded IP dosing logs were reviewed for 20 sites after Study 30072 had been completed. A list of clinical sites with unblinded monitoring visits/unblinded IP dose log review was not collected during the CRO inspection. The unblinded IP dosing log review identified a lack of IP dose documentation in 58 subjects at 5 clinical sites. Most striking was a lack of IP dose documentation for all study visits in 24 of 33 (72%) subjects at one site. According to the sponsor, the unblinded IP dosing log review for 20 sites identified dosing errors at 10 sites affecting 33 subjects; however, this is not a complete list since IP dose documentation was lacking at some sites such that dose verification could not be performed. The sponsor stated that the majority of the documented dose errors were errors in the volume of placebo administered and were primarily due to unblinded study personnel referring to the wrong tables in the pharmacy manual. The sponsor identified 5 subjects with risperidone dosing errors. The full extent of dosing errors in Study 30072 is unknown since unblinded monitoring/IP dose log review was not conducted for all clinical sites and, for the sites that did undergo review, a lack of IP dose documentation was identified such that IP doses could not be verified.

IP dosing errors also occurred in 50 subjects for the last study visit of Study 30078. This error involved only those subjects randomized to the risperidone every 2 months arm, an arm in which subjects received monthly injections of placebo alternating with risperidone to maintain the study blind. Due to this error, 31 subjects received placebo for two consecutive months and 19 subjects received risperidone for two consecutive months. Site-specific letters listing the expected and actual treatments for these subjects were sent to the 20 impacted sites and safety assessments were completed at the follow-up visits. The sponsor did not include specific information for these subjects' follow-up visits in the NDA submission. If Study 30078 provides additional supportive evidence of efficacy, we recommend that the review division conduct a sensitivity analysis with regard to these 50 subjects.

The sponsor identified 11 subjects with duplicate enrollment after Study 30072 had been completed. Specifically, most subjects with duplicate enrollment participated in Study 30072 and were also enrolled as new subjects (not roll-over subjects) at different clinical sites for Study 30078. Nine of these subjects received overlapping doses of risperidone injections; the most significant was a subject with triplicate enrollment who received 15

months of overlapping risperidone injections. Many of these subjects continued to receive overlapping risperidone injections after the initial NDA cut-off date, so subject-specific data (i.e., adverse events, clinical labs) was not submitted. For six of these duplicate subjects, overlapping IP administration could have impacted efficacy. Three subjects randomized to placebo in Study 30072 also received overlapping doses of risperidone in Study 30078. Three subjects randomized to risperidone monthly or every 2 months in Study 30072 also received overlapping doses of risperidone in Study 30078, thereby receiving more frequent injections. We recommend that the FDA statistician perform a sensitivity analysis regarding these 6 subjects.

At Site #14810 (Dr. Lapeyra), the unblinded study staff administering IP in Protocol 30072 wrote dose volumes on case report forms filed with subject study documents for 11 of 26 randomized subjects. Since dose volumes differed between placebo and risperidone, blinded study personnel could have been unblinded if viewing dose volumes on these study documents. Due to the potential for unblinding, we recommend that the FDA statistician perform a sensitivity analysis regarding these 11 subjects to assess the robustness of the results reported by the sponsor.

II. BACKGROUND

Risperidone extended-release suspension for subcutaneous injection is being developed under NDA 213586 (IND 124384) for the treatment of schizophrenia. There are currently two marketed long-acting injectable formulations of risperidone: Perseris® subcutaneous injection administered once every month and Risperdal Consta® intramuscular injection administered every 2 weeks.

The sponsor has submitted two Phase 3 studies, Protocols TV46000-CNS-30072 (Study 30072) and TV46000-CNS-30078 (Study 30078), to support the safety and efficacy of risperidone ER suspension to be administered as a subcutaneous injection every month or every 2 months.

Protocol TV46000-CNS-30072 (Study 30072; The RISE Study)

Title: "A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of risperidone extended-release injectable suspension (TV-46000) for subcutaneous use as maintenance treatment in adult and adolescent patients with schizophrenia"

Subjects: 542

Sites: 59 sites; United States (51), Eastern Europe (8)

Study Initiation and Completion Dates: 6/1/2018 to 12/3/2020

Database Lock: 12/16/2020

This was a double-blind, randomized, relapse prevention study in subjects with schizophrenia. Included were males or females, 13 to 65 years of age; DSM-5 diagnosis of schizophrenia for >1 year with diagnosis reconfirmed by Structured Clinical Interview for DSM-5 (SCID-5); ≥1 episode of relapse in the last 24 months; responsive to antipsychotic treatment in the past year; and Positive and Negative Syndrome Scale (PANSS) total score <100 at screening.

The study was comprised of three phases:

Oral conversion and stabilization phase
This phase included a screening period (up to 4 weeks) and an oral conversion and stabilization stage (Stage 1) of up to 12 weeks.

Following the screening period, subjects not already on oral or injectable risperidone were converted to open-label oral risperidone, 2 to 5 mg/day, to ensure that they tolerated risperidone and that the doses were adequate to treat their symptoms. Subjects who were already on risperidone but could still benefit from the study, based on the investigator's judgement, could also participate in the oral stabilization stage. Adolescent subjects received a maximum dose of 4 mg/day.

Double-Blind Maintenance Phase
This period included the baseline visit and the relapse prevention stage (Stage 2)
Subjects were assessed for stability at the baseline visit.

Stability was defined as meeting all of the following criteria for at least 4 consecutive weeks prior to the baseline visit:

- Outpatient status
- PANSS total score ≤80
- A score of ≤4 on each of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content
- Clinical Global Impression-Severity (CGI-S) score ≤4
- Clinical Global Impression-Severity of Suicidality (CGI-SS) score ≤2 on Part 1 and ≤5 on Part 2

Subjects meeting criteria for stability were randomized (1:1:1) to one of the following arms:

- Risperidone extended release (ER) suspension subcutaneous injection once every month (q1m)
- Risperidone ER suspension subcutaneous injection once every 2 months (q2m)
- Placebo subcutaneous injection once every month (q1m)

The risperidone subcutaneous injection dose was equivalent to the oral dose subjects received in the stabilization stage (Stage 1). The injection site chosen for a subject was to

remain consistent throughout the study. Injection sites included the upper arm (in select sites) or abdomen. To maintain the study blind, subjects randomized to the risperidone q2m arm received monthly injections that alternated between placebo and risperidone injections. During this phase, study visits occurred every 4 weeks with weekly telephone contact between study visits.

Subjects continued in the relapse prevention stage (Stage 2) until they experienced a relapse event, met study discontinuation or withdrawal criteria, or remained relapse-free until the study was terminated because at least 90 relapse events had occurred.

Follow-up
For subjects not entering the extension study (Study 30078), two follow-up study visits occurred 4 weeks and 8 weeks after the last dosing visit.

The primary efficacy endpoint was the time to impending relapse. Relapse was defined as *one or more of the following items*:

1. CGI-I ≥5 and
   - an increase to a score of >4 with an absolute increase of ≥2 on any of the following PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content *or*
   - an increase to a score of >4 on any of the following PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content and an absolute increase of ≥4 on the combined score for these individual items
2. Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs)
3. CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
4. Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage

Protocol TV46000-CNS-30078 (Study 30078; The SHINE Study)

Title: "A study to evaluate the safety, tolerability, and effect of risperidone extended-release injectable suspension (TV-46000) for subcutaneous use as maintenance treatment in adult and adolescent patients with schizophrenia"

Subjects: 103 at time of NDA submission

Sites: 14 sites in the United States

Study Initiation and Completion Dates: 4/17/2019 – 12/2/2021

Database Cut-Off Date: 9/1/2020

This was a double-blind, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of risperidone ER suspension for subcutaneous injection in subjects with schizophrenia. Subjects who did not experience a relapse and completed Study 30072 were eligible for this study (roll-over subjects). Inclusion criteria for new (*de novo*) subjects included 13 to 65 years of age; diagnosis of schizophrenia for >1 year (or > 6 months for subjects 13-17 years of age) and >1 episode of relapse in the last 24 months; responsive to antipsychotic treatment in the past year; PANSS total score <100 at screening.

The study was comprised of three phases, similar to Study 30072:

Oral conversion and stabilization phase
Subjects who had not participated in Study 30072 participated in the pre-treatment phase which included the screening and conversion to oral risperidone (Stage 1). These new (*de novo*) subjects had to meet the same stability criteria as Study 30072 for at least 4 consecutive weeks prior to the baseline visit.

Double-Blind Maintenance Phase (up to 56 weeks)
New subjects meeting criteria for stability were randomized (1:1) to one of the following arms:

- Risperidone ER suspension subcutaneous injection once every month (q1m)
- Risperidone ER suspension subcutaneous injection once every 2 months (q2m)

Subjects who did not experience a relapse and completed Study 30072 (roll-over subjects) began the study at this phase. Subjects who were treated with risperidone q1m or q2m in Study 30072 continued that assigned arm in this study. Subjects who were treated with placebo in Study 30072 were randomized (1:1) to receive risperidone q1m or q2m equivalent to the oral dose on which they were stabilized in Stage 1 of Study 30072. During this phase, study visits occurred every 4 weeks with weekly telephone contact between study visits.

Subjects continued in this study until they experienced a relapse. Relapse was defined the same as Study 30072.

Follow-up
Two follow-up study visits occurred 4 weeks and 8 weeks after the last dosing visit.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

III. RESULTS

1. Mohammed Bari, M.D.
   Site #14771
   Synergy San Diego
   7922 Palm Street; West Lower Level
   Lemon Grove, CA 91945
   Inspection Dates: 10/18/2021 – 10/22/2021

   At this site for Study 30072, 40 subjects were screened, 29 were enrolled in the open-label oral risperidone stabilization phase, 15 were randomized into the double-blind maintenance phase, and 6 subjects completed the study. Of the 29 subjects who were enrolled in the oral risperidone stabilization phase, 14 discontinued due to the following: withdrawal of consent (7), noncompliance (1), loss to follow-up (1), subject moved (2), did not meet stabilization criteria (2), and adverse event (1). Subject # (b) (6) discontinued due to the adverse event, erectile dysfunction.

   Nine subjects discontinued the study after randomization due to withdrawal of consent (6), loss to follow-up (2), and adverse event (1). Subject # (b) (6) randomized to placebo, discontinued due to the adverse event, acarodermatitis; the narrative for this adverse event was included in the NDA submission. For the 6 subjects completing the study, two experienced relapses and four completed the study without a relapse and continued into Study 30078.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 29 enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (relapse).

   The primary efficacy endpoint was the time to impending relapse. Efficacy data verification focused on date of relapse and relapse criteria (e.g., PANSS scores, CGI-I scores, hospitalization). Sponsor data line listings for the primary efficacy endpoint were verified against paper source at the site; no discrepancies were noted.

   Of note, the sponsor's protocol deviation line listing identified two of 15 randomized subjects at this site for which incorrect doses of investigational product (IP) were administered. These deviations were described as "unblinded dosing volume of IP administered was incorrectly calculated with subject receiving XXml instead of XXml"; that is, the actual dose administered in error was not provided in the line listing.

During the inspection, it was verified that these two subjects, both randomized to risperidone, received twice the subcutaneous dose that they were supposed to receive based on the oral risperidone dose taken during the open-label stabilization phase (see Table 1). The unblinded study personnel who administered IP stated that they had referred to the table describing the volume of drug product to withdraw/expel from the vial in the pharmacy manual rather than the table of dosing volumes to administer. These dosing errors were identified during an unblinded monitoring visit on (b) (4) approximately 6 to 7 months after the errors occurred (refer to (b) (4) inspection summary for clinical monitoring). The site did not report these dosing errors to the IRB.

Listing 16.2.5.1.2, "Study Drug Administration by Treatment Group" does not reflect the incorrect doses administered. This listing provides the dose that should have been administered as the dose that was actually administered, despite stating in the sponsor's protocol deviation line listing that an incorrect dose was administered.

Table 1. Incorrect Dose of Risperidone Administered Study 30072 (Site 14771)

Subject	Treatment Arm	Visit/Week	Date	Incorrect Dose Administered	Correct Dose
(b) (6)	Risperidone once every 2 months	Visit 6/Baseline	(b) (6)	200 mg (0.6 ml)	100 mg (0.3 ml)
		Visit 8/Week 8		200 mg (0.6 ml)	100 mg (0.3 ml)
	Risperidone once every month	Visit 6/Baseline		200 mg (0.6 ml)	100 mg (0.3 ml)
		Visit 7/Week 4		200 mg (0.6 ml)	100 mg (0.3 ml)
		Visit 8/Week 8		200 mg (0.6 ml)	100 mg (0.3 ml)
		Visit 9/Week 12		200 mg (0.6 ml)	100 mg (0.3 ml)

*Data provided by sponsor via information request

Another issue was that the unblinded study coordinator did not document the volume of IP administered for some visits for four of 15 randomized subjects. For three of these subjects, doses were not documented for 4 of 6 study visits. Due to a lack of dose documentation, the IP dose administered could not be verified. The undocumented IP doses administered were identified on (b) (4) during the unblinded monitoring visit (refer to (b) (4) inspection summary for clinical monitoring). The sponsor included these undocumented doses as protocol deviations.

Finally, two minor adverse events were not reported to the sponsor. Subject # (b) (6) discontinued the study during the open-label oral risperidone stabilization phase due to "erectile dysfunction." Subject # (b) (6) randomized to the placebo arm experienced a "left leg abrasion."

Reviewer's comment:
IP dosing errors occurring in two of 15 randomized subjects were identified during an unblinded monitoring visit. These subjects received twice the dose of risperidone they should

have received based on the dose conversion from the oral risperidone dose in the open-label oral stabilization phase and the risperidone arm to which they were randomized. These dose errors were made due to an error by the unblinded study coordinator when referring to the incorrect table in the pharmacy manual. These subjects did not appear to experience any adverse events related to these dosing errors: Subject (b) (6) did not report any adverse events and Subject (b) (6) reported an adverse event of upper respiratory infection. IP dosing errors occurred at other clinical sites; please refer to the (b) (4) inspection summary.

2. Kenia Castro, M.D.
   Site #14865
   Reliable Clinical Research LLC
   4160 W 16 Avenue, Suite 301
   Hialeah, FL 33012
   Inspection Dates: 12/27/2021 – 1/7/2022

   This site did not enroll any subjects in Study 30072 but did enroll in Study 30078. Therefore, all subjects enrolled at this site for Study 30078 were new subjects (not roll-over subjects).

   At this site, for Study 30078, 34 subjects were screened, 18 were enrolled in the open-label oral risperidone stabilization phase, 12 were randomized into the double-blind maintenance period, and 8 subjects completed the study. Of the 18 subjects who were enrolled in the open-label oral risperidone stabilization phase, 6 discontinued due to the following: not meeting stabilization criteria (3), noncompliance (2), and loss to follow-up (1). Four subjects discontinued the study after randomization due to the following: withdrawal of consent (2), loss to follow-up (1), and other, "withdrawal by principal investigator" (1). The "withdrawal by principal investigator" should have been categorized as withdrawal due to worsening of AE (pre-existing poorly controlled diabetes mellitus in Subject # (b) (6)) as noted below.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 18 enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, and protocol deviations.

   The primary objective of this study was to evaluate the long-term safety and tolerability of risperidone for subcutaneous administration and, therefore, no placebo arm was included in the study design. Efficacy data were included as exploratory endpoints and were not verified during this inspection.

   Investigational Product (IP) Administration
   The sponsor's protocol deviation line listing identified 9 of 18 randomized subjects who were administered IP subcutaneous injections in the arm instead of the abdomen. These IP arm

injections were administered from (b) (6) and involved a total of 19 injections. The protocol states that subcutaneous injections were to be administered in the abdomen unless the clinical site is one selected by the sponsor for injection of IP into the back of the upper arm instead of the abdomen. Site #14865 was not one of those selected clinical sites.

It is unknown when these protocol deviations were identified by the CRO, (b) (4) but an email sent to the site on (b) (4) references a (b) (4) retraining that addressed this issue. The email also stated that the clinical site could continue administering IP injections in the arm for those subjects who had been receiving injections in the arm but that all new randomized subjects must be administered IP injections in the abdomen.

The unblinded physician who administered the IP injections stated that many subjects had refused abdominal injections, so he decided to administer IP in the upper arm rather than discontinuing the subjects. According to an (b) (4) site monitoring follow-up letter dated (b) (4) the unblinded physician had discussed administration of IP injections in the arm with Dr. Castro (the clinical investigator).

Reviewer's comment: The protocol specified that IP was to be injected into the abdomen. The sponsor was evaluating an alternate injection site, the back of the upper arm, in a subset of clinical sites that did not include Site #14865. Since proposed product labeling includes both injection sites, it appears unlikely that administration of IP in the arm rather than the abdomen at this clinical site would impact the safety assessment for this investigational product. However, the clinical investigator should have discussed the alternate injection site with the sponsor before IP administration.

Protocol Eligibility Deviation/Unreported Adverse Event
This site enrolled one subject (Subject # (b) (6)) who was not eligible for the study due to poorly controlled diabetes mellitus (DM). The subject completed the open label oral risperidone stabilization phase and was randomized to risperidone q2m on (b) (6) despite continuing elevated blood glucose levels. The subject was finally discontinued from the study on (b) (6) due to elevated blood glucose levels ((b) (6) mg/dL).

Reviewer's comment: Atypical antipsychotics are known to possibly increase blood sugars in patients with DM (especially if the DM is poorly controlled). Therefore, this unreported adverse event is unlikely to affect the overall safety results of this study. However, the subject was put at risk with worsening of poorly controlled DM during the study which resulted in the subject's discontinuation from the study.

Serious Adverse Events
Other than the worsening of poorly controlled pre-existing diabetes mellitus in Subject # (b) (6), there was no evidence of under-reporting of adverse events. Four SAEs were reported for this site:

- Subject # (b) (6) enrolled but not randomized, hospitalized for worsening of schizophrenia
- Subject # (b) (6) randomized to risperidone q2m, hospitalized for psychotic disorder
- Subject # (b) (6) randomized to risperidone q2m, hospitalized for a panic attack
- Subject # (b) (6) randomized to risperidone q2m, hospitalized for aggression

All SAEs were reported to the sponsor according to protocol. Narratives for these SAEs were included in the NDA submission.

3. Jose Gamez, M.D
   Site #14787
   Galiz Research, LLC
   7100 W 20th Avenue, Suite 802
   Hialeah, FL 33016
   Inspection Dates: 10/25/2021 – 10/28/2021

   At this site for Study 30072, 47 subjects were screened, 39 were enrolled in the open-label oral risperidone stabilization phase, 25 were randomized into the double-blind maintenance period, and 15 subjects completed the study. Of the 39 subjects who were enrolled in the open-label oral risperidone stabilization phase, 14 discontinued due to the following: withdrawal of consent (10), loss to follow-up (2), or did not meet stabilization criteria (2). Ten subjects discontinued the study after randomization due to the following: withdrawal of consent (5), loss to follow-up (2), subject moved (2), or early termination by error (1). Specifically, due to some confusion of the site personnel regarding the protocol schedule of events, the site early terminated Subject # (b) (6) randomized to risperidone q1m, at study day 85 in error. For the 15 subjects completing the study, 5 experienced relapses and ten completed the study without a relapse and continued into Study 30078.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 25 randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (relapse).

   The primary efficacy endpoint was the time to impending relapse. Efficacy data verification focused on date of relapse and relapse criteria (e.g., PANSS scores, CGI-I scores, hospitalization). Sponsor data line listings for the primary efficacy endpoint were verified against paper source at the site; no discrepancies were noted. No under-reporting of adverse events was noted.

4. Olga Lapeyra, M.D
Site #14810
Behavioral Clinical Research, Inc.
14211 Commerce Way
Miami Lakes, FL 33016
Inspection Dates: 10/12/2021 – 10/25/2021

At this site for Study 30072, 77 subjects were screened, 66 were enrolled in the open-label oral risperidone stabilization phase, 26 were randomized into the double-blind maintenance period, and 11 subjects completed the study. Of the 66 subjects who were enrolled in the open-label oral risperidone stabilization phase, 40 discontinued due to the following: loss to follow-up (22), withdrawal of consent (12), adverse events (2), noncompliance (1), use of investigational product within 3 months of screening (1), or did not meet randomization criteria (2). The discontinuations due to adverse events during the open-label oral risperidone stabilization phase were Subject # (b) (6) who had an abnormal ECG (left ventricular hypertrophy) identified at the baseline visit and Subject # (b) (6) who experienced uterine polyps. Narratives for these discontinuations due to adverse events were included in the NDA submission.

Fifteen subjects discontinued the study after randomization due to withdrawal of consent (4), loss to follow-up (5), adverse events (4), and noncompliance (2). Discontinuations due to adverse events included:

- Subject # (b) (6) randomized to risperidone q1m, experienced hand tremor and weight loss
- Subject # (b) (6) randomized to risperidone q2m, experienced urinary incontinence
- Subject # (b) (6) randomized to placebo, had an increase in ALT/AST
- Subject # (b) (6) randomized to risperidone q1m, experienced a tremor (unspecified)

Narratives for all discontinuations due to adverse events were included in the NDA submission.

For the 11 subjects completing the study, 2 subjects experienced relapses and 9 subjects completed the study without a relapse. Seven of the subjects completing the study without a relapse continued into Study 30078.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 26 randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (relapse).

The primary efficacy endpoint was the time to impending relapse. Efficacy data verification focused on date of relapse and relapse criteria (e.g., PANSS scores, CGI-I scores, hospitalization). According to the clinical investigator, PANSS and CGI-I scores were entered directly into the electronic data capture (EDC) system by raters; therefore, no paper source was available at the site. A compact disc containing the archived eCRFs was provided to the site by the sponsor. Sponsor efficacy data line listings were verified against the archived eCRFs and EDC audit trails were reviewed; no discrepancies were noted.

Lack of Dose Volume Administration Documentation and Potential Unblinding
For 11 of 26 randomized subjects, the unblinded research assistant administering IP did not document the volume of IP administered for one or more study visits on a drug administration log. For 6 of these subjects, there was no IP dose documentation for any study visits. During a monitoring visit by the CRO, (b) (4) the unblinded monitor noticed that the unblinded research assistant was writing the IP volume on the subject's case report form (CRF), which was filed with the subject's other study records. At some point in time (it is unclear when), these volumes were "marked out," although the monitor noted that the IP volume could still be read through the mark-out for some subjects. This issue was noted in the sponsor's protocol deviation line listing for only 4 of these 11 subjects. The monitor noted that recording IP volume on the subject's CRF could potentially unblind the study. These 11 subjects included 4 randomized to placebo, 5 randomized to risperidone q1m, and 2 randomized to risperidone q2m.

Reviewer's comment: Lack of adequate IP volume documentation was an issue across clinical sites; please refer to the (b) (4) inspection summary below. At this site, IP volume could not be verified since the "marked-out" volumes on source records could not be easily deciphered. As noted, it is not known when these volumes were "marked-out" by the unblinded research assistant. Due to the potential for unblinding, we recommend that the FDA statistician perform a sensitivity analysis regarding these 11 subjects.

5. (b) (4)

This inspection covered (b) (4) monitoring activities of clinical sites participating in Study 30072 and Study 30078. The inspection focused primarily, but not exclusively, on the four clinical investigator sites that had been selected for inspection for Study 30072 (Site #s 14771, 14787, 14810) and Study 30078 (Site #14865).

Study records reviewed included, but were not limited to, monitoring plan, transfer of regulatory obligations (TORO); SOPs; organization and personnel; clinical investigator and site qualification; selection of monitors; monitoring procedures; record retention; investigator

agreements; financial disclosure; electronic data capture systems; quality assurance; safety reporting process; protocol deviation process; and investigational product management.

Obligations transferred to (b) (4) from Teva Pharmaceuticals included project management, clinical trial management, clinical monitoring, feasibility, study start-up, identification of sites, data management, and training.

IP Dosing Errors and Lack of IP Dose Administration Documentation - Study 30072

(b) (4)

Reviewer comments: The monitoring plan states that 100% source document review and verification for all enrolled subjects would be conducted. One of the items included for source document review and verification was "administration of IMP (investigational medicinal product)." This is not defined further in the monitoring plan but would typically include IP dose verification.

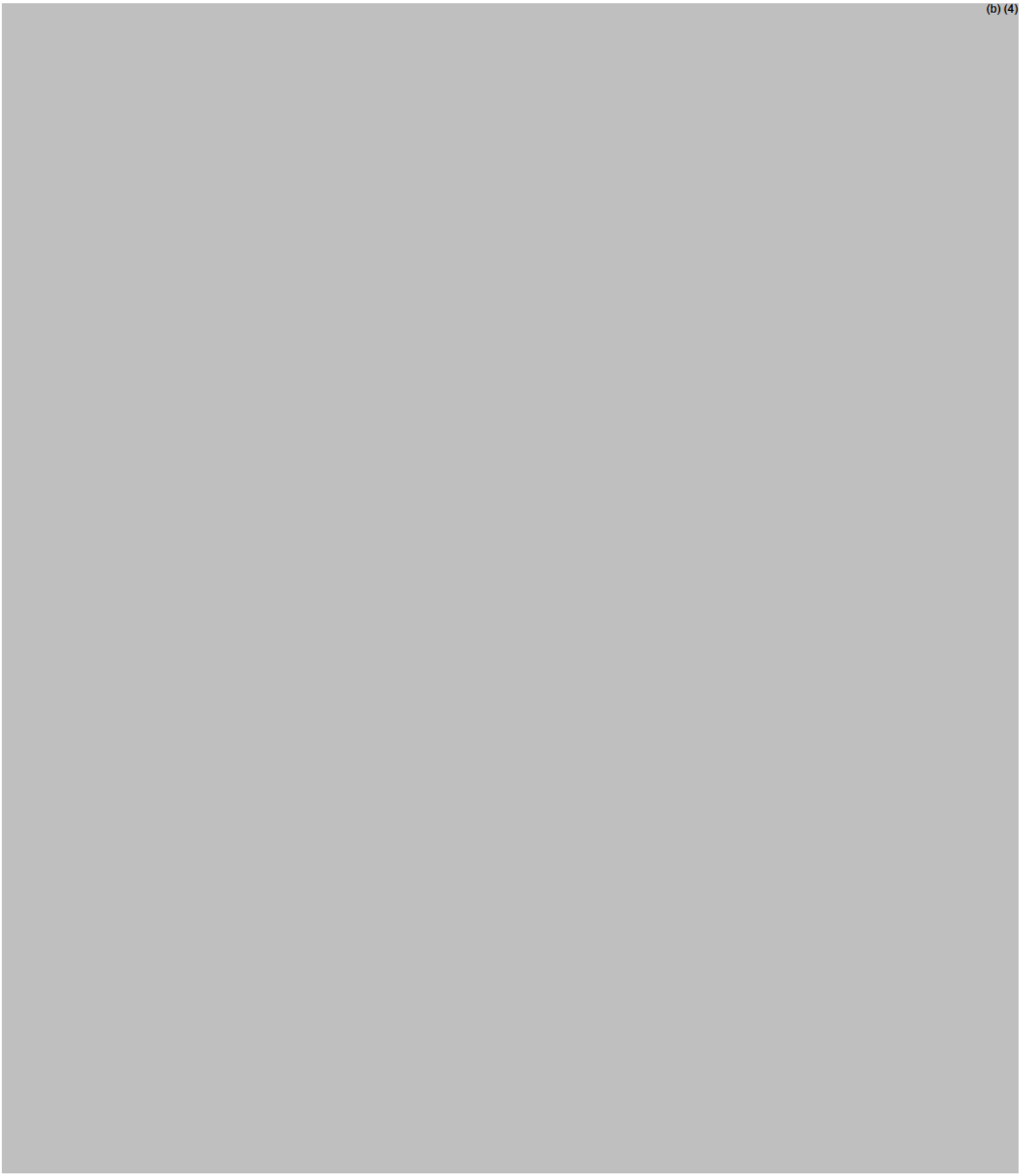
Approximately one year after Study 30072 was initiated, IP dose errors were inadvertently identified during a blinded monitoring visit at one clinical site, which resulted in unblinded monitoring visits being performed for 19 of the 59 clinical sites (which sites is unknown, as was the process of selecting these sites). It appears that these results were not shared with the sponsor for more than one year, i.e., not until approximately one month before the study was completed.

As a result of the findings from the unblinded monitoring visits at the 19 sites, unblinded dosing logs were reviewed for 20 sites at the end of the study. Findings for these 20 sites were that dosing errors occurred in 34 subjects at 10 sites for 195 study visits (this was later corrected to 33 subjects).

The identity of the sites chosen for unblinded monitoring visits and IP dose log review are not known. It is not known whether a particular site had both unblinded monitoring visits and IP dose log review. If there was no overlap of the sites audited, a maximum of 39 of 59 (66%) sites were monitored/reviewed for dosing errors and/or lack of dose documentation. ***Therefore, the full extent of dose errors and lack of dose documentation for all sites is not***

known.

(b) (4)



(b) (4)

Reviewer comments: According to the sponsor, the majority of the dose errors that were identified in the 12/2020 unblinded IP dose log review involved incorrect volume of placebo administered, either in the placebo study arm or the alternating placebo injections in the risperidone q2m study arm. There were 5 documented risperidone dosing errors identified by the sponsor. Subject # (b) (6) *the one subject who received the lower risperidone dose, was lost to follow-up after the baseline visit. Three of the subjects receiving higher risperidone doses than should have been administered experienced adverse events usually associated with risperidone that started after receiving risperidone injections.*

Due to the identified lack of IP dose documentation, the extent of dosing errors could not be determined. The 59 protocol deviations described as a lack of dose documentation occurred at 5 sites (#s 14771, 14799, 14809, 14810, and 14811) and involved 58/543 subjects (10.7%). However, this may not be a complete list of lack of IP dose documentation since unblinded monitoring visits/IP dose log review were not conducted for all sites. The most significant documented deviation was a lack of IP dose documentation for <u>any</u> study visits for 24 of 33 (73%) subjects at Site #14809. Therefore, the full extent of dose errors and lack of dose documentation for all sites is not known.

<u>Dosing Errors and Unblinding - Study 30078</u>

(b) (4)

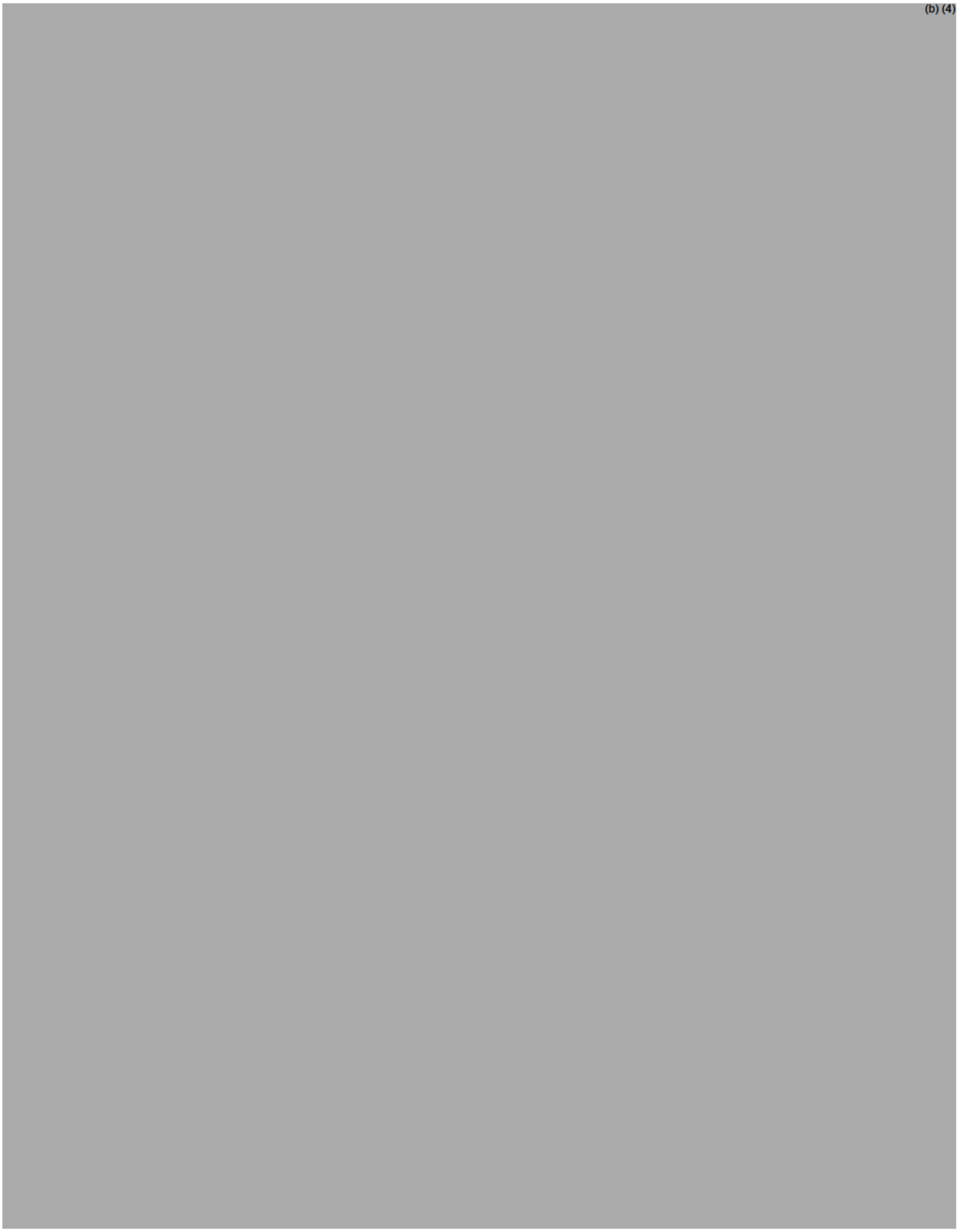
(b) (4)

Reviewer comments: Risks of administering two consecutive doses of placebo for subjects randomized to the risperidone q2m arm include a greater risk of relapse. Risks of administering two consecutive doses of risperidone for subjects randomized to the risperidone q2m arm include a greater risk of adverse events. Per protocol, two safety follow-up visits were conducted after Visit 20/ET. The sponsor did not include specific information for these subjects for these visits in the NDA submission. If Study 30078 provides additional supportive evidence of efficacy, we recommend that the review division conduct a sensitivity analysis with regard to these 50 subjects.

Duplicate Subject Enrollment – Study 30072 and 30078

(b) (4)

(b) (4)



Reviewer comments: The enrollment of subjects at multiple clinical sites increases risk to the subjects and to data reliability.

The NDA submission does not include specific subject information for these duplicate subjects. The original NDA submission data cut-off was 9/1/2020. The 120-day safety update data cut-off date was 5/1/2021, but the only subject-specific data that would be included in this update would be narratives for deaths, SAEs, and withdrawal due to adverse events; all other safety data would be pooled data.

For six of these duplicate subjects, overlapping investigational product administration could have impacted efficacy. Three subjects randomized to placebo in Study 30072 also received overlapping doses of risperidone in Study 30078. Three subjects randomized to risperidone q1m or q2m in Study 30072 also received overlapping doses of risperidone in Study 30078, thereby receiving more frequent injections. We recommend that the FDA statistician perform a sensitivity analysis regarding these 6 subjects.

{See appended electronic signature page}

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OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

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03/18/2022 10:56:30 AM

PHILLIP D KRONSTEIN
03/18/2022 11:08:03 AM

KASSA AYALEW
03/18/2022 11:31:15 AM

HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	March 10, 2022
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 213586
Drug Constituent Name and Strengths	Uzedy[a] (risperidone) extended-release injectable suspension, 50 mg/0.1 mL, 75 mg/0.2 mL, 100 mg/0.3 mL, 125 mg/0.4 mL, 150 mg/0.4 mL, 200 mg/0.6 mL, 250 mg/0.7 mL
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Prefilled Syringe
Rx or OTC:	Prescription (Rx)
Applicant Name:	Teva Neuroscience, Inc. (Teva)
FDA Received Date:	June 17, 2021, October 25, 2021, January 07, 2022
OSE RCM #:	2021-1234
DMEPA 1 Human Factors Evaluator:	Seung Hoon Lee, BS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[a] The proposed proprietary name, Uzedy, was found conditionally acceptable on January 13, 2022.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report submitted under NDA 213586 for the Uzedy (risperidone) extended-release injection.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed prefilled syringe (PFS) device constituent part that is intended to treat schizophrenia. The proposed product will be administered by a healthcare professional. Uzedy injection will be supplied in seven strengths:

- 50 mg/0.1 mL
- 75 mg/0.2 mL
- 100 mg/0.3 mL
- 125 mg/0.4 mL
- 150 mg/0.4 mL
- 200 mg/0.6 mL
- 250 mg/0.7 mL

Each carton will consist of one PFS with tray, safety needle, and instructions for use (IFU) embedded in the prescribing information. The PFS consists of a glass luer-lock prefilled syringe with a plastic plunger, plastic finger flanges and a safety needle (see Figure 1). For additional product information, please see Table 3 in Appendix A.

Figure 1. Uzedy PFS with Safety Needle Attached

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

- On July 16, 2019, the Applicant submitted their HF validation study protocol under IND 124384 for Agency review and feedback. We reviewed the protocol and provided recommendations to the Applicant[b].

[b] Flint, J. Human Factors Validation Study Protocol Review for Risperidone extended-release injectable suspension (IND 124384). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 09 SEPT 2019. RCM No.: 2019-1540.

- On June 17, 2021, the Applicant submitted the results of their HF validation study results report in their marketing application under NDA 213586, which is the subject of this review.

1.3 MATERIALS REVIEWED

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

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

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

2.1 SUMMARY OF HF VALIDATION STUDY DESIGN

Table 2 presents a summary of the HF validation study design. We note that the Applicant implementation all our previous recommendation. See Appendix C and D for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	A total of 23 healthcare providers:

	• 10 adult nurses* • 1 pediatric nurse* • 3 mental health nurses • 4 psychiatrists • 6 retail pharmacists *One participant reported as both an adult nurse and a pediatric nurse.
Training	No training was provided to the 23 participants.
Test Environment	The test room was set up to simulate a healthcare setting. The test room had furniture and work surfaces typical of a standard clinical environment.
Sequence of Study	• Study introduction • Select doses based on simulated prescriptions to assess participants' ability to distinguish different doses. • Complete a single injection scenario • Knowledge-based questions • Interview of participant regarding any observed or reported use-related issues to determine the root cause. • Collection of subjective feedback

3 RESULTS AND ANALYSES

Table 3 describes the study results, the Applicant's analyses of the results, and DMEPA 1's analyses and recommendations.

Table 3. Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the critical task "store in the refrigerator at 36° F to 46° F (2° C to 8° C) in the original carton to protect from light" there were 6 use errors. The subjective data and the Applicant's root cause analysis indicated: • Two participants saw "room temperature" on the carton or in the IFU (e.g., "30 minutes at room temperature") and assumed it referred to the storage instructions for the product. One of these participants chose not to read the IFU based on familiarity with similar products. • One participant assumed the Uzedy PFS should be at room temperature based on its viscosity and chose not to read instructions based on familiarity with similar products. • One participant reported that in their experience they do not refrigerate other antipsychotic medications, so they assumed that the product would not require refrigeration either. The participant did not locate the IFU or check the carton for storage information. Two participants reported that they would freeze the medication. The participants thought that the statement "TRADENAME is solid at refrigerated (b) (4) temperature" implied that the medication should be frozen. The Applicant stated that the IFU has been updated iteratively during the design and development and through subsequent formative human factors studies. Additionally, the Applicant stated that the labeling is aligned with good practice guidance. The	Our review of the study results identified subjective feedback that indicted the use errors we due to negative transfer and misinterpretation of the IFU storage information. One participant stated that they would freeze the medication, due to the IFU storage information that state, "TRADENAME is solid at refrigerated (b) (4) temperature". Our review of the labels and labeling (user interface, etc.) finds that the labels and labeling do not include information warning users not to freeze the Uzedy PFS. Our review of the labels and labeling (user interface, etc.) finds that the storage information can be improved to clearly state that the Uzedy PFS should not be frozen. We provide recommendations in Table A to address this concern. We have determined that this change can be implemented without submitting additional validation testing for Agency review.

	storage information is consistent with other approved injectable products on the market. The likelihood of these errors occurring has been reduced as far as possible. Based on the URRA, if this task is omitted or not performed correctly there is risk of injecting degraded or expired drug. The Applicant did not propose any risk mitigation strategies in response to these use errors.	
2.	For the critical task "allow product to sit in its packaging at room temperature (68° to 77° F [20° to 25° C]) for at least 30 minutes" there were 2 use errors. The subjective data and the Applicant's root cause analysis indicated: One participant reported that they would leave carton out at room temperature, but thought rubbing the PFS between hands to warm it was also acceptable. This use error was attributed to the user's prior clinical experience that warming the medication by rubbing between the hands was an acceptable way to bring the product to room temperature. One participant reported that they would flick the syringe to warm. The Applicant stated that the instruction to leave the product at room temperature prior to use is presented on the carton, in the Quick Tips, and in the IFU.	Our review of the study results identified subjective feedback that participants relied on previous injection experience (negative transfer). Our review of the labels and labeling (user interface, etc.) finds that the carton and the IFU contain instructions and/or images to support these tasks. We did not identify additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risks in these cases are acceptable.

	(b) (4)  Based on the URRA, if the tasks noted are omitted or not performed correctly there is a risk of injecting degraded or expired product. The Applicant did not provide any risk mitigation strategies in response to these use errors.	
3.	We note that there were use errors, use difficulties, and close calls for several critical tasks that appear to be caused by negative transfer (participants relied on previous antipsychotic drugs experience when performing the tasks below. They also transferred their knowledge of other antipsychotic drugs to answer the questions below). For example, for the tasks to check for tampered seal, damaged syringe, medication color, bubble, particulate, and expiration date, the participants usually do not initially inspect the carton or the syringes but would notice it during use. We address these critical tasks collectively below: • For the critical task "check tamper evident seals are intact" there were 5 use errors. • For the critical knowledge task "Where should you store this product?" there was 1 close call.	Our review of the study results identified subjective feedback that indicated the majority of these use errors were due to negative transfer and participants not reading the IFU. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains instructions and/or images to support these tasks. We did not identify additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risks in these cases are acceptable.

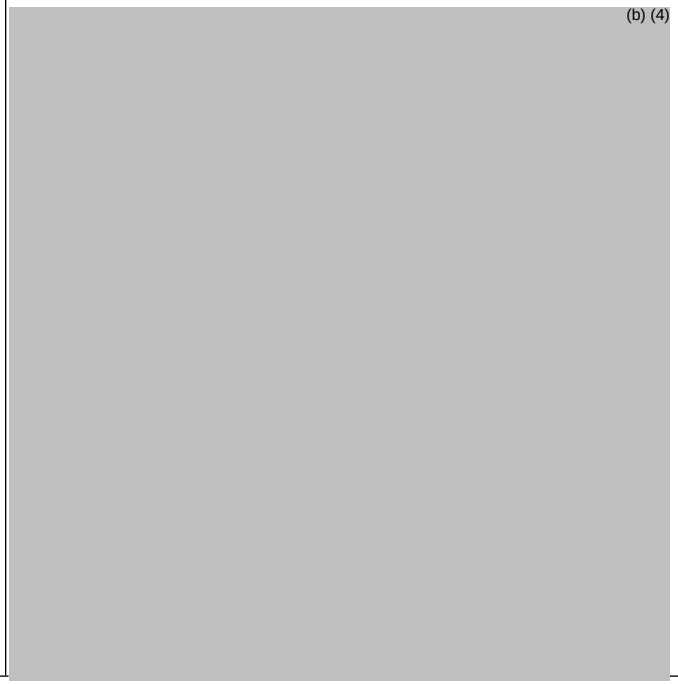
	• For the critical task “check that the syringe is not damaged” there were 7 use errors. • For the critical task “check that the expiration date that appears on syringe label” there were 12 use errors. • For the critical task “check that the drug in the syringe is white to off-white, opaque in color” there were 4 use errors. • For the critical knowledge task “What should the liquid medication look like?” there were 4 use errors. • For the critical task “check the needle packaging is sealed and undamaged” there were 3 use errors. • For the critical task “put gloves on before handling safety needle” there was 1 use error. • For the critical task “activate (lock) the safety needle shield” there were 3 use errors and 1 use difficulty. • For the critical task “wait for 2-3 seconds after the entire dose is delivered” there were 6 use errors, 2 close calls, and 2 use difficulties. • For the critical task “check that the bubble is at the tip cap side of the syringe” there were 3 use errors and 9 use difficulties. • For the critical task “choose an injection site” there were 3 use errors. • For the critical task “pinch at least 1 inch of the area of cleaned skin with your free hand” there were 3 use errors. • For the critical task “insert the needle into subcutaneous tissue” there were 2 use errors. • For the critical task “dispose of the needle sheath” there were 6 use errors.	

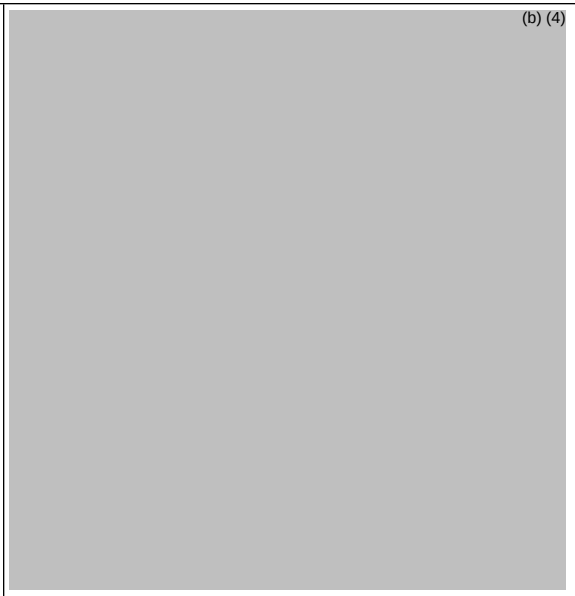
	The Applicant stated that the majority of these use errors were due to negative transfer and participants not reading the IFU. The IFU has been tested iteratively and developed. The likelihood of these errors occurring has been reduced as far as possible. Based on the URRA, if the tasks noted are omitted or not performed correctly there is risk of: • injection of wrong drug • breach of container closure integrity or delay in dose • injecting degraded or expired drug • improper aseptic technique • underdose • injecting to wrong depth (intramuscular) The Applicant did not provide any risk mitigation strategies in response to these use errors, close call and use difficulties.	
4.	For the critical task "check that name appears on syringe label" there were 6 use errors. For the knowledge task "What, if anything, should you check about this product when you pick it up from the pharmacy or before you inject it?" there were 2 use difficulties. For the critical task "check that the correct dose appears on the syringe label" there were 6 use errors. The subjective data and the Applicant's root cause analysis indicated: • Five participants expected the name and dose on the carton to match the name and dose on the PFS. • One participant expressed that the text on the carton was bigger and easier to read and, therefore, chose to check the	Our review of the study results identified subjective feedback that indicated the participants had difficulties reading the drug name and dose on the syringe label. Although the Applicant indicated that the root cause for these difficulties were attributed to the black text displayed against the black plunger stopper making it difficult to read the text based on the image, there were no subjective feedback indicating that was the reason for the difficulty. Our review of the labels and labeling (user interface, etc.) indicate that both name and dose are differentiated by different colors on the cartons. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.

	carton for the medication name rather than on the PFS label. The subjective data and the Applicant's root cause analysis indicated: Two participants reported difficulty in reading the drug name on the PFS label. The Applicant stated that this difficulties were attributed to the black text being displayed against the black plunger stopper making it difficult to read the text. (b) (4) The Applicant noted that these difficulties could manifest to use errors if the users were unable to distinguish between the black text and the plunger stopper. Additionally, the Applicant stated that the syringe label does not use color coding (b) (4) (b) (4) The syringe label has been designed from a best practice perspective and is aligned with other approved injectable product. No new or unique risks are introduced. The likelihood of these errors occurring has been reduced as far as possible.	

	(b) (4)  Based on the URRA, if the tasks noted are omitted or not performed correctly there is a risk of: • injecting the wrong drug • overdose The Applicant did not provide any risk mitigation strategies in response to these use errors.	
5.	For the critical task "flick with downward whipping motion to move the bubble to the cap of the syringe" there were 8 use errors. The subjective data and the Applicant's root cause analysis indicated: • Negative Transfer and Not Reading the IFU: Four participants noticed the red tag on the syringe and/or the quick tip inside the carton, but did not read either or refer to Step 5. They stated that they chose not to read IFU due to familiarity with similar products or because they were focused on other aspects of using the Uzedy PFS. Although, one of these participants did acknowledge that the intended	Our review of the study results identified subjective feedback that majority of participants relied on previous injection experience (negative transfer) and did not read the IFU. Additionally, one participant did not locate IFU because they thought that the PI only included prescribing information and did not think it would include instructions. Additionally, another participant indicated that they were uncertain about the amount of force to use when flicking the syringe and was concerned with using too much force so they chose to flick the PFS using only the range of motion in his wrist.

	technique was unfamiliar and is not required for any other similar products. • Not Reading the IFU: One participant stated that the red tag prompted him to review the IFU generally, but he did not read Step 5. • Mental Model: One participant knew to move the bubble to the tip cap based on Step 5, but misunderstood how to move it. They thought that flicking the syringe with the tip cap upwards would force the bubble to the tip cap, and chose to hold the barrel near the finger grip because they thought it would provide a sturdier grip. • Inconspicuous instruction location: One participant shook the PFS based on prior experience with other medications. They did not locate IFU because they thought that the PI only included prescribing information and did not think it would include instructions. • Unclear instruction interpretation: One participant performed Step 5 based on their interpretation of the movement described by the text and images of Step 5 in the IFU. The participant was uncertain about the amount of force to use when flicking the syringe and was concerned with using too much force so they chose to flick the PFS using only the range of motion in his wrist. The Applicant stated that the iterative design of the IFU and the syringe tag, gives clear and obvious guidance to the user on the need to complete this step, along with how to complete this step, has reduced the likelihood of these errors occurring as far as possible. Additionally, the Applicant stated that the need to shake the syringe before removing the tip cap is presented in the Quick Tips	The Applicant also stated in the URRA that only in the case of 100 mg (2 monthly dosing) does the consequence of not executing the flicking step correctly may lead to a below therapeutic dose for 2 days at the end of the dosing period (two months). We reached out to the Division of Psychiatry (DP) medical officer (MO) to ask about the clinical impact of underdose if this task is omitted or not performed correctly. The MO indicated that although the risk of symptom exacerbation is present, usually relapse after drug discontinuation requires more than few days. The MO agrees with the Applicant that the risk of symptom exacerbation is low. The MO recommended that the label should include information stating that if the task of flicking or whipping motion to move the bubble to cap is not performed correctly, this could result in a decreased amount of drug administration with consequent potential risk of symptom exacerbation. Our review of the labels and labeling (user interface, etc.) finds that the carton and IFU can be improved. The user interface can be improved by providing the IFU that is currently provided in the PI as a separate, stand-alone document. Additionally, the IFU can be improved to include information as to how much force to use when flicking the prefilled syringe. We provide a recommendation for the division and in Table A for the Applicant to address this concern. We have determined that this change can be implemented without submitting additional validation testing for Agency review.

	on the carton, the syringe tag on the PFS, and in the IFU as depicted below: (b) (4) 	

	 (b) (4) Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. The Applicant did not provide mitigation strategies in response to these use errors.	
6.	For the critical task "holding the syringe vertically by the white collar, bend and snap off the cap" there were 3 use difficulties. The subjective data and the Applicant's root cause analysis indicated: Negative Transfer: Three participants thought to twist cap first due to prior experience with another medication or due to the perforation around the cap edge. Based on the URRA, if this task is omitted or not performed correctly there is risk of delay in dose (≤5 days).	Our review of the study results identified subjective feedback that indicated all these use difficulties were due to negative transfer. All three participants relied on previous experience to twist the cap for removal (negative transfer).

	The Applicant did not provide any risk mitigation strategies in response to these use difficulties.	(b) (4)  Our review of the labels and labeling (user interface, etc.) finds that the IFU includes instructions and/or images to support this task. Additionally, we note that these instructions and images are similar to other currently marketed risperidone products with the same intended use, user and user environment. We did not identify additional changes to the user interface to further reduce the risks associated with these use difficulties We find that the residual risks in these cases are acceptable.
7.	For the critical task "push on the plunger using a slow, firm, and steady push until the entire dose is delivered" there were 4 use errors and 2 use difficulties. The subjective data and the Applicant's root cause analysis indicated: • Drug Viscosity Issues: The participants reported feeling resistance or a 'stop' and interpreted this feedback to mean	Our review of the study results identified subjective feedback that indicated the use errors and use difficulties were due to drug viscosity. On October 19, 2021, we issued an information request (IR) to request data or information to support that the intended users will be able to reliably deliver the full dose of medication. The Applicant responded to the IR[c] on

[c] Nguyen, P. Information Request for NDA 213586. Silver Spring (MD): FDA, CDER, OSE, PMS (US); 25 OCT 2021. Available from: \\CDSESUB1\evsprod\nda213586\0013\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5354-other-stud-rep\human-factors-studies\injection-force-report.pdf

	that the injection was complete. In addition, two of these participants reported that they did look at the device and thought that plunger was all the way down. • One of these participants expressed that it was difficult to differentiate between the medication and the collar since both are (b) (4) • Two participants experienced difficulty pushing the plunger to the bottom of the barrel but were ultimately able to successfully deliver a full dose. Both of the users attributed this to the viscosity of the mediation making it difficult to injection. The Applicant stated that in the event of an insufficient dose, schizophrenia symptoms may recur. This risk is mitigated as low as possible through labeling mitigations included in the IFU. The IFU informs the user that the drug is viscous and instructs them to push the plunger to the bottom of the barrel to deliver a complete dose as depicted below. Additionally, the Applicant also stated that Risperidone Extended-Release Injectable Suspension (ERIS) is administered by a healthcare professionals on a monthly (Q1M) or every two month (Q2M) frequency and it is routine clinical practice to assess the patient around the time of administration. Symptom deterioration towards the end of the dose interval could be detected at this routine assessment and appropriate dosing adjustments would then take place. Furthermore the Applicant stated that the risk is reduced as low as possible enabling the	October 25, 2021 and provided data from their design verification report. The Applicant noted that the phase 3 long term safety study showed that complete dose was consistently administered throughout the study. Additionally, the Applicant noted that the sustaining injection force (24.8 N) is considerably less than the lowest mean grip strength (63.5 N) and the lowest recorded grip strength (44.4 N).[d] We sought input from the Office of Product Quality (OPQ) to determine the acceptability of the Applicant's justification regarding the sustaining injection force submitted in the IR response. The OPQ reviewer indicated that the drug product is inherently very viscous and consequently requires significant sustaining force to administer the drug. The OPQ reviewer found that the Applicant's justification reasonable and recommended warning about viscosity in the labeling. Our review of the labels and labeling (user interface, etc.) finds that the IFU includes information warning the user about the drug viscosity. Below is the IFU statement: "IMPORTANT: TRADENAME is viscous. Resistance will be experienced during dose delivery." We note that the carton labeling can be improved to also include this statement.

[d] Mathiowetz, V., et al. (1985) Grip and Pinch Strength: Normative Data for Adults, Arch Phys Med Rehabil 66:69-71, Table 5: Average Performance of All Subjects on Palmar Pinch.

	benefits provided by the Risperidone ERIS to outweigh the potential risk of an under dose. Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. The Applicant did not provide any risk mitigation strategies in response to these use errors and use difficulties.	We provide recommendations in Table A to address this concern. We have determined that this change can be implemented without submitting additional validation testing for Agency review.
8.	For the critical task "checks that the stopper is at the base of the syringe barrel" there were 9 user errors. The subjective data and the Applicant's root cause analysis indicated: • Mental Model: Six participants were relying on the tactile feedback of feeling the plunger stop moving to determine if the injection was complete. • Two participants checked the stopper position in the PFS but did not identify that there was medication remaining in the syringe. One of these participants expressed that it was difficult to differentiate between the medication and the collar since both are white. Mental Model: One participant reported that they did not notice that medication remained and thought the PFS was empty based on feeling that the plunger stopped moving. • Negative Transfer: One participant could not determine whether the stopper was completely at the bottom of the barrel but thought it was acceptable to remove the needle from the skin. This user thought that some medication remaining in the PFS would be acceptable based on other injection devices where not all the medication exits the PFS. They also reportedly thought that they had pushed the plunger fully.	Our review of the study results identified subjective feedback that indicated that the use errors were due to participants relying on the tactile feedback of feeling the plunger stop moving to determine if the injection was complete. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains instructions and/or images to support this task. We did not identify additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risks in these cases are acceptable.

	The Applicant stated that the IFU includes the instruction to check that the plunger stopper is at the white collar as depicted below: (b) (4)  Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. The Applicant did not propose any risk mitigations strategies in response to these use errors.	

Table 4: Identified Issues and Recommendations for Division of Psychiatry			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	We note that the instructions for use (IFU) are only included in the prescribing information (PI).	There were use errors identified in your HF validation study that indicated some users did not expect that the instructions would be embedded in the PI.	We recommend providing the IFU as an additional stand-alone document. The following recommendations apply to the IFU in the PI and in the stand-alone IFU.

Table A: Identified Issues and Recommendations for Teva (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The IFU does not include a warning statement that the product should not be frozen.	We are concerned if the user freezes the product, there is a risk of injecting degraded or expired drug. The human factors (HF) validation study identified subjective feedback that indicated that the participant misinterpreted the statement "TRADENAME is solid at refrigerated (b) (4) temperature" to mean the product can be frozen.	We recommend revising the IFU to include a warning statement that the product should not be frozen.
2.	Step 5 does not include information to let the user know that if the task of flicking with a downward whipping motion to move the bubble to the cap of the prefilled syringe is omitted or not performed correctly this could result in a decreased amount of drug administration with consequent potential risk of symptom exacerbation.	The task to "flick with downward whipping motion to move the bubble to the cap of the syringe" may be overlooked because the instruction does not include the reason why this task is important.	We recommend revising the IFU to include information to let the user know that if the task of flicking with a downward whipping motion to move the bubble to the cap of the prefilled syringe is omitted or not performed correctly that this could result in a decreased amount of drug administration with consequent potential risk of symptom exacerbation.

3.	Step 5 does not include information to let the user know how much force to use when flicking the prefilled syringe.	We are concerned if this task is omitted or not performed correctly there is risk of underdose. The HF validation study identified subjective feedback that the participant was uncertain about the amount of force to use when flicking the syringe and was concerned with using too much force so they chose to flick the PFS using only the range of motion in his wrist.	We recommend revising Step 5 to clearly emphasize on how much force to use when flicking the prefilled syringe.
Carton Labeling (Prefilled Syringe)			
1.	Carton labeling does not include information to let the user know that the IFU is embedded in the Prescribing Information (PI).	We are concerned if the user does not locate the IFU, there is risk of incorrect use of the prefilled syringe. The HF validation study results identified subjective feedback that indicated that the participant did not locate IFU because they thought that the PI only included prescribing information and did not think it would include instructions.	We recommend revising carton labeling to include information to let the user know that the IFU is embedded in the PI.
2.	Carton labeling does not include an important information statement to let the user know that the product is viscous.	We are concerned if the user is not informed on the viscosity of the product, there is risk of not delivering the full dose.	We recommend revising carton labeling to include an important information statement about the viscosity of the product.

		The HF validation study results identified subjective feedback that indicated that the viscosity of the medication made the injection difficult.	

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Additionally, our evaluation of the label and labeling identified areas of vulnerability that may lead to medication errors.

Above, we have provided recommendations in Table 4 for the Division of Psychiatry and Table A for Teva Neuroscience, Inc. We ask that the Division of Psychiatry convey Table A in its entirety to Teva Neuroscience, Inc. so that recommendations are implemented prior to approval of this Application.

4.1 RECOMMENDATIONS FOR TEVA NEUROSCIENCE, INC.

Our evaluation of the results of your human factors (HF) validation study indicates that there are additional mitigations that can be implemented to address use difficulties that occurred with critical tasks. Additionally, our review of the labels and labeling identified areas of vulnerability that may lead to medication errors. We provide these recommendations in Table A and we recommend that you implement these recommendations and submit the revised labels and labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for risperidone that Teva Neuroscience, Inc. submitted on June 17, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Atypical antipsychotic
Active Ingredient (Drug or Biologic)	Risperidone extended release
Indication	Treatment of schizophrenia
Route of Administration	Subcutaneous
Dosage Form	50 mg/0.1 mL, 75 mg/0.2 mL, 100 mg/0.3 mL, 125 mg/0.4 mL
Strengths	50 mg, 75 mg, 100 mg, 125 mg monthly or 100 mg, 150 mg, 200 mg, 250 mg every 2 months
Dose and Frequency	50 mg, 75 mg, 100 mg, 125 mg monthly or 100 mg, 150 mg, 200 mg, 250 mg every 2 months
How Supplied	Carton, tray, PFS ,safety needle, and Prescribing Information (b) (4) [redacted]
Storage	Refrigerated (36-46° F)
Container Closure/Device Constituent	Prefilled syringe (b) (4) [redacted]
Intended Users	Healthcare professionals
Intended Use Environment	Healthcare settings

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On October 29, 2021, we searched the L:drive and AIMS using the terms, "213586" and "risperidone" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[b], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:

\\CDSESUB1\evsprod\nda213586\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5354-other-stud-rep\human-factors-studies\human-factors-sum-rpt.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

\\CDSESUB1\evsprod\nda213586\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5354-other-stud-rep\human-factors-studies\human-factors-sum-rpt.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

(b) (4)

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following risperidone labels and labeling submitted by Teva.

- Container label (Prefilled Syringe) received on January 24, 2022
- Carton labeling received on January 24, 2022
- Instructions for Use (image not shown) received on June 17, 2021, available from EDR via:

  \\CDSESUB1\evsprod\nda213586\0001\m1\us\draft-labeling-text.pdf
- Prescribing Information (Image not shown) received on June 17, 2021, available from EDR via:

  \\CDSESUB1\evsprod\nda213586\0001\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images

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

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