CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209885Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209885

Review #1

Drug Name/Dosage Form	SD-809 Austedo (deutetrabenazine)
Strength	6 mg, 9 mg, 12 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals, Inc.
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Facility	Michael Shanks	Branch1/DIA/OPF
Regulatory Business Process Manager	Teshara Bouie	Branch 1/DRBPM1/OPRO
Application Technical Lead	David Claffey	Branch 1/DNDP 1/ONDP

Submissions Reviewed

SUBMISSION	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD #1	30 DEC 2016	All

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Refer to Overall Quality Assessment for NDA 208082 (March 7, 2017). All recommendations are unchanged.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112975	Development of deutetrabenazine for Huntington's disease.
IND	120631	Development of deutetrabenazine for drug-induced tardive dyskinesia.
NDA	21894	Approved NDA for Xenazine® (tetrabenazine) tablets currently held by Valeant Pharmaceuticals. Reference drug for 505(b)(2) submission.
NDA	208082	Approved NDA for use of deutetrabenazine to treat chorea associated with Huntington's Disease.

2. CONSULTS: N/A

Executive Summary

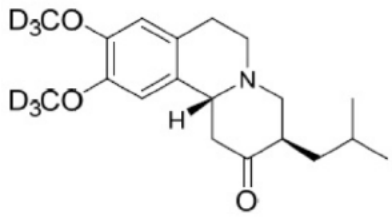
I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective. All CMC information was referenced to NDA 208082 which was approved 3 APR 2017. The manufacturing and testing sites were reevaluated in this review cycle and found to be acceptable.

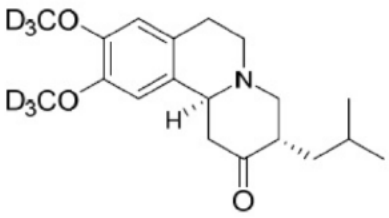
II. Summary of Quality Assessments

A. Product Overview

Deutetrabenazine (TBZ-d_6) (**1**) is approved for treatment of chorea associated with Huntington's disease. This application proposes its use in the treatment of tardive dyskinesia. Chemically, deutetrabenazine is an analog of an approved drug, tetrabenazine (TBZ) (**2**) in which the hydrogen atoms at the 9- and 10-methoxy (-OCH_3) substituents of tetrabenazine are replaced by deuterium. Both deutetrabenazine and tetrabenazine are racemic mixtures. The absolute stereochemistry of the 3*R*,11b*R* enantiomers is shown in the figures below.



RR - Deutetrabenazine



SS - Deutetrabenazine

TBZ is metabolized *in vivo* to α-(+) and (-) and β- (+) and (-) isomers dihydrotetrabenazine (HTBZ) (**3**), which provide systemic exposure for pharmacological activity. However, rapid metabolism of the HTBZ isomers by CYP2D6 to the 9- and 10-O-desmethyl metabolites results in large fluctuations in plasma concentrations and the need for frequent dosing.

The rationale for replacement of the methoxy substituents (-OCH_3) with (d_3)-methoxy (-OCD_3) substituents is that the deuterium kinetic isotope effect reduces the rate at which CYP2D6 breaks down the deuterated analogs of HTBZ relative to non-deuterated HTBZ metabolites. This results in longer half- lives for the active metabolites and less fluctuation in plasma concentrations.

Deutetrabenazine tablets are round, (b) (4) coated tablets containing 6 mg, 9 mg, or 12 mg deutetrabenazine. Deutetrabenazine tablets contain excipients, and have physical characteristics, (b) (4) However, the applicant did not seek an (b) (4) and did not submit data to support such a claim in neither this nor the referenced NDA.

The proposed product will share a PI with the approved Austedo product. No CMC changes to the PI or the container labels are proposed.

Proprietary Name of the Drug Product	Austedo
Non Proprietary Name of the Drug Product	Deutetrabenazine Tablets
Non Proprietary Name of the Drug Substance	Deutetrabenazine
Proposed Indication(s) including Intended Patient Population	Treatment of tardive dyskenisia
Duration of Treatment	Chronic
Maximum Daily Dose	48 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

The OPQ review team made an approval recommendation for the referenced NDA 208082. The applicant made no CMC changes since this approval action. A manufacturing site assessment was made in this review cycle – each were found to be acceptable.

The applicant included a claim for categorical exclusion from environmental assessment to under 21 CFR §25.31(b) This action is predicted to increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The calculated level was (b) (4) ppm, (b) (4) times lower than the 1 ppm level.

Facilities

All facilities proposed for manufacture and testing of deutetrabenazine and Austedo (deutetrabenazine) tablets are currently acceptable.

C. Novel Approaches

The applicant did not employ any novel approaches.

D. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

E. Life Cycle Knowledge Information/Final Risk Assessment

See Attachment 1.

ATTACHMENT 1

Final Risk Assessment for Referenced NDA 208082 Deutetrabenazine Tablets

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability	Impurities due to: (b) (4)	L	(b) (4)	Acceptable	
Content uniformity 6 mg tablet	Low dose, particle size/shape, segregation, flow property	M		Acceptable	
Content uniformity 9 mg, 12 mg tablets		L		Acceptable	
Physical (solid state) stability	Formulation, process parameters, (b) (4)	M		Acceptable	
Microbial limits	Formulation, raw materials, process parameters, (b) (4)	L		Acceptable	
Alcohol dose dumping	Formulation, solubility of rate controlling excipient and/or API	L		Acceptable	
Dissolution	Particle size, (b) (4) hardness, size, shape, (b) (4) coat, formulation, process parameters	M		Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

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David Claffey

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