CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216354Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	February 17, 2023
From	Natalie Getzoff, MD Teresa Buracchio, MD
Subject	Summary Memo
NDA/BLA # and Supplement #	216354
Applicant	Teva Neuroscience, Inc
Date of Submission	April 21, 2022
PDUFA Goal Date	February 21, 2023
Proprietary Name / Non-Proprietary Name	Austedo XR (deutetrabenazine extended release)
Dosage Form(s) / Strengths	6, 12, and 24 mg osmotic extended-release tablets
Applicant Proposed Indication(s)/Population(s)	*Treatment of chorea associated with Huntington's Disease and treatment of tardive dyskinesia*
Action or Recommended Action:	Approval

1. Background

The applicant has submitted a New Drug Application (NDA) for Austedo XR (deutetrabenazine extended-release) tablets. The applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on the findings of safety and effectiveness for the listed drug, Xenazine (tetrabenazine, NDA 021894), the innovator product (Austedo tablets, NDAs 208082 and 209885, referred henceforth in this review as deutetrabenazine BID), and on data from a bioequivalence study for establishing a pharmacokinetic (PK) bridge between deutetrabenazine XR to deutetrabenazine BID. Deutetrabenazine BID is supplied as 6, 9, and 12 mg tablets and dosed BID at doses 12 mg or greater. The applicant intends to market deutetrabenazine XR in 6, 12, and 24 mg tablets for dosing once daily (QD).

Austedo (BID) was approved on April 3, 2017 (NDA 208082) for treatment of chorea associated with Huntington's disease and on August 30, 2017, for the treatment of tardive dyskinesia. The applicant proposes the same indications for deutetrabenazine XR as for deutetrabenazine BID. The recommended starting dose for deutetrabenazine BID is 6 mg twice daily with a recommended maximum dosage of 48 mg (24 mg BID), taken orally. The proposed starting dose for deutetrabenazine XR is 12 mg once daily.

2. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

The drug product consists of a bilayer core tablet with an active layer and a swellable push layer covered by a semipermeable coat. A (b) (4) hole is drilled into each tablet, creating an opening through which the drug is pushed as the core starts swelling. The applicant plans to market three dosage strengths, strengths, i.e., 6 mg, 12 mg, and 24 mg. The product is supplied in a 30-count HDPE bottle as a trade pack and starter, "blister" packs containing (b) (4) tablets.

Stability and release testing were found to be acceptable for all three dosage strengths and the two packaging configurations. The stability data provides adequate support for a shelf-life of 18 months for the 6 mg tablet in the HDPE bottle and all three dosage strengths in the blister packs and 24 months for the 12 mg and 24 mg ER Tablets in HDPE container at USP Controlled Room Temperature. OPQ determined that the manufacturing process for the drug product appears to be satisfactory based on its process selection, in-process controls, final product release test, and executed submission batch records. All manufacturing facilities for this product were found to be acceptable. There were no outstanding issues identified in the OPQ review.

OPQ Recommendation: Approval.

3. Nonclinical Pharmacology/Toxicology

There were no nonclinical data included in the submission. The applicant is relying on nonclinical data from the Austedo BID NDA.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Min Li, with Team Leader Dr. Bilal AbuAsal.

A Phase 1, open-label, pharmacokinetic study (TV50717-BE-10179) that compared the multi-dose bioavailability at steady state of deutetrabenazine XR to deutetrabenazine BID in healthy subjects served as the pivotal study for the application.

Study TV50717-BE-10179 was an open-label, randomized, crossover, repeated dose study in healthy subjects under fed condition, that compared the PK of deutetrabenazine (parent) and the active metabolites at steady state between the test formulation (deutetrabenazine XR, 24 mg QD) and the approved deutetrabenazine 12 mg BID. A total of 262 subjects were enrolled and randomized, and PK data of 241 subjects were available for the test (XR) and reference (BID) treatments. Mean plasma concentration-time profiles of deutetrabenazine (parent) and total (α+β)- dihydrotetrabenazine (HTBZ) for the test (XR) and reference (BID) formulations were measured at steady state (Days 6 and 7) after administration of the study drug.

Bioequivalence Assessment

The following table from the OCP review provides a summary of the comparative bioavailability data from the pivotal bioequivalence study.

Table 1: Bioequivalence assessment of PK parameters at steady state between the XR formulation (24 mg QD) and the BID formulation (12 mg BID) in Study TV50717-BE-10179 (OCP analysis)

Analyte	Treatment	n	GeoMean	Comparison	GeoMean Ratio (%)	90% CI lower	90% CI upper
Parent	$AUC_{0\text{-}24h,ss}$ (pg*hr/mL)						
	A: Test (XR)	239	2087.5	T/R	115.2	110.4	120.3
	B: Reference (BID)	235	1811.5				
	$C_{max,ss}$ (pg/mL)						
	A: Test (XR)	239	183.4	T/R	95.0	90.5	99.7
	B: Reference (BID)	236	193.1				
α-HTBZ	$AUC_{0\text{-}24h,ss}$ (ng*hr/mL)						
	A: Test (XR)	239	320.3	T/R	95.4	94.2	96.7
	B: Reference (BID)	235	335.7				
	$C_{max,ss}$ (ng/mL)						

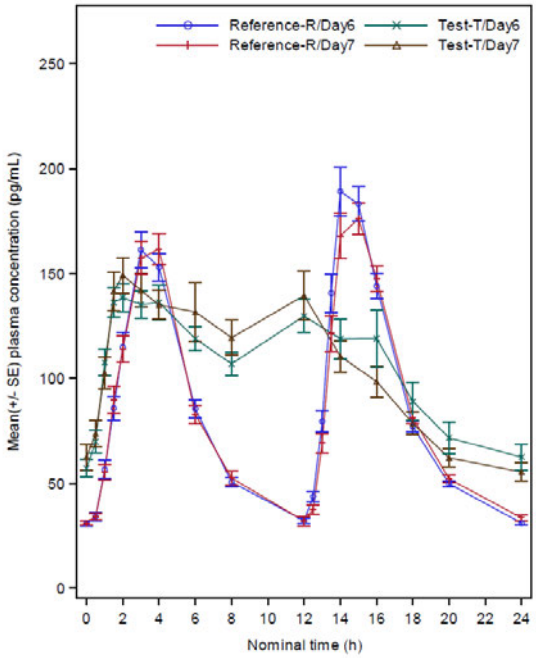
Analyte	Treatment	n	GeoMean	Comparison	GeoMean Ratio (%)	90% CI lower	90% CI upper
	A: Test (XR)	239	18.16	T/R	79.5	78.2	80.9
	B: Reference (BID)	236	22.82				
β-HTBZ	$AUC_{0\text{-}24h,ss}$ (ng*hr/mL)						
	A: Test (XR)	239	320.3	T/R	94.1	92.4	96.0
	B: Reference (BID)	235	335.7				
	$C_{max,ss}$ (ng/mL)						
	A: Test (XR)	239	8.6	T/R	74.8	73.1	76.6
	B: Reference (BID)	236	11.6				
Total (α+β)-HTBZ	$AUC_{0\text{-}24h,ss}$ (ng*hr/mL)						
	A: Test (XR)	239	453.5	T/R	95.1	93.7	96.5
	B: Reference (BID)	235	477.1				
	$C_{max,ss}$ (ng/mL)						
	A: Test (XR)	239	26.9	T/R	77.7	76.3	79.1
	B: Reference (BID)	236	34.6				

Source: Clinical pharmacology reviewer's analysis (from Table 3, OCP review)

The results show that the $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ of the parent drug met the BE criteria as shown in 90%CI range of geometric mean ratio (GMR) between 80-125%. For the two major active metabolites (individually and as a sum), the $C_{max,ss}$ for the test product is slightly smaller than those of the reference, although $AUC_{0\text{-}24h,ss}$ met the BE criteria. The GMRs of $C_{max,ss}$ for active metabolites were smaller than 80% (in the range of 74.8%-77.7%), not meeting the BE criteria.

Deutetrabenazine XR had a lower $C_{max,ss}$ (~22% lower for total active metabolite) and different PK profile shapes when compared to deutetrabenazine BID (Figure 1). The applicant evaluated the clinical relevance of these PK and PK profile shape differences on the tardive dyskinesia and Huntington's disease populations using population PK and Exposure-Response analyses and evaluation of a switch cohort for a long-term safety study.

Figure 1: Mean Plasma Concentrations (±SD) vs Time of the Parent (as Individual and Total) at Steady State



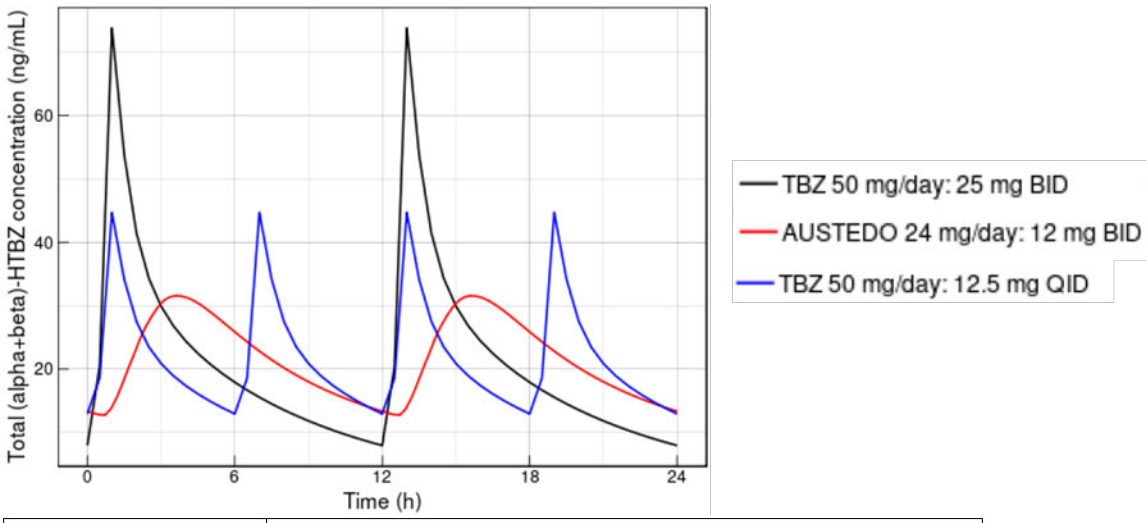
The applicant developed a PK model based on PK data from Study TV50717-BE-10175 (dose proportionality study) and Study TV50717-BE-10179 (steady state relative BA study) and then used to predict and compare PK exposures at steady state between the XR and BID formulations. For the maximal daily dose of 48 mg, the XR product resulted in 9% lower $C_{min,ss}$ (BID: 23.52 ng/mL vs. QD: 21.39 ng/mL), 9% lower $C_{avg,ss}$ (BID: 41.37 ng/mL vs. QD: 37.63 ng/mL), and 26% lower $C_{max,ss}$ (BID: 66.83 ng/mL vs. QD: 49.49 ng/mL) of total (α+ β)-HTBZ concentrations at the mean level when compared to the BID product.

The $C_{max,ss}$ of total (α+ β)-HTBZ concentrations was used to predict change from baseline (CFB) in Abnormal Involuntary Movement Scale (AIMS) score in subjects with TD and CFB in Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS) in subjects with HD using the E-R model. The lower $C_{max,ss}$ of the XR product as compared to the BID product was a key concern; therefore, $C_{max.ss}$ was used as the predictor of efficacy endpoints in the E-R analysis. If the $C_{max,ss}$ was considered a main driver of efficacy, deutetrabenazine XR 48 mg QD would lead to an average of 13.4% lower CFB in AIMS scores in TD and 11% lower CFB in UHDRS scores in HD subjects when compared to deutetrabenazine 24 mg BID.

The impact of PK shape on efficacy was evaluated based on efficacy results from a switch cohort of an open label extension long-term safety study (Study SD-809-C-16). Study SD-809-C-16 included a cohort of 37 patients with HD and chorea who were switched overnight from Xenazine to a dosing regimen of Austedo BID predicted to provide comparable exposures to total (α+β)-HTBZ metabolites. No dose adjustment was allowed during the first week after the switch. Simulated PK profiles of total (α+β)-HTBZ from Xenazine (12.5 mg QID) comparing to Austedo BID for 50 mg/day (25 mg BID) suggested comparable daily AUC but lower C_{max} after

switching to Austedo BID (Figure 2). However, the efficacy was maintained post-one week of switch in these HD subjects: the mean (SD) TMC score at baseline and at Week 1 post-switch was 12.46 (5.22) and 11.76 (5.11), respectively. This finding suggests that differences in PK profile shapes and C_{max} may have no impact on efficacy, as long as concentrations are in the range of previously approved dosing regimens.

Figure 2: Concentration-time profiles of simulated total (α+β)-HTBZ from tetrabenazine comparing to the Switched Austedo BID Formulation for 50 mg/day Tetrabenazine (12.5 mg QID and 25 mg BID)



Regimen	Exposure			
	C_{min} (ng/mL)	C_{av} (ng/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
Tetrabenazine 25 mg BID	7.933	21.901	73.841	525.615
Tetrabenazine 12.5 mg QID	12.922	21.906	44.693	525.742
AUSTEDO BID 12 mg BID	12.741	21.596	31.570	518.305

Source: Applicant's PMX-22-09, Page 9, Table 1

Food Effect

Food effect for deutetrabenazine XR was assessed in Study TV50717-BE-10165, during which healthy volunteers were administered a 24 mg dose of deutetrabenazine XR in a fasted state and after a high-fat meal along with a single-dose relative BA assessment between the XR and the BID products. T_{max} occurred more rapidly for all analytes (parent drug and metabolites) in the fasted state (median T_{max} 1 hour) compared to that in the fed state (median T_{max} 4 hours) after administration of a 24-mg XR tablet. The terminal $t_{1/2}$ was similar for all analytes after administration of the 24-mg XR formulation under fasted or fed conditions. The C_{max} and AUC met the BE criteria, indicating no clinically meaningful food effect for the QD product.

Dose Proportionality Assessment

Study TV50717-BE-10175 was a Phase 1, open-label, single center, randomized, 4-period, 4-sequence crossover study that assessed the dose proportionality following the administration

of a single dose of deutetrabenazine XR administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg under fed condition in healthy subjects. The dose proportionality of TEV-50717 (parent) and α-HTBZ and β-HTBZ metabolites (individually and as a sum) was assessed. Dose proportionality was demonstrated for both Cmax and AUC after single doses of the QD tablet across the clinical dose range (6, 12, 24, and 48 mg). The relative BA with regard to Cmax, AUC_{0-t}, $AUC_{0-\infty}$ of all the analytes demonstrated BE between 2×6 mg and 1×12 mg QD osmotic tablets. A linear PK was demonstrated across the dosage strengths and the full clinical range (6-48 mg).

OCP Recommendation: OCP recommends approval based on the based on the adequate scientific bridge established between this proposed XR product and the cross-referenced drug, Austedo tablets, for the treatment of chorea associated with Huntington's disease (HD) and tardive dyskinesia (TD) in adults.

5. Clinical/Statistical-Efficacy

The effectiveness of Austedo XR is based on the demonstration of bioequivalence to the innovator drug.

6. Safety

The safety of deutetrabenazine XR is based on the demonstration of bioequivalence to Austedo BID. Dr. Kenneth Bergmann, the clinical reviewer for this application, reviewed the new safety data in this submission. The safety review focused on the pivotal US bioequivalence study (Study TV50717-BE-10179), as well as two other bioavailability studies (TV50717-PK-10175 and TV50717-BE-10165), all performed in healthy volunteers.

- Study TV50717-BE-10179
  Study 10179 was a Phase 1, open-label, single-center, randomized, 2-period, 2-sequence, crossover repeated dose study under fed conditions to assess BE and relative BA at steady state after repeated administration of deutetrabenazine XR 24 mg QD compared to repeated administration of deutetrabenazine 12 mg BID in healthy subjects who were extensive or intermediate CYP2D6 cytochrome P450 (CYP) 2D6 metabolizers.

  A total of 262 subjects were randomized and were analyzed for safety, although only 243 subjects received the investigational product. The two groups (test → reference and reference → test) were well matched with regard to age (mean 38.8 and 38.3 years, respectively), sex (70% and 62% men, respectively), and race (87% and 87% white, respectively).

- Study TV50717-PK-10175
  Study 10175 was a Phase 1, open-label, single center, randomized, crossover study to assess the dose proportionality of deutetrabenazine (parent) and α-HTBZ, β-HTBZ, and α+β-HTBZ metabolites following the administration of a single dose of deutetrabenazine XR tablets (2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg) under fed conditions in healthy subjects, who were known extensive or intermediate CYP2D6 metabolizers.

  A total of 116 subjects were randomized to one of 4 treatment sequences and all were analyzed for safety. The four treatment groups (sequences ABDC, BCAD, CDBA, and DACB) were well matched with regard to age (mean 39.7, 41.9, 41.2, and 40.7 years, respectively) and weight (80.4, 73.3, 73.0, and 74.3 kg, respectively). The gender distribution was 69%, 48%, 59%, and 48% males, in the treatment groups, respectively.

- Study TV50717-PK-10165
  Study 10165 was a Phase 1, open-label, randomized, crossover study to assess the relative BA of deutetrabenazine (parent) and metabolites, after oral administration of deutetrabenazine XR 24 mg QD compared to deutetrabenazine 12-mg tablets bid (12 hours apart). All 84 subjects enrolled in Study 10165 successfully completed it. The 6 study sequence groups were matched regarding age and weight and the gender distribution was balanced.

Disposition of subjects in the pooled safety population

A total of 443 subjects received 851 doses of deutetrabenazine XR in Studies 10179, 10175, and 10165, combined. No deaths or serious adverse events were reported. Fifty-eight subjects (13%) discontinued participation in the studies, 45 in Study 10179 (17%), 13 (11%) in Study 10175, and 0 in Study 10165. In Study 10179, discontinuation due to adverse events (AEs) occurred in 11 subjects (6 in the deutetrabenazine XR group and 5 in the deutetrabenazine BID group). AEs leading to discontinuation in the deutetrabenazine XR group included anxiety (n=2), and alanine aminotransferase increased, aspartate aminotransferase increased, asymptomatic COVID-19, COVID-19, and rhinorrhea (each in 1 subject). In the deutetrabenazine BID group AEs leading to discontinuation included headache in 2 subjects, and COVID-19, back pain, dizziness, and influenza-like illness (1 subject each). As noted by Dr. Bergmann in his review, the doses administered to subjects in Study 10179 were well above the labeled starting dose for deutetrabenazine.

During Study 10175, two subjects discontinued due to AEs, 1 after receiving 2x6mg deutetrabenazine XR tablets (vomiting) and 1 after receiving 2x24mg deutetrabenazine XR tablets (COVID-19). No subjects discontinued during Study 10165.

Adverse events

During Study 10179, 243 subjects received one or more doses of deutetrabenazine XR and at least 1 treatment emergent adverse event (TEAE) was reported for 28 subjects (12%) when administered deutetrabenazine XR and 22 subjects (9%) when administered deutetrabenazine BID. Headache was the most frequently reported TEAE while receiving either deutetrabenazine

XR or BID (7 [3%] during each period). The only other TEAEs that occurred in more than one subject while receiving deutetrabenazine XR were influenza-like illness and oropharyngeal pain (3 subjects each), and diarrhea, anxiety, and rhinorrhea, (2 subjects each). Dizziness and influenza-like illness each occurred in 2 subjects while receiving deutetrabenazine BID.

In Study 10175, 116 subjects received at least one dose of deutetrabenazine XR, 14 (12%) of whom experienced at least one TEAE. The only TEAE that occurred in more than one subject was influenza-like illness, which occurred in 2 subjects after administration of 2x24 mg deutetrabenazine XR. All other TEAEs occurred in only 1 subject each.

A total of 84 subjects received deutetrabenazine XR during Study 10165, 8 (10%) of whom experienced any TEAE. The only adverse events that occurred in more than 1 subject were headache and presyncope, reported in 3 (4%) and 2 (2%) subjects, respectively.

Laboratory findings

One subject (# (b) (6)) experienced elevated transaminases in Study 10179: increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on Day 8 after completing 7 days of deutetrabenazine XR 24 mg QD exposure. The increased ALT (349 IU/L, reference range 0 to 44 IU/L) and increased AST (133 IU/L, reference range 0 to 40 IU/L) resolved without treatment after 15 days. Another subject had a reported increase in creatinine, but no other details were submitted. No other laboratory abnormalities were reported in Studies 10179, 10175, or 10165.

No clinically significant vital signs changes or ECG abnormalities were reported.

Clinical recommendation: Dr. Bergmann identified no new safety signal observed with administration of deutetrabenazine XR. He recommends approval of this supplement and I agree with his recommendation.

7. Advisory Committee Meeting

None required, as this drug is not a new molecular entity.

8. Pediatrics

The submission did not include any pediatric data. Because Parkinson's disease generally does not occur in the pediatric population, a full waiver was granted for pediatric studies under Pediatric Research Equity Act (PREA).

9. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

The Division of Medication Error and Prevention Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP) provided consultations on the product labeling.

10. Recommendations/Risk-Benefit Assessment

The applicant has provided substantial evidence of the effectiveness and safety of Austedo XR (extended release deutetrabenazine tablets) based on bioequivalence to the listed and cross-referenced drugs.

No new safety signals were identified.

There are no outstanding unresolved issues.

Specific postmarketing risk management activities are not needed.

Agreement has been reached with the applicant on product labeling.

We agree with the review team that this NDA should be approved.

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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02/17/2023 10:59:14 AM

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02/17/2023 11:03:59 AM