CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216354Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	216354		
Applicant Name	Teva Neuroscience, Inc.		
Drug Product Name	AUSTEDO XR (deutetrabenazine)		
Dosage Form	Extended-release tablet		
Proposed Strength(s)	6 mg, 12 mg, 24 mg		
Route of Administration	Oral		
Maximum Daily Dose	48 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of chorea associated with Huntington's disease and treatment of tardive dyskinesia in adults		
Drug Product Description	Round, 9 mm, film-coated tablets with black imprint. A laser drilled hole may be visible. 6 mg: Grey with "Q6" printed on one side 12 mg: Blue with "Q12" printed on one side 24 mg: Purple with "Q24" printed on one side		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Controlled room temperature, 20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	N/A
	Drug Product/ Labeling	Venkateswara Pavuluri	Martha Heimann
	Manufacturing	Vicky He	Chengjiu Hu
	Biopharmaceutics	Jia Leo	Ta-Chen Wu

	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

The following expiration dating periods are granted for AUSTEDO XR (deutetrabenazine) extended-release tablets when stored at controlled room temperature, 20°C to 25°C:

6 mg tablets in 30-count bottles: 18 months
12 mg and 24 mg tablets in 30-count bottles: 24 months
6 mg, 12 mg, and 24 mg tablets in blister packs: 18 months

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends **APPROVAL** of NDA 216354 for AUSTEDO XR (deutetrabenazine) extended-release tablets, 6 mg, 12 mg, and 24 mg. The applicant has provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - N/A

The Applicant cross-references approved NDA 208082 for all information to support the drug substance, deutetrabenazine.

Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA 216354
Assessment Cycle Number	01
Drug Product Name/ Strength	AUSTEDO® XR Deutetrabenazine Extended-Release Tablet/ 6 mg, 12 mg, and 24 mg
Route of Administration	Oral
Applicant Name	Teva Neuroscience, Inc.
Therapeutic Classification/ OND Division	Neurologic Disorders /DN1
RLD/RS Number	NDA 021894 Xenazine® (Tetrabenazine) Tablet
Proposed Indication	Chorea associated with Huntington's Disease (HD) and Tardive Dyskinesia (TD)
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The proposed deutetrabenazine once daily (QD) tablet is the extended-release version of the currently marketed AUSTEDO® Tablets (twice daily, BID). This 505(b)(2) application relies on the FDA's previous finding in efficacy and safety of the Listed Drug (LD) Xenazine® (Tetrabenazine) Tablet (NDA 021894). The purpose of developing deutetrabenazine extended-release tablet is to provide a new QD dosage form in addition to the approved BID AUSTEDO® Tablet, with desired benefit of increased patient compliance. The key Biopharmaceutics review findings with respect to the proposed dissolution method and acceptance criteria, in vitro alcohol dose-dumping potential, Extended-Release (ER) claim, and formulation bridging are summarized below.

Dissolution Method:

The Applicant proposed USP Apparatus II (paddle) with Japanese sinkers at 75 rpm in 500 mL of 0.05 M Potassium Biphthalate pH 3.0, 37°C. The selection of the dissolution parameters is acceptable. Investigation of method's discriminating ability was performed but not considered optimal performed appropriately; for example, much greater changes in amount of (b) (4) than what the Division typically recommends (±10-20% of the target/range). Considering the design of the drug product, i.e., (b) (4) osmotic system, and zero order drug release mechanism, different sizes of laser-drilled orifice was shown to have no impact on drug release, the proposed dissolution method is deemed acceptable.

Dissolution Acceptance Criteria:

The Applicant initially proposed dissolution acceptance criteria of "1 hr (b) (4)%, 8 hr (b) (4)%, 16 hr NLT (b) (4)%" and subsequently revised dissolution acceptance criteria to "1 hr (b) (4)%, 8 hr (b) (4)%, 16 hr NLT (b) (4)%", which were deemed permissive. The Applicant accepted the Division's recommended "1 hr (b) (4)%, 8 hr (b) (4)%, 16 hr NLT (b) (4)%" as quality control for batch release and on stability for the proposed drug product.

In Vitro Alcohol Dose Dumping:

The in vitro alcohol dose dumping study conducted in 0.1N HCl medium up to 12 hours and in the proposed dissolution medium up to 2 hours with 5%, 20%, 40% alcohol for all strengths. Results showed the lack of in vitro alcohol dose-dumping potential compared to control (0%). The Applicant justified for the adequacy of the study design based on the provided information and consequently the study results were accepted, based on the totality of the information and data provided, in a communication with the Division during the review cycle. The Applicant was advised in the communication to provide justification with respect to labeling implication pertinent to alcohol consumption.

Extended-Release Claim:

The Applicant conducted a steady state bioequivalence (BE) study (TV50717-BE-10179) for the proposed deutetrabenazine QD tablet and the marketed BID tablet (AUSTEDO®) and evaluated the food effect on the pharmacokinetics of the proposed deutetrabenazine QD tablet in study TV50717-BE-10165. The PK profile of deutetrabenazine from the proposed QD tablet when given once-daily exhibited an extended/flatter plasma concentration-time profile that is encompassed within peak and through levels produced by the marketed BID tablet (AUSTEDO®), and consequently resulted in a smaller degree of fluctuation at steady-state in comparison. Additionally, the proposed product was shown to be devoid of food- and alcohol-induced dose-dumping potential. The Clinical Pharmacology review team confirmed the acceptability of both steady-state BE study and food effect study. In vitro dissolution profile data provide supportive evidence of the proposed deutetrabenazine QD tablet having characteristics of an extended-release drug product. This Reviewer concludes that the available information and data meet the requirement as per 21 CFR 320.25(f) and support the extended-release claim for the proposed deutetrabenazine QD tablet (AUSTEDO® XR).

Formulation bridging:

The proposed commercial formulation and the formulation used in pivotal clinical studies are the same as the final formulation of the formulation development program. No in vivo bridging study is needed.

Recommendation:

From a Biopharmaceutics perspective, NDA 216354 for AUSTEDO® XR Deutetrabenazine Extended-Release Tablet/ 6 mg, 12 mg, and 24 mg ADEQUATE.

FDA-approved dissolution method and acceptance criteria:

Apparatus	Medium/ Temperature	Volume	Speed	Acceptance Criteria
USP Apparatus II (paddle) with Japanese sinkers	0.05 M Potassium Biphthalate pH 3.0 /37°C	500 mL	75 rpm	1 hr (b)(4) – (b)(4)% 8 hr (b)(4) – (b)(4)% 16 hr NLT (b)(4)%

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	4/21/2022
Sequence 0007 /Response to Biopharmaceutics IR 1	9/30/2022
Sequence 0010 /Response to Biopharmaceutics IR 2	12/19/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:
No BCS designation was requested.

Solubility:

Table 1. Deutetrabenazine solubility across pH 1.2 – 6.8

Media	Solubility at 37°C in mg/mL
0.1N HCL	12.9
0.05M Potassium Biphthalate pH 3.0	6.7
0.05M Acetate Buffer pH 4.5	0.8
0.05M Potassium Phosphate pH 6.8	0.05

Reviewer's comment:
The Applicant submitted the aqueous solubility data for the drug substance (deutetrabenazine) over the physiological pH range 1.2 to 6.8. As shown in ***Table 1,*** *deutetrabenazine has low solubility as per BCS criteria and the solubility is pH dependent.*

Permeability:

No permeability data were provided.

Dissolution: Refer to B.2 section

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

1. Dissolution Method

The proposed dissolution method is shown in **Table 2**.

Table 2. Proposed dissolution method

Sample	Lot: WSR5920-95 ((b) (4) API)
Apparatus	USP Apparatus II (Paddle) with Japanese Sinkers
Volume	500 mL
Speed	75 rpm
Vessels	Regular Vessels
Medium	0.05M Potassium Biphthalate pH 3.0

1) Dissolution Method Development

(b) (4)

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(b) (4)

2) Discriminating Ability of the Proposed Dissolution Method

In the original submission, the Applicant used a DoE study for the ER coating formulation to demonstrate the discriminating ability of the proposed dissolution method. The investigation was not performed appropriately, and data were not accepted because more than one variable were changed in variant formulations at the same time. This Reviewer provided guidance for the Applicant on proper evaluation of method's discriminating ability via an Information Request dated 8/31/2022 (**Appendix**).

In response, the Applicant provided data evaluating the discriminating ability of the proposed dissolution method against (b) (4)

(b) (4)

The Applicant also evaluated the discriminating ability at (b) (4) rpm rotation speed. The data showed no advantage of (b) (4) rpm in discriminating ability of the dissolution method compared to 75 rpm.[1]

[1] \\CDSESUB1\EVSPROD\nda216354\0007\m1\us\quality-response-fda-questions.pdf (Appendix I)

Figure 8. Dissolution profiles of deutetrabenazine QD tablet 24 mg with different amounts of (b) (4)

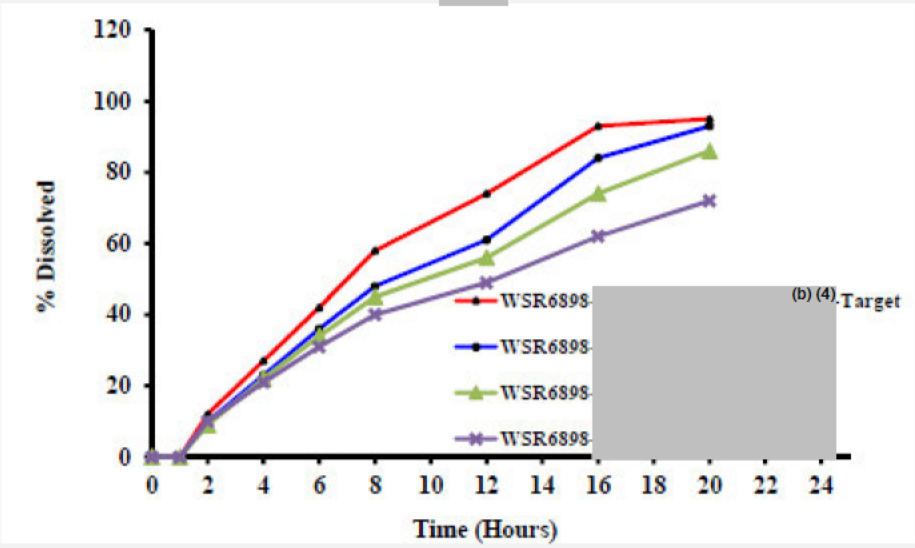
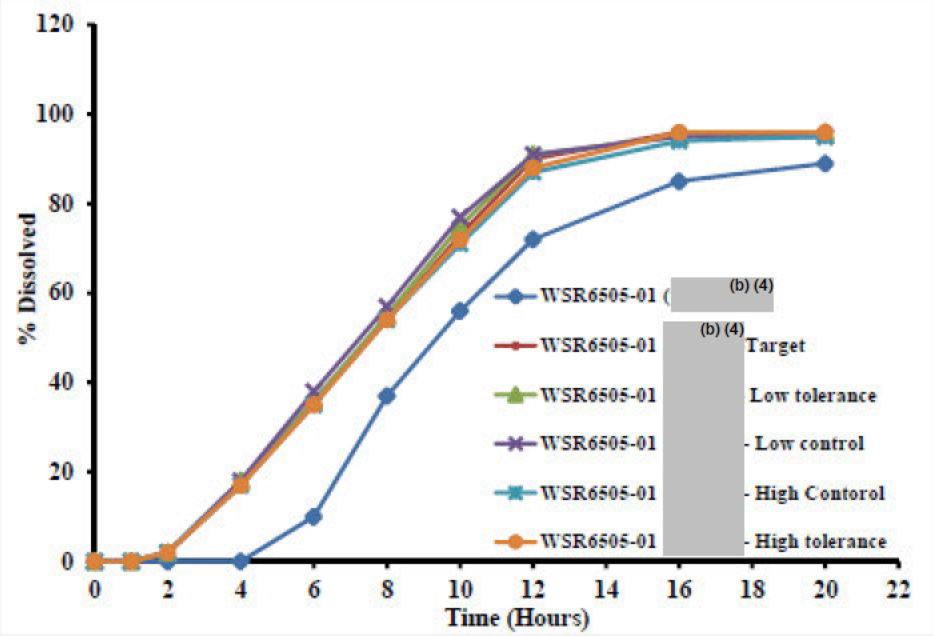


Figure 9. Dissolution profiles of deutetrabenazine QD tablet 24 mg with different sizes of laser-drilled orifice



Reviewer's overall comment on the dissolution method:

The Applicant provided data to support the selection of medium pH, medium volume, apparatus, and rotation speed. The selection of the dissolution parameters is acceptable. The Applicant also provided data to evaluate the discriminating ability of the proposed dissolution method. Although the data showed that the method is able to detect changes in (b) (4) tablets, the method is not considered discriminating because the change in (b) (4) amount is much greater than Agency typically recommended target ± 10-20% range and the (b) (4) tablet is not a

critical quality attribute. However, due to the design of the drug product, i.e., the (b) (4) osmotic system, the drug release follows a zero order. Based on the totality of the information, this Reviewer considers the proposed dissolution method acceptable.

2. Dissolution Acceptance Criteria

The dissolution acceptance criteria of "1 hr (b) (4)%, 8 hr (b) (4) 16 hr NLT (b) (4)%" were initially proposed based on the analysis of the stability dissolution data, which was deemed unacceptable. Consequently, the Applicant was requested to submit dissolution profile data for pivotal clinical batches and registration batches and propose a new set of dissolution acceptance criteria in an Information Requested dated 8/31/2022 (**Appendix**). In response, the Applicant provided the requested dissolution profile data for the registration batches (3 batches for each strength) and proposed a new set of dissolution acceptance criteria of "1 hr (b) (4)%, 8 hr (b) (4)%, 16 hr NLT (b) (4)%" accordingly.

The Applicant did not provide batch number of the pivotal clinical batch. Based on clinical study information, 24 mg strength was used in the pivotal bioequivalence study. Based on the average dissolution profile data of three 24 mg registration batches, including the pivotal bio-batch 240911R06 (**Table 8 – 10**), the dissolution acceptance criteria of "**1 hr (b) (4)%, 8 hr (b) (4)%, 16 hr NLT (b) (4)%**" are supported and were recommended to the Applicant in the information requested dated 12/5/2022 (**Appendix**). In response, the Applicant accepted the recommended dissolution acceptance criteria.

Table 8. Dissolution profiles data for deutetrabenazine QD tablet 24 mg, Lot # 240911R04

Manufacturing Date: 10/23/2020

Test Date: 02/01/21

Notebook Reference: WSR5966 p.29

	Amount (%) Dissolved																
Time (hrs.)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (b) (4)	Mean (n=12)	STDEV	%RSD	Min	Max (b) (4)
0													0	NA	NA		
1													29	1.1	3.9		
2													29	1.0	3.4		
4													38	0.9	2.4		
6													49	1.5	3.0		
8													60	2.0	3.3		
10													72	2.6	3.6		
12													84	3.2	3.8		
16													101	2.9	2.9		
20													103	3.0	2.9		

Table 9. Dissolution profiles data for deutetrabenazine QD tablet 24 mg, Lot # 240911R05

Manufacturing Date: 12/04/2020

Test Date: 02/03/21

Notebook Reference: WSR6526 p.52

	Amount (%) Dissolved																
Time (hrs.)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (b) (4)	Mean (n=12)	STDEV	%RSD	Min	Max (b) (4)
0													0	NA	NA		
1													27	0.8	2.8		
2													28	0.8	2.8		
4													36	1.0	2.8		
6													46	1.5	3.2		
8													57	1.6	2.8		
10													68	1.8	2.6		
12													80	2.5	3.1		
16													97	1.7	1.7		
20													98	1.4	1.4		

Table 10. Dissolution profiles data for deutetrabenazine QD tablet 24 mg, Lot # 240911R06

Manufacturing Date: 12/07/2020

Test Date: 02/03/21

Notebook Reference: WSR6145 p.23

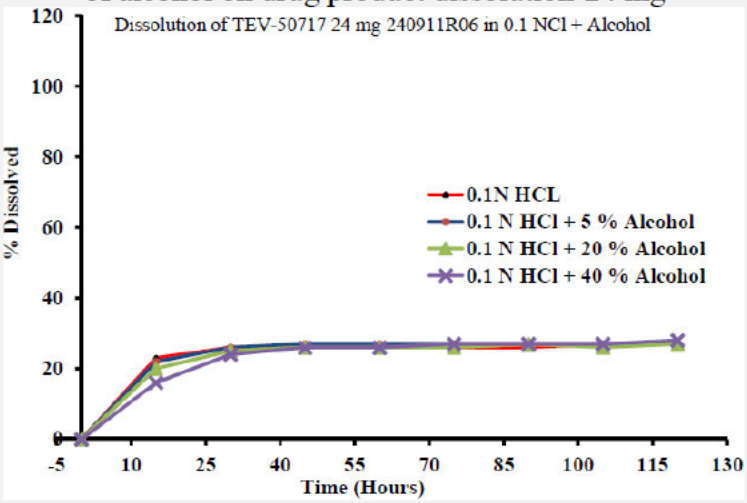
	Amount (%) Dissolved																
Time (hrs.)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (b) (4)	Mean (n=12)	STDEV	%RSD	Min	Max (b) (4)
0													0	NA	NA		
1													27	0.8	2.8		
2													27	0.9	3.2		
4													34	0.8	2.3		
6													44	1.1	2.5		
8													54	1.4	2.5		
10													65	1.7	2.7		
12													75	2.1	2.8		
16													93	1.4	1.5		
20													96	1.0	1.0		

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: *{Adequate}*

The originally submitted in vitro alcohol dose-dumping study was deemed inadequate due to the omission of detailed dissolution data for study in 0.1N HCl medium (up to 12 hours) (**Figure 10**) and no study conducted in the proposed dissolution medium, per 2019 BA Draft Guidance. The Applicant was requested to re-evaluate the alcohol dose-dumping potential in the Information Request dated 12/5/2022 (**Appendix**).

Figure 10. Representative dissolution profiles for TEV-50717 once daily tablet for effect of alcohol on drug product dissolution-24 mg



In response, the Applicant provided detailed dissolution data up to 2 hours for alcohol dose-dumping study in 0.1N HCl medium with 0%, 20%, and 40% ethanol and in proposed dissolution medium (0.05M Potassium Biphthalate pH 3.0) with 0% and 40% alcohol for all strengths of the proposed drug product. The provided data showed no increase in drug release at all tested alcohol levels for all strengths vs. control (0%). Based on the provided data, no in vitro alcohol dose dumping potential is observed.

A General Advice Letter (**Appendix**) was communicated to the Applicant during the review cycle regarding the adequacy of the study design. Based on the totality of the information and data provided, the Division accepted the study results. The Applicant was also advised in the communication to provide justification with respect to labeling implication pertinent to alcohol consumption.

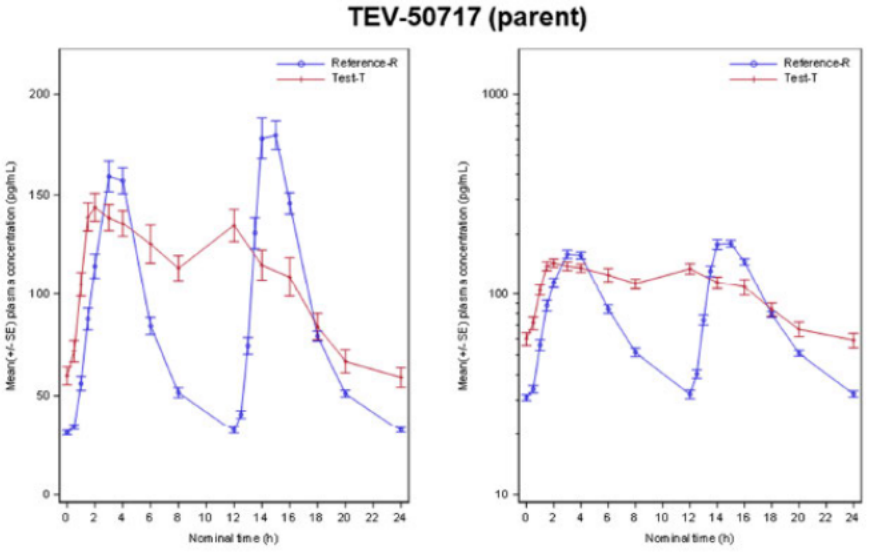
B.11 EXTENDED-RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: *{Adequate}*

The Applicant conducted a steady state bioequivalence (BE) study (TV50717-BE-10179) for the proposed deutetrabenazine QD tablet and the marketed BID tablet (AUSTEDO®) and evaluated the food effect on the pharmacokinetics of the proposed deutetrabenazine QD tablet in study TV50717-BE-10165. As shown in results of the steady state BE study (**Figure 11** and **Table 11**), the PK profile of deutetrabenazine from the proposed QD tablet

when given at a lesser dosing frequency (QD) exhibited an extended/flatter plasma concentration-time profile (with wider range of Tmax,ss values), as intended, that is encompassed within peak and through levels produced by the marketed BID tablet (AUSTEDO®), and consequently resulted in a smaller degree of fluctuation (1.68) at steady-state in comparison (1.68 vs. 2.19). The results of food effect study (**Figure 12**) show that the proposed product is devoid of significant food effects and food-induced dose-dumping potential (also a lack of alcohol dose-dumping potential). This Reviewer confirmed with Dr. Min Li in Clinical Pharmacology review team (Office Clinical Pharmacology) that both the steady state BE study for the proposed QD tablet and the marketed BID tablet (AUSTEDO®) (BE was established) and the food effect study are acceptable. It is also noted as supportive evidence that the in vitro dissolution profiles of the proposed deutetrabenazine QD tablet show characteristics of an extended-release drug product. This Reviewer concludes that the available information and data meet the requirement as per 21 CFR 320.25(f) and support the extended-release claim for the proposed deutetrabenazine QD tablet (AUSTEDO® XR).

Figure 11. Plasma concentrations vs time for deutetrabenazine at steady state (mean of day 6 and 7) after administration of QD formulation (test) and AUSTEDO BID (reference) (TV50717-BE-10179)

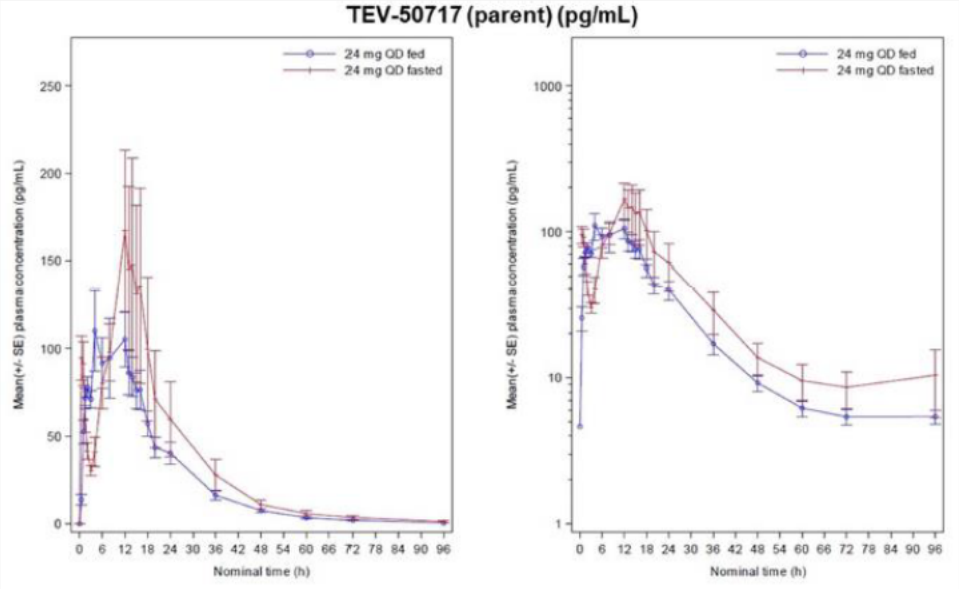


* Linear (Left) and Semi-Log Scale (Right)

Table 11. Summary of pharmacokinetic parameters for deutetrabenazine at steady-state after administration of QD formulation (test) and AUSTEDO BID (reference) (TV50717-BE-10179)

Parameter		QD formulation	AUSTEDO BID
TEV-50717 (parent)			
$C_{max,ss}$ (pg/mL)	n_{obs}	478	470
	Geom. mean (%CV)	182.78 (67.6)	191.52 (54.0)
$t_{max,ss}$ (h)	n_{obs}	478	470
	Median	3.00	3.00
	Min, Max	0.00, 24.00	1.00, 8.00
$AUC_{0\text{-}24h,ss}$ (pg×h/mL)	n_{obs}	469	466
	Geom. mean (%CV)	2064 (59.6)	1798 (40.0)
$C_{min,ss}$ (pg/mL)	n_{obs}	478	470
	Geom. mean (%CV)	33.02 (60.7)	25.09 (46.7)
$C_{av,ss}$ (pg/mL)	n_{obs}	469	466
	Geom. mean (%CV)	85.98 (59.6)	74.92 (40.0)
Degree of fluctuation	n_{obs}	469	466
	Geom. mean (%CV)	1.68 (34.1)	2.19 (38.0)
Swing	n_{obs}	478	470
	Geom. mean (%CV)	4.40 (64.5)	6.51 (56.7)
CL_{ss}/F (L/h)	n_{obs}	469	466
	Geom. mean (%CV)	11631 (59.6)	13348 (40.0)
C_{trough} (pg/mL)	n_{obs}	478	470
	Geom. mean (%CV)	41.96 (79.9)	29.10 (46.4)

Figure 12. Plasma concentrations vs time for deutetrabenazine after administration of 24 mg QD formulation under fasted and fed conditions (TV50717-BE-10165)



* Linear (Left) and Semi-Log Scale (Right)

BB.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

The Applicant conducted 7 Phase 1 clinical studies (**Table 12**) to support formulation development. The final formulation (similar to the Pilot 3 formulation) contains (b) (4) of the active pharmaceutical ingredient (API) in the bilayer tablet core, (b) (4) API in the immediate-release coating, and (b) (4) ER coating. Since the final formulation (**Table 13**) was used in pivotal clinical studies and is the proposed commercial formulation, no additional in vivo bridging is needed.

Table 12. Phase 1 clinical studies to support formulation development[2]

Study	Formulation	IR component (% dose)	ER component (%dose) /ER coating (%)
TV50717-BA-10150	4 ER formulations-only prototypes	(b) (4)	
TV50717-BA-10158, TV50717-FE-10163, and TV50717-BA-10171	Pilot 1		
TV50717-BA-10172 and TV50717-BE-10166[a]	Pilot 2		
TV50717-BA-10176	Pilot 3		

[a] In Study TV50717-BE-10166, the formulation was at production scale.

[2] \\CDSESUB1\EVSPROD\nda216354\0001\m2\27-clin-sum\summary-biopharm.pdf

Table 13. Final formulation of deutetrabenazine QD tablet[3]

Component	Amount per Tablet (mg)			Function	Standard/Grade
Deutetrabenazine	6.00	12.00	24.00	Active ingredient	In-house/GMP
Butylated Hydroxyanisole	(b) (4)			Anti-oxidant	NF
Butylated Hydroxytoluene				Anti-oxidant	NF
Polyethylene Oxide (b) (4)				Controlled release agent	NF
(b) (4)				Controlled release agent	NF
Hypromellose (b) (4) (b) (4)				Binder	USP
Sodium Chloride				Osmotic agent	USP
FD&C Red No. 40[1]				Coloring agent	Supplier
Magnesium Stearate				Lubricant	NF
Cellulose Acetate (b) (4)				Drug release-controlling polymer	NF
(b) (4)				Drug release controlling polymer	NF
Polyethylene Glycol 3350				Drug release controlling polymer	NF
Hydroxypropyl Cellulose				Binder	NF
(b) (4)				Coating pigment	Supplier
				Coating pigment	Supplier
				Coating pigment	Supplier
				Printing agent	Supplier
				Coating solvent	USP
				Coating solvent	NF
				Solvent	USP
Isopropyl Alcohol[2]				Printing solvent	USP
Total	337.0	338.7	342.2	-	-

1 FD&C Red No. 40 is listed in FDA's Inactive Ingredients Database and is within the recommended limit. (b) (4)

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

[3] \\CDSESUB1\EVSPROD\nda216354\0001\m2\23-qos\descrip-comp-dp.pdf

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Jia Leo

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION (*as submitted in eCTD SN 0003, dated 24-MAY-2022*)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Items in Proposed Labeling	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)

	(choose "Adequate", "Inadequate", or "N/A")	
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Extended-release Tablets: 6 mg, 12 mg, and 24 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt form

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution,	N/A	Oral extended release tablet dosage form to be taken as whole tablet, and doesn't require any special preparation before administration.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	• Swallow AUSTEDO XR whole. Do not chew, crush, or break tablets.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt form
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not a salt form
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	vesicular monoamine transporter 2 (VMAT2) inhibitor
Chemical name, structural formula, molecular weight	Adequate	Racemic mixture of (RR, SS)-deutetrabenazine
If radioactive, statement of important nuclear characteristics.	N/A	Deutetrabenazine contains 6 atoms of deuterium, a non-radioactive hydrogen isotope.
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	No statement on Gluten included
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	Deutetrabenazine is racemic mixture containing the following structures:
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Inadequate	Include the statement, "Dispense in original container"

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Inadequate	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Street address not listed, but per 21 CFR 201.1(i) street address may be omitted if it is shown in a current city directory or telephone directory.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	• Swallow AUSTEDO XR/AUSTEDO tablets whole with water. Do not chew, crush, or break AUSTEDO XR/AUSTEDO tablets before swallowing. If you cannot swallow AUSTEDO XR/AUSTEDO tablets whole, tell your healthcare provider. You may need a different medicine.
Storage and handling information (if applicable)	Adequate	**How should I store AUSTEDO XR/AUSTEDO?** • Store AUSTEDO XR/AUSTEDO tablets at room temperature, between 68°F to 77°F (20°C to 25°C). • Keep the bottle tightly closed to protect AUSTEDO XR/AUSTEDO from light and moisture. **Keep AUSTEDO XR/AUSTEDO tablets and all medications out of reach of children.**
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Inadequate	To include a statement indicating the inclusion of (1 unit of 1 g) desiccant canister in the bottles, in PI under section 16.1 How Supplied and Medication Guide under "How should I store.."
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Street address not listed, but per 21 CFR 201.1(i) street address may be omitted if it is shown in a current city directory or telephone directory.

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

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Item	Items in Proposed Labeling (bottle label and blister cards) (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Final decision deferred to DMEPA
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	Consistent with the exemption under 21 CFR 201.100(b)(3)
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Not a salt form
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Inadequate	Require an identifying lot or control number for both bottles and blisters, from which it is possible to determine the complete manufacturing history of the package of the drug. In addition, the Blisters containing two different dosage strengths packaged in multiple rows also need to link Lot/EXP to respective dosage strengths. The format for the expiration date must be defined to include a year, month, and non-zero day, with the month in either numerical (YYYY-MM-DD) or in alphabetical (YYYY-MMM-DD) format.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (bottle label and blister cards) (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Reviewer Note on Blister Cards: This limited information provided for Blister cards (on primary container label) is acceptable, per 21 CFR 201.10(i), due to space limitation. These blister cards supplied to patients as starter kits, include required minimum information, i.e., proprietary name, established name, strength(s) of drug and "manufactured for" printed on the blister card, along with the day of dosing against each blister pocket. These blisters are in turn inserted into outer shell packs, i.e., blisters for dosing on days 1-14 into one outer shell (Identified as Weeks 1-2) and blisters for days 15-28 into another (Identified as Weeks 3-4).

Item	Items in Proposed Labeling (blister shell packs and outer carton) (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[4], (font size and prominence)	Adequate	Final decision on Font size and design deferred to DMEPA
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Not a salt form
Net contents (e.g., tablet count, volume of liquid)	Adequate	Provided net contents in terms of number of tablets of each dosage strength present on both blister cards and outer carton.
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	Separate NDC numbers assigned for each of the blister cards and outer carton
Lot number and expiration date	Inadequate	Lot number and Expiration missing on the outer carton. There is designated space provided for the two blister cards, but Lot /EXP formats were not provided. Require an identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug. The format for the expiration date must be defined to include a year, month, and non-zero day, with the month in either numerical (YYYY-MM-DD) or in alphabetical (YYYY-MMM-DD) format.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	

[4] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	**Items in Proposed Labeling (blister shell packs and outer carton)** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments about Carton Labeling** (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Inadequate.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information and Medication Guide:

1. We acknowledge the inclusion of "Child resistant pack" for starter kits in of prescribing information under section 16.1 How Supplied. We advise you to include similar statements for tablets supplied in bottles, i.e., about child resistant caps.
2. In PI section 16.2 Storage and on all container labels include the statement, "Dispense in original container".
3. Include street address (number and street name) as part of manufacturer's information under section 17 Patient Counseling Information of Prescribing Information and at the end of Medication Guide, required Per 21 CFR 201.1(i).
4. In the Medication Guide, under section titled "How should I store AUSTEDO XR/AUSTEDO?" include the statement "Do not discard the Desiccant canister in the bottle until the last dose of AUSTERDO XR/AUSTEDO is consumed.

Container and Carton labeling (sent to sponsor as of 10-JAN-2023):

5. We took note of the space allotted for Lot/EXP information on all packaging components. However, an identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug is needed. Provide the format to be used for assigning Lot / Batch numbers to the various professional samples and trade packaging configurations. Also see a separate comment on EXP format to be used.
6. We noted that proposed starter kits contain tablets of all three dosage strengths in each carton, with at least two strengths in each of packaged blister /shell pack unit. Confirm by incorporating a statement in either in module 3.2.P.8 or other appropriated sections of the submission that the expiry date assigned to the combination blisters, shell pack units and outer carton of starter kit (required) will not exceed the shortest expiry date of the batch of tablets, among the three dosage strengths.

Overall Assessment and Recommendation:

Inadequate. As of this review, this application is **NOT** deemed ready for approval in its present form per 21 CFR 314.125(b)(8) from the CMC labeling/labels perspective until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, PhD, R. Ph; 13-JAN-2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Martha R. Heimann, PhD; 17-JAN-2023

Venkateswara Pavuluri

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Martha Heimann

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

Date: **03-FEB-2023**

From: **Venkateswara R. Pavuluri, PhD, R. Ph.**
Drug Product Reviewer, DNDPII
Office of New Drug Products

Through: **Julia C. Pinto, PhD (for Martha R. Heimann, PhD).**
Branch Chief, Br3/ DNDPII
Office of New Drug Products

To: **CMC Labeling Review for AUSTEDO® XR (NDA 216354)**
Subject: Final Recommendation APPROVAL

At the time when initial Labeling Review of NDA 216354 was completed on 17-JAN-2023, this NDA was not recommended for approval 21 CFR 314.125(b)(6) from the CMC labeling/labels perspective due to deficiencies listed below. The NDA for this drug product was otherwise complete and adequate from the drug product perspective, per the review dated 17-JAN-2023. This labeling memo is based on the Amendments (SN 0012, dated 17-JAN-2023; SN 0014, dated 31-JAN-2023).

Labeling/Label Deficiencies identified in CMC Labeling review as of 17-DEC-2022:

A. Prescribing Information and Medication Guide:

1. *We acknowledge the inclusion of "Child resistant pack" for starter kits in of prescribing information under section 16.1 How Supplied. We advise you to include similar statements for tablets supplied in bottles, i.e., about child resistant caps.*

   Applicant's Response (eCTD SN 0014 dated 31-JAN-2023): Applicant proposes to add "Child-resistant package" to the AUSTEDO XR bottle labels in accordance with *FDA Guidance for Industry, Child-Resistant Packaging Statements in Drug Product Labeling.*

Reviewer's Evaluation: Adequate.

2. *In PI section 16.2 Storage and on all container labels include the statement, "Dispense in original container".*

   Applicant's Response: Applicant added "***Dispense in original container***" to the main panel of the shell packs, as the inner blister cards are locked into the shellacks and do not separate. Since the outer carton prominently

states “***Dispense in this sealed carton***”, Applicant stated that it reinforce both that dispensers should not open the kit and the product should be dispensed in the original container.

Applicant proposed to add an alternate statement, “***Dispense in original container or in a tight container as defined in USP***” to support use of the original container, while still allowing for dispensing in a tight container when necessary to dispense fewer than 30 tablets, as directed by physician orders during the titration phase where physicians may prescribe tablet strengths in quantities smaller than 30 in order to achieve the target dose and up-titration in weekly increments or when prescriptions are written for less than a 30 day supply.

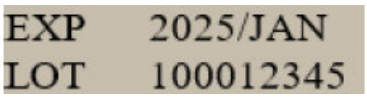
Reviewer’s Evaluation: Adequate.

Container and Carton labeling (sent to sponsor as of 10-JAN-2023):

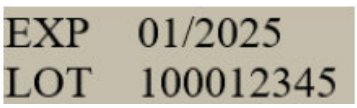
3. *We took note of the space allotted for Lot/EXP information on all packaging components. However, an identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug is needed. Provide the format to be used for assigning Lot / Batch numbers to the various professional samples and trade packaging configurations. Also see a separate comment on EXP format to be used.*

Applicant’s Response (eCTD SN 0012 dated 17-JAN-2023):

Applicant stated that the shaded areas identified as ‘Serialization Coding Area’ or ‘Lot/Exp Coding Area’ on carton and container labeling for AUSTEDO XR will be completed at the manufacturing site(s), with online printing within these areas. The formats for AUSTEDO XR titration kits and bottles were provided. For the titration kits, the expiration date will be printed in the format “YYYY/MMM”.



For AUSTEDO XR bottles, the expiration date format currently in use at the facility is “MM/YYYY”.



Applicant further stated that the packaging facility for bottles is in the process of replacing the hardware and software that prints the bottle label expiration date. Once in place, the new system will be configured to print the expiration date in the format “YYYY/MM”. They intend to implement this change in advance of new USP labeling requirements, i.e. USP General Chapter <7> Labeling Official Date of) September 2023.

Reviewer's Evaluation: **Adequate**. Applicant provided sample formats of Lot number and Expiry date selected for titration kits (sample and commercial packs) and HDPE bottles.

4. *We noted that proposed starter kits contain tablets of all three dosage strengths in each carton, with at least two strengths in each of packaged blister /shell pack unit. Confirm by incorporating a statement in either in module 3.2.P.8 or other appropriated sections of the submission that the expiry date assigned to the combination blisters, shell pack units and outer carton of starter kit (required) will not exceed the shortest expiry date of the batch of tablets, among the three dosage strengths.*

   Applicant's Response (eCTD SN 0012 dated 17-JAN-2023): Applicant agreed to assign the shortest of the expiry dates among the three dosage strengths to the combination blisters, shell pack units and outer carton of titration kit and included the below statement in Section 3.2.P.8.1:

"Therefore, 6 mg samples at the intermediate condition of 30°C/65%RH were tested from the 3 months stability time point and 12 mg samples from the 6 months stability point, and all data have remained within the proposed commercial specifications up to 12 months for all attributes. **Based on the obtained stability data and since all tablet strength are co-packaged in the same blister pack, a shelf life of 18 months for 6 mg, 12 mg, and 24 mg is proposed for the blister. The shelf life assigned to the combination blisters, shell pack units and outer carton of starter kit will not exceed the shortest shelf life of the batch of tablets, among the three dosage strengths.** Future shelf life extension will be supported by real time stability data according to the stability testing protocols."

Reviewer's Assessment: Adequate. Applicant agreed to suggested Agency recommendation and a statement of commitment incorporated in module 3.2.P.8.1.

Recommendation:

The CMC label/labeling issues identified in the labeling review have been satisfactorily resolved, as reproduced in attachment below. This application is recommended for APPROVAL from the CMC labeling/label perspective.

Venkateswara R. Pavuluri, PhD, R. Ph.,
Drug Product Reviewer
DNDP II, ONDP

Julia C. Pinto, PhD,
Branch Chief, Branch 3, DNDP II, ONDP

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Venkateswara Pavuluri

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Julia Pinto

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Date: 2/03/2023 02:44:16PM
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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/

JULIA C PINTO
02/07/2023 09:19:57 AM