CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208082Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approve

NDA 208082

Review 2

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
Drug Substance	Gene Holbert	Branch1/DNDAPI/ONDP
Drug Product	Martha Heimann	Branch 1/DNDP 1/ONDP
Process	N/A	
Microbiology	N/A	
Facility	Wayne Seifert	Branch1/DIA/OPF
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heimann	Branch 1/DNDP 1/ONDP

Submissions Reviewed

SUBMISSION	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD #: 21	April 14, 2016	Drug Substance
SD #: 23	May 09, 2016	Drug Substance, Drug Product
SD #: 26	October 3, 2016	Drug Product

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Refer to Overall Quality Assessment, Review No. 1, dated April 26, 2016.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	112975	Development of deutetrabenazine for Huntington's disease.
IND		(b) (4)
NDA	21894	Approved NDA for Xenazine® (tetrabenazine) tablets currently held by Valeant Pharmaceuticals. Reference drug for 505(b)(2) submission.
NDA		(b) (4)

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

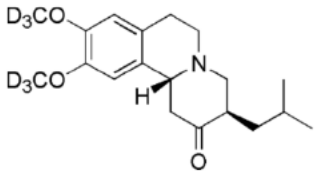
I. Recommendations and Conclusion on Approvability

From a quality perspective, approval of NDA 208082 is recommended. The applicant has adequately addressed the outstanding deficiencies from the original review.

II. Summary of Quality Assessments

A. Product Overview

Deutetrabenazine (TBZ-d_6) (**1**) is a new chemical entity indicated for treatment of chorea associated with Huntington's disease (HD). 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.



1: Deutetrabenazine

(b) (4)

Deutetrabenazine tablets are round, [redacted] (b) (4) -coated tablets containing 6 mg, 9 mg, or 12 mg deutetrabenazine. Deutetrabenazine tablets contain excipients, and have physical characteristics, such as dissolution profile, that are characteristic of extended-release products. However, the applicant is not seeking an extended-release claim and did not submit data to support such a claim.

Proprietary Name of the Drug Product	Austedo is proposed
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 chorea associated with Huntington's disease
Duration of Treatment	Chronic
Maximum Daily Dose	48 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

The OPQ review team identified one major deficiency related to control of the bulk drug substance, and two minor deficiencies. The applicant addressed the deficiencies in the resubmission. There are no other CMC changes.

Drug Substance

The drug substance specification submitted in the original NDA -did not include a test for [redacted] (b) (4) , a known genotoxic substance used in manufacture of deutetrabenazine. The applicant submitted a validated GC method for determination of [redacted] (b) (4) in the drug substance.

Drug Product

The applicant submitted a revised post-approval stability protocol that includes placing the first three commercial batches on long-term and accelerated stability studies, and withdrawing and/or discussing any out of specification batches with the Agency. The applicant also revised the claim for categorical exclusion from environmental assessment to include a statement that to Teva's knowledge, no extraordinary circumstances exist.

Facilities

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

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