# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 216354Orig1s000

# OTHER REVIEW(S)

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

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

# Memorandum

**Date:** 02/08/2023

**To:** Edwin George Clinical Reviewer, M.D.
Division of Neurology Products (DN1)

Stacy Metz, Regulatory Project Manager, (DRO-N)

Tracy Peter, Associate Director for Labeling, (DN I/II)

**From:** Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

**Subject:** OPDP Labeling Comments for Austedo XR (deutetrabenazine) extended-release tablets, for oral use

**NDA**: 216354

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In response to DN I consult request dated May 5, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for Austedo XR (deutetrabenazine) extended-release tablets, for oral use.

**Labeling**: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNI on January 25, 2023, and are provided below.

**Medication Guide:** A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on January 31, 2023.

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 17, 2023, and January 31, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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SAMUEL A FASANMI
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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy Initiatives**
**Division of Medical Policy Programs**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | January 31, 2023 |
| To: | Stacy Metz, PharmD<br>Senior Regulatory Project Manager<br>**Division of Neurology 1 (DN1)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Nyedra W. Booker, PharmD, MPH<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Samuel Fasanmi, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) |
| Drug Name (established name: | AUSTEDO XR (deutetrabenazine) |
| Dosage Form and Route: | extended-release tablets, for oral use |
| Application Type/Number: | NDA 216354 |
| Applicant: | Teva |

# 1 INTRODUCTION

On April 21, 2022, Teva submitted for the Agency's review an original New Drug Application (NDA 216354) for AUSTEDO XR (deutetrabenazine) extended-release tablets, for oral use.

The proposed indication for AUSTEDO XR (deutetrabenazine) extended-release tablets, for oral use is for the following:

- Chorea associated with Huntington's disease
- Tardive dyskinesia

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology 1 (DN1) on May 5, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for AUSTEDO XR (deutetrabenazine) extended-release tablets, for oral use.

At the request of DN1, DMPP will retain the current track changes as appropriate to the AUSTEDO XR patient labeling review so that specified DN1 proposed edits to the MG are maintained in one version of the patient labeling.

# 2 MATERIAL REVIEWED

- Draft AUSTEDO XR (deutetrabenazine) extended-release tablets, for oral use MG received on April 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on January 25, 2023.
- Draft AUSTEDO® XR (deutetrabenazine extended-release tablets) MG, received on April 21, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on January 27, 2023.
- Draft AUSTEDO XR (deutetrabenazine) extended-release tablets, for oral use Prescribing Information (PI) received on April 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 25, 2023.

# 3 REVIEW METHODS

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

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

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
01/31/2023 02:41:41 PM

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | January 19, 2023 |
| Requesting Office or Division: | Division of Neurology 1 (DN 1) |
| Application Type and Number: | NDA 216354 |
| Product Name and Strength: | Austedo XR (deutetrabenazine) extended-release tablet, 6 mg, 12 mg, 24 mg |
| Applicant/Sponsor Name: | Teva Neuroscience, Inc. (Teva) |
| OSE RCM #: | 2022-2546-1 |
| DMEPA 2 Safety Evaluator: | Chad Morris, PharmD, MPH |
| DMEPA 2 Acting Team Leader: | Stephanie DeGraw, PharmD |

## 1 PURPOSE OF MEMORANDUM

Teva submitted revised container labels and carton labeling received on January 17, 2023 for Austedo XR. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Austedo XR (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 ASSESSMENT AND CONCLUSION

Teva implemented most of our recommendations, except revising the color scheme for the Austedo XR professional sample titration kit, which overlap with the currently available Austedo professional sample titration kit. We reviewed Teva's justification, (b) (4) (b) (4) (b) (4) and we find it acceptable. Therefore, we have no additional recommendations for the carton and container labels at this time.

[a] Morris, C. Label and Labeling Review for Austedo XR (NDA 216354). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 DEC 22. RCM No.: 2022-2546.



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STEPHANIE L DEGRAW
01/19/2023 09:41:10 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

| | |
|---|---|
| Date of This Review: | December 22, 2022 |
| Requesting Office or Division: | Division of Neurology 1 (DN 1) |
| Application Type and Number: | NDA 216354 |
| Product Name and Strength: | Austedo XR (deutetrabenazine) extended-release tablet, 6 mg, 12 mg, 24 mg |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Teva Neuroscience, Inc. |
| FDA Received Date: | April 21, 2022; May 24, 2022 |
| TTT ID #: | 2022-2546 |
| DMEPA 2 Safety Evaluator: | Chad Morris, PharmD, MPH |
| DMEPA 2 Acting Team Leader: | Stephanie DeGraw, PharmD |



Reference ID: 5099765

## 1 REASON FOR REVIEW

As part of the approval process for Austedo XR (deutetrabenazine) extended-release tablet, the Division of Neurology 1 (DN 1) requested that we review the proposed Austedo XR prescribing information (PI), medication guide (MG), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

### 1.1 BACKGROUND

NDA 216354 is a 505(b)(2) NDA and the listed drug product is Xenazine, NDA 021894.

Austedo (deutetrabenazine) tablets were approved on April 3, 2017 under NDA 208082 for the treatment of chorea associated with Huntington's disease and tardive dyskinesia. Austedo tablets are typically administered twice daily (i.e., all doses that are 12 mg or greater should be administered in divided doses). Under NDA 216354, the Sponsor is proposing an extended-release tablet formulation of deutetrabenazine for the same indication that allows for once daily dosing. The Sponsor is proposing one PI for both Austedo and Austedo XR.

## 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

The proposed PI, MG, carton labeling, and container labels 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 the Division and in Section 5 for Teva Neuroscience, Inc.



Reference ID: 5099765

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

| Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Full Prescribing Information – Section 2 Dosage and Administration | | | |
| 1. | In Section 2.1, Table 1, Important Administration Instructions can be improved for completeness, balance, and consistency. | Incomplete, imbalanced, and inconsistent presentation of important administration instructions may increase the risk for confusion and misinterpretation. | We recommend adding a statement to the third row as the third bullet point) that states to administer Austedo XR once daily, similar to the twice daily statement in the third row, third bullet point for Austedo. |
| Full Prescribing Information – Section 16 How Supplied/Storage and Handling | | | |
| 1. | The description of the package configuration for the Patient Starter kit does not use the same terms that are on the carton and blister pack labeling, and the contents statement contains the ambiguous symbol "/". | Inconsistent and unclear descriptions of packaging contents may increase the risk for confusion. | We recommend revising the language describing the package configuration and contents to align with carton and outer shell labeling.<br><br>For example, consider revising (b) (4) [redacted] to read:<br><br>"Each starter kit carton contains two child-resistant blister packs containing 21 extended-release tablets each in the following configuration:<br><br>• Weeks 1-2 Blister Pack contains two foil cards<br>o Week 1 Foil Card: seven 12 mg extended-release tablets<br>o Week 2 Foil Card: seven 6 mg and seven 12 mg extended-release tablets |

| Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | | • Weeks 3-4 Blister Pack contains two foil cards<br>o Week 3 Foil Card: seven 24 mg extended-release tablets<br>o Week 4 Foil Card: seven 6 mg and seven 24 mg extended-release tablets"<br>or similar language. |
| Medication Guide | | | |
| 1. | In the Section "How should I take Austedo XR/Austedo" the frequency is separated from the route of administration. | Can be improved for readability. | We recommend revising the statement (b) (4) to read:<br>"If you take AUSTEDO XR, take your dose by mouth once per day, with or without food." |

5 RECOMMENDATIONS FOR TEVA NEUROSCIENCE, INC.

| Table 3. Identified Issues and Recommendations for Teva Neuroscience, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| General: All Container Labels and Carton Labeling | | | |
| 1. | The format for the expiration date is not defined. | We are unable to assess from a medication error perspective. | To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.<br>FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. |

| Table 3. Identified Issues and Recommendations for Teva Neuroscience, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | | 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.<br><br>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.<br><br>Please specify whether the month will be represented with numerical or alphabetical characters.<br><br>FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date. |
| 2. | The (b) (4) color scheme used to help differentiate the 24 mg extended-release tablets from other strengths overlaps with the overall trade dress and the proprietary name for Austedo XR/Austedo. | Since bottles and cartons of Austedo XR will likely be close to each other on pharmacy shelves, the use of the (b) (4) color scheme for the 24 mg strength, overall trade dress, and the proprietary name minimizes the difference between the strengths, which may lead to wrong strength or dosage form selection errors. | We recommend revising the color scheme of the 24 mg strength, so the strength appears in its own unique color and the color does not overlap with any other colors utilized in the overall trade dress or the proprietary name. |

| Table 3. Identified Issues and Recommendations for Teva Neuroscience, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 3. | The blue color scheme used to differentiate the 12 mg extended-release tablets from other strengths is similar to the blue color scheme for the Austedo 9 mg tablets. | Since bottles of Austedo XR and Austedo will likely be close to each other on pharmacy shelves, similar or overlapping color schemes for products that differ in product characteristics (in this case, strength and dosage form), may increase the risk for product selection errors. | We recommend revising the blue color scheme for the 12 mg extended-release tablets to a color that is not used in your current Austedo product line or proposed Austedo XR product line extension. |
| Trade Bottle Labels and Outer Carton Labeling | | | |
| 1. | Product identifier is missing. | In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. | We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.<br><br>[1]The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf |
| Trade and Professional Sample Blister Card Labeling | | | |
| 1. | The blister card labeling contains the word (b) (4). | Each blister card is only one component of the (b) (4), which is composed of a carton containing two blister packs. | We recommend revising the word (b) (4) on the blister cards to read "pack" or similar. |
| Professional Sample Outer Carton Labeling | | | |

| Table 3. Identified Issues and Recommendations for Teva Neuroscience, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 1. | Provided the proposed product is approved, there will be a Professional Sample Titration Kit on the market for Austedo and Austedo XR. Both starter kits outer carton labeling contains similar color font and artwork. | We are concerned that having professional sample titration kits for different products with similar color schemes (that is white carton with purple text) will increase the risk for product selection errors.<br><br>We note, there are some differences in carton artwork and color scheme such as the logo, strength boxes, and auxiliary information; however, we are concerned these differences may be overlooked in the office setting without the use of barcode technology.<br><br>Additionally, it is possible the packages may be stored so that only the end of the carton is facing outward, which increases the risk for look-alike confusion, since the differences between the products are less than if the front or back panels are faced outward. | We recommend you reconsider and revise the color scheme for the professional sample outer carton for Austedo XR to help mitigate the risk for product selection errors in the prescriber use environment. |
| Professional Sample Blister Card and Carton Labeling | | | |
| 1. | The outer carton and blister pack labeling contains the word (b) (4). | (b) (4) packs are intended for sale and therefore do not meet the statutory definition of a professional sample. The use of the term (b) (4) on professional sample | We recommend revising the word (b) (4) to state “Titration” or similar. |

| Table 3. Identified Issues and Recommendations for Teva Neuroscience, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | | labeling should not be used.[a] | |

[a] See the final rule (b) (4)

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Austedo XR that Teva Neuroscience, Inc. submitted on April 21, 2022, the listed drug (LD), and Austedo.

| Table 4. Relevant Product Information for Listed Drug, Austedo, and Austedo XR | | | |
|---|---|---|---|
| Product Name | Xenazine[b] (NDA 021894) | Austedo[c] (NDA 208082) | Austedo XR (NDA 216354) |
| Initial Approval Date | 08/15/2008 | 04/03/2017 | n/a |
| Active Ingredient | tetrabenazine | deutetrabenazine | |
| Indication | Treatment of chorea associated with Huntington's disease | Treatment of chorea associated with Huntington's disease and tardive dyskinesia. | |
| Route of Administration | Oral | | |
| Dosage Form | Tablet | | Extended-release (ER) tablet |
| Strength | 12.5 mg, 25 mg | 6 mg, 9 mg, 12 mg | 6 mg, 12 mg, 24 mg |
| Dose and Frequency | The starting dose should be 12.5 mg/day given once in the morning. After 1 week, the dose should be increased to 25 mg/day given as 12.5 mg twice a day. XENAZINE should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. If a dose of 37.5 to 50 mg/day is needed, it | Recommended starting dosage: 12 mg per day (6 mg twice daily). Administer doses of 12 mg or above in two divided doses. Recommended dose titration: increase at weekly intervals in increments of 6 mg per day based on reduction of chorea or tardive dyskinesia, and tolerability, up to a maximum recommended | Recommended starting dosage: 12 mg once daily. Recommended dose titration: increase at weekly intervals in increments of 6 mg per day based on reduction of chorea or tardive dyskinesia, and tolerability, up to a maximum recommended daily dosage of 48 mg. |

[b] Xenazine Prescribing Information. Available at: http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/ac768bab-8afa-4446-bc7f-caeeffec0cda/spl-doc?hl=xenazine

[c] Austedo Prescribing Information. Available at: http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/7ea3c60a-45c7-44cc-afc2-d87fa53993c0/spl-doc?hl=austedo

| | | | |
|---|---|---|---|
| | should be given in a three-times-a-day regimen. The maximum recommended single dose is 25 mg. | daily dosage of 48 mg (24 mg twice daily).<br><br>If switching from tetrabenazine, the initial Austedo recommended initial dose is based on the current tetrabenazine dose.<br><br>In patients using Strong CYP2D6 inhibitors or are poor CYP2D6 metabolizers, the maximum recommended dose is 36 mg (maximum single dose of 18 mg). | If switching from tetrabenazine, the initial Austedo XR recommended initial dose is based on the current tetrabenazine dose.<br><br>In patients using Strong CYP2D6 inhibitors or are poor CYP2D6 metabolizers, the maximum recommended dose is 36 mg. |
| How Supplied | Bottles containing 112 tablets | Bottles containing 60 tablets | Bottles containing 30 ER tablets<br><br>Starter kits containing 42 ER tablets (14-6 mg, 14-12 mg, 14-24 mg) in the following configuration:<br><br>Weeks 1-2 Carton<br>(21 ER tablets)<br>Week 1 Blister Pack: 7-12 mg<br>Week 2 Blister Pack: 7-6 mg, 7-12 mg<br><br>Weeks 3-4 Carton<br>(21 ER tablets)<br>Week 3 Blister Pack: 7-24 mg<br>Week 4 Blister Pack: 7-6 mg, 7-24 mg |
| Storage | Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. | Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture. | |

| | | | |
|---|---|---|---|
| Container Closure[def] | HDPE bottle with (b) (4) cap | | 30-count Bottle: HDPE bottle with child-resistant cap<br><br>21-count Blister Pack: (b) (4) (b) (4) |

[d] Xenaxine container closure specifications available at: \\CDSESUB1\EVSPROD\nda021894\0069\m3\32-body-data\32p-drug-prod\xenazine\32p7-cont-closure-sys\container-closure-system.pdf

[e] Austedo container closure specifications available at: \\CDSESUB1\EVSPROD\nda208082\0188\m3\32-body-data\32p-drug-prod\sd-809-tablets\32p7-cont-closure-sys\container-closure-system.pdf

[f] Austedo XR container closure specifications available at: \\CDSESUB1\EVSPROD\nda216354\0001\m3\32-body-data\32p-drug-prod\tabs-all\32p7-cont-closure-sys\container-closure-system.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 25, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Austedo XR and NDA 216354. Our search did not identify any previous label and labeling reviews.

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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,[9] along with postmarket medication error data, we reviewed the following Austedo XR labels and labeling submitted by Teva Neuroscience, Inc. on April 21, 2022 and May 24, 2022.

- Container labels
  - Trade 30-count bottles, received on April 21, 2022
  - Trade and Professional Sample 21-count foil card, received on May 24, 2022
- Carton labeling received on May 24, 2022
  - Trade and Professional Sample 21-count blister pack
  - Trade and Professional Sample 42-count outer carton
- Prescribing Information and Medication Guide (Images not shown) received on May 24, 2022, available from \\CDSESUB1\EVSPROD\nda216354\0003\m1\us\propose-labeling-text-track.doc

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



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12/22/2022 08:11:40 PM

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: December 06, 2022

TO: Partha Roy, Ph.D.
Director, Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

Teresa Buracchio, M.D.
Acting Director, Division of Neurology I (DNI)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Sarmistha Sanyal, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Watson Therapeutics Inc., Miramar, FL

## 1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of NON-RESPONSIVE Study TV50717-BE-10179 (NDA 216354) conducted at Watson Therapeutics Inc., Miramar, FL. The NON-RESPONSIVE NON-RESPONSIVE inspection for NDA 216354 was conducted under FEI#3010806998 (FEI corresponding to the clinical investigator).

There were no discussion items and the Form FDA 483 was not issued at the inspection close-out for either applications.

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable.

**2. Inspected Studies:**

NON-RESPONSIVE

**NDA 216354**

**Study Number:** TV50717-BE-10179
**Study Title:** An open-label, randomized, repeated Dose, 2-Treatment, 2-Period, 2-Sequence crossover study with full replicate design in healthy subjects to assess the bioequivalence and relative bioavailability at steady-state between once daily administration of a 24-mg Extended Release Tablet of TEV-50717 and twice daily administration of a 12-mg AUSTEDO® Tablet.
**Dates of conduct:** 02/16/2021 – 04/29/2021

**Clinical site:** Teva Pharmaceutical industries, Ltd. dba Watson Therapeutics Inc., 3400 Enterprise Way Miramar, FL 33025-3941

**3. Inspectional Findings**

ORA investigator Sheri Stephenson inspected Watson Therapeutics Inc., Miramar, FL site from October 03-31, 2022 and this timeframe covers audit of both applications.

The previous onsite inspection of Watson Therapeutics Inc. was conducted from June 18 – June 27, 2019. At the conclusion of the inspection, there were no discussion items, no Form FDA 483 was issued and the final classification was NAI.

The current inspection (covering both studies) included auditing the following items:
- Case report forms (CRFs)
- Informed consent process
- Protocol deviations
- Institutional review board approvals

- Test article accountability and storage
- Study sample collection, processing and storage
- Randomization
- Adverse events

At the conclusion of the inspection, investigator Stephenson did not issue Form FDA 483 and there were no discussion items with the firm management.

CC:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/
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Draft: SS 11/28/2022, 12/3/22, 12/5/22, 12/6/22
Edit: SA 11/30/22, 12/2/2022, 12/5/22, 12/6/22; JC 12/5/2022

OSIS File #: BE 9524 (NDA 216354)
NON-RESPONSIVE

**eNSpect Assignment ID: 200451**
**eNSpect Op ID: 227557 (NDA 216354)**
NON-RESPONSIVE

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/s/

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SARMISTHA SANYAL
12/06/2022 11:52:00 AM

STANLEY AU
12/06/2022 01:52:06 PM
Team Lead

SEONGEUN CHO
12/06/2022 01:54:13 PM

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: November 10, 2022

TO: Teresa Buracchio, MD
Director (Acting)
Division of Neurology I
Office of New Drugs

Partha Roy, Ph.D.
Director
Office of Bioequivalence
Office of Generic Drugs

FROM: Monica Javidnia, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A Benson, Ph.D.
Deputy Director
DGDSI
OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4)
(b) (4)

**1. RRA Summary**

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion of Studies TV50717-BE [Deutetrabenazine]), NON-RESPONSIVE
NON-RESPONSIVE

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

**2. Reviewed Studies**

**Study TV50717-BE-10179 (NDA 216354)**

An Open-label, Randomized, Repeated Dose, 2-Treatment, 2-Period, 2-Sequence Crossover Study with Full Replicate Design in Healthy Subjects to Assess the Bioequivalence and Relative Bioavailability at Steady State Between Once Daily Administration of a 24-mg Extended Release Tablet of TEV-50717 and Twice Daily Administration of a 12-mg AUSTEDO® Tablet (Phase 1)

Sample Analysis Period: (b) (4)

NON-RESPONSIVE

NON-RESPONSIVE

**3. Scope of RRA**

OSIS scientist Monica Javidnia, Ph.D. reviewed the analytical portion of the above studies conducted at (b) (4)
(b) (4)

The RRA included an examination of records and processes for method validation, and study sample analysis. The RRA also included interviews with the firm's management and staff, a facility tour, and review of chromatograms, raw study data, sponsor correspondence, training records and CVs, select SOPs, equipment, sample shipment and receipt records, calibration and maintenance records, freezer logs, and audit trails.

**4. RRA Observations**

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

**4.2 Specific concerns from OND**

The consult request from the review division (Division of Neurology I) for Study TV50717-BE-10179 (NDA 216354) included a concern regarding the simultaneous quantification of deutetrabenazine (parent) and its metabolites α- and β-HTBZ, as the metabolites' $C_{max}$ were lower for the test drug than the reference drug. Through review of the sample receipt documentation, method validations, and method performance, I found no reason to suspect the analytical method was inadequate for simultaneous quantification of the parent drug and its metabolites from the biological samples submitted to the analytical site.

Draft: MJ 11/04/2022
Edit: HAI 11/08/2022; KAB 11/10/2022

ECMS: http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f881cf5430
OSIS File #: BE 9524, 9595, 9596, 9568, 9700, 9650, 9532

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/s/

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MONICA JAVIDNIA
11/10/2022 10:45:00 AM

HASAN A IRIER
11/10/2022 11:11:32 AM

KIMBERLY A BENSON
11/10/2022 11:21:14 AM