CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213586Orig1s000

OTHER ACTION LETTERS

NDA 213586

COMPLETE RESPONSE

Teva Neuroscience, Inc.
Attention: Levana Volovsky
Director, Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380

Dear Ms. Volovsky:

Please refer to your new drug application (NDA) dated and received June 17, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for risperidone extended-release injectable suspension.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

Our review identified investigational product (IP) dosing errors including several instances of patients receiving IP doses higher than the assigned dose, lack of documentation of IP administration, and dually and triply enrolled patients. Because of these data quality issues, the dosing data from Study TV-46000-CNS-30072 and Study TV-46000-CNS-30078 cannot be relied upon based on the information contained in the application. Given the differences in the PK profile between the listed drug and TV-46000 and the potential for trough levels to lead to relapse in patients, it is important to understand what IP doses patients actually received. The application does not contain adequate evidence for the Agency to make an efficacy finding for this new formulation because the doses of IP that provided benefit to patients could not be verified and thus cannot be described in the product label. In addition, the exposure-response relationship of the safety findings could not be evaluated.

To resolve these deficiencies, submit results of an independent third party audit or post-study monitoring by the sponsor/Clinical Research Organization (CRO) for all sites and all subjects to establish the extent of IP dosing errors and lack of IP dose documentation and to determine what study data can be relied upon for regulatory decision making. In addition, submit relevant updated analyses and dosing datasets based on the audit findings.

Alternatively, submit a new adequate and well-controlled clinical efficacy and safety

study to confirm product efficacy, establish the effective dose range of the product, and inform the safety of the product for the effective dose range.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

- We note that the use instructions are currently located only in Section 2 of your proposed Prescribing Information. We request that you submit a separate, stand-alone Instructions for Use (IFU) document for review.

  In addition, revise the statement on the carton labeling to state "Please read complete instructions prior to use" rather than "(b) (4) (b) (4) ".

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comment for All Syringe Labels and Carton Labeling			
1.	The primary statement of strength (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 50 mg to read 50 mg/0.14 mL). With implementation of this revision, the (b) (4) unnecessary and should be deleted.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(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-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.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
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 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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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.

PROPRIETARY NAME

Please refer to correspondence dated, January 13, 2022, which addresses the proposed proprietary name, Uzedy. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial

response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call LCDR Jasmeet (Mona) Kalsi, Regulatory Project Manager, at (240) 402-8977.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

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/

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