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APPLICATION NUMBER:

208082Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 28, 2017
From	Gerald D. Podskalny, DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208082 (Resubmission)
Applicant	Teva Pharmaceuticals, Inc.
Date of Submission	October 3, 2016
PDUFA Goal Date	April 3, 2017
Proprietary Name / Established (USAN) names	Austedo/Deutetrabenazine
Dosage forms / Strength	Oral tablets 6mg, 9mg and 12 mg strengths
Proposed Indication(s)	Chorea (b) (4) Huntington's disease
Recommended:	1. ***Approval***

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. Its estimated prevalence is 5/100,000 in the US (Kay C., 2014). The disease causes progressive dementia, motor disability including chorea and psychiatric symptoms. Symptoms typically begin between ages 30 to 50 years. Disease related disability causes death in 15-20 years after the onset of symptoms. Death is most often due to pneumonia but suicide is more frequent among patients with HD (Roos, 2014). Although it is possible to detect the genetic abnormality in utero, there are no treatments that alter the progression of the disease. Tetrabenazine (Xenazine) was approved on August 15, 2008, (NDA 21894) for the treatment of HD associated chorea. It is remains the only drug approved for treatment of HD. Tetrabenazine is rapidly and extensively metabolized to α-HTBZ and β-HTBZ metabolites, which are active and bind reversibly to VMAT2. The α-HTBZ and β-HTBZ metabolites of tetrabenazine are inhibitors of VMAT2 in the central nervous system and deplete presynaptic monoamines, including dopamine, which reduces chorea in patients with HD. Austedo (deutetrabenazine, aka. SD-809) is a deuterated form of tetrabenazine and it follows the same metabolic pathway and tetrabenazine. Systemic exposure (AUC) to total (α+β)-HTBZ following deutetrabenazine administration is approximately 2-fold greater than with tetrabenazine, which is the rationale for administering a lower dose of deutetrabenazine compared to Xenazine.

2. Background

On May 29, 2015, Teva Pharmaceuticals submitted a 505(b)(2) NDA for Austedo (deutetrabenazine). The NDA referenced the FDA's previous finding of efficacy and safety for Xenazine (NDA 21894). The primary support for the safety and efficacy of Austedo is provided by the clinical trials conducted by the applicant. Deutetrabenazine (dTBZ) was determined to be a new molecular entity and the application was reviewed under the Program. Deficiencies in product quality and clinical pharmacology and nonclinical portions of the NDA

led to the FDA issuing a Complete Response letter on May 27, 2016. The clinical pharmacology deficiencies were central to the reason for the FDA's action. There was insufficient information to determine whether the M1 and M4 metabolites of dTBZ were major or minor circulating human metabolites. If these metabolites were found to be major metabolites in humans, the sponsor would need to show that the M1 and M4 metabolites were adequately assessed in the nonclinical studies included in the application.

The FDA's Controlled Substance Staff (CSS) also requested information to assess whether withdrawal of deutetrabenazine (dTBZ) was associated with signs of dependence and rebound. Additional clinical information was requested regarding adverse events that led to changes in the dose of dTBZ. The additional information requests did not impacted the approvability of the application.

Deutetrabenazine was received orphan designation from the Office of Orphan Product Development. The original dTBZ NDA (NDA-208082) was filed under a standard review clock on August 10, 2015. The applicant's Class 2 resubmission of the NDA application for dTBZ was received on October 3, 2016. This review addresses the applicant's response to the CR issues and the issues that did not impact the approvability of the application for each review discipline. The comments (verbatim) from the CR letter are provided at the beginning Review discipline and the applicant's response and my review comments follow.

Table 1: NDA (b) (4) Resubmission Review Team Members

Quality Review Team	See Table 2 in the CMC/Device Section
Christopher Toscano, PhD Lois Freed, PhD	Nonclinical Reviewer Nonclinical Supervisor (Memo)
Kristina Dimova, PhD Sreedharan Sabarinath, Ph.D.	Primary Reviewer Office of Clinical Pharmacology Team Leader:
Kenneth Bergmann, MD	Clinical Reviewer
Xiangmin Zhang, PhD	Division of Biometrics I
Alicja Lerner, MD, PhD Michael Klein, Ph.D.	Medical Officer Controlled Substance Staff Director Controlled Substance Staff
Loretta Holmes, BSN, PharmD Chad Morris, PharmD, MPH	Division of Medication Error Prevention and Analysis (DMEPA)
Aline Moukhtara, RN, MPH Mathilda Fienkeng, PharmD, RAC	Regulatory Review Officer Team Leader, OPDP
Sharon W. Williams, MSN, BSN, RN Marcia Williams, PhD LaShawn Griffiths, MSHS-PH, BSN, RN Mathilda Fienkeng, PharmD, RAC	Regulatory Review Officer Division of Medical Policy Programs (DMPP) Team Leader, DMPP Associate Director DMPP Team Leader OPDP Office of Prescription Drug Promotion (OPDP)

3. CMC/Device

Table 2: 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

Deficiencies in the Complete Response Letter

PRODUCT QUALITY

1. *The drug substance specification does not include a test for* (b) (4)*. We acknowledge your commitment dated February 22, 2016, to add a test and acceptance criterion of not more than* (b) (4) *(ppm)* (b) (4) *as part of the drug substance specification and to amend the NDA with this test, acceptance criterion, and method validation report on or before March 22, 2016. However, the test method was not submitted until April 14, 2016, and validation data were not provided until May 9, 2016. These amendments to the NDA will be reviewed in the next cycle.*

2. *In your post-approval stability protocol, you indicate that at least one production batch of the product in the commercial packaging will be placed on long term stability annually. Because the registration stability batches were not manufactured at full commercial scale, we request that you update your post-approval stability commitment to include placing the first three commercial batches of each strength of the drug product on long-term stability through the proposed shelf life, and on accelerated stability for 6 months as per ICH Q1A(R2). The data should be tabulated and submitted in the annual report with a commitment to withdrawing or discussing any out of specification results in the distributed drug product to the Agency.*

3. *Per 21 CFR 25.15(d), revise your claim for categorical exclusion to include a statement that, to the applicant's knowledge, no extraordinary circumstances exist.*

Resubmission Review

Gene W. Holbert, Ph.D. in the Division of New Drug API, ONDP reviewed the information related to the drug substance. Kasturi Srinivasachar, Ph.D. Acting Branch Chief completed the secondary review of the drug substance quality information.

The applicant revised the drug substance specification to include a specification for (b) (4) (b) (4) content of not more than (b) (4). At the maximum recommended dose of 48 mg/day, the daily dose of (b) (4) would be (b) (4) which is below the threshold of toxicological concern of 1.5 µg/day from chronic dosing. Dr. Holbert considered the drug substance specification adequate.

The sponsor used headspace gas chromatography for the analytical method to test for (b) (4) (b) (4) content. Dr. Holbert reviewed the method validation for the determination of (b) (4) (b) (4) content. The list of the assay specifications is included in his review. He considered the analytical method adequate and validated for the intended use.

The sponsor also revised the claim for categorical exclusion from environmental assessment to include a statement that to the applicant's knowledge, no extraordinary circumstances exist.

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

OPQ's Assessment and Recommendation
From a quality perspective, approval of NDA 208082 is recommended. The applicant has adequately addressed the outstanding deficiencies from the original review.

4. Nonclinical Pharmacology/Toxicology

Deficiencies in the Complete Response Letter
The toxicokinetic analyses of metabolites in the pivotal nonclinical studies of deutetrabenazine are limited to quantitation of the primary metabolites of deutetrabenazine (i.e., alpha and beta- DHTBZ). If the results of the pending clinical pharmacology analyses identify additional major circulating human metabolites, you will need to demonstrate that each has been adequately assessed in the appropriate nonclinical studies or that plasma exposure to each does not exceed that in humans with Xenazine.

Resubmission Review
Dr. Christopher Toscano was the nonclinical reviewer for the original NDA and this resubmission for dTBZ. Drs. Toscano and Freed concluded the nonclinical studies included in the NDA were adequate to support approval. The need for additional nonclinical studies was dependent on whether or not the M1 or M4 metabolites were determined to be a major circulating metabolite as defined in ICH M3(R2) (i.e., > 10% of total drug-related exposure). The Office of Clinical Pharmacology (OCP) determined the concentrations of M1 and M4 do not exceed the 10% of the total drug related material; therefore, the M1 and M4 metabolites are not major human metabolites of deutetrabenazine.

The resubmission included several additional study reports for completed pharmacology, pharmacokinetic, pharmacokinetic drug interaction and genetic toxicology studies of the M1 and M4 metabolites. This included several high-throughput screens to evaluate M1 and M4 binding to the rat adrenergic α2 receptor and the human adrenergic α2C receptor. Dr. Toscano's review findings for theses study reports are summarized below.

- M1 binding to the rat adrenergic α2 receptor and the human adrenergic α2C receptor was demonstrated but M4 did not demonstrate relevant binding in similar studies.

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