APPLICATION NUMBER:

208082Orig1s000

OFFICE DIRECTOR MEMO
Office of Drug Evaluation-I: Decisional Memo

<table>
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<th>Date: April 3, 2017</th>
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<tr>
<td>From: Ellis F. Unger, M.D., Director</td>
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<td>Office of Drug Evaluation-I, Office of New Drugs, CDER</td>
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<td>Subject: Office Director Decisional Memo</td>
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<td>NDA #: 208082</td>
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<td>Applicant Name: Teva Pharmaceuticals, Inc.</td>
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<td>Date of Submission: October 3, 2016</td>
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<td>PDUFA Goal Date: April 3, 2017</td>
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<td>Proprietary Name: Austedo</td>
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<td>Established (USAN) Name: Deutetetabenazine (SD-809)</td>
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<td>Dosage Forms/Strengths: Oral tablets: 6 mg, 9 mg, and 12 mg</td>
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<td>Indication: Treatment of chorea in patients with Huntington's disease.</td>
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<td>Action: Approval</td>
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Material Reviewed/Consulted - Action Package, including:

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- Statistical Review: Xiangmin Zhang; Kun Jin; Hsien Ming Hung
- Pharmacology Toxicology: Chris Toscano; Lois Freed; Paul Brown
- Office of Pharmaceutical Quality: Wendy Wilson-Lee; Martha Heimann; Gene Holbert; Sherita McLamore-Hines; Masih Jaigirdar; Don Obenhuber
- Office of New Drug Quality Assessment Biopharmaceutics Review: Jing Li; Okpo Eradiri; Angelica Dorantes
- Controlled Substance Staff: Alicja Lerner; Michael Klein
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- Cross-Discipline Team Leader: Gerald (Dave) Podskalny
- Deputy Director, Division of Neurology Products: Eric Bastings
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OSE = Office of Surveillance and Epidemiology
1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Deutetrabenazine will be approved for the treatment of chorea associated with Huntington’s disease. The drug is a deuterated form of tetrabenazine, which was approved for the same indication in 2008. Both drugs are vesicular monoamine transporter 2 (VMAT2) inhibitors, and the activity of both drugs is related to their metabolites, \( \alpha \)- and \( \beta \)-dihydrotetrabenazine. Deuteration affects the metabolism and pharmacokinetics of the drug, such that for equivalent doses, exposure to the active metabolites of deutetrabenazine is approximately twice that of tetrabenazine, and the half-life is longer. This is a 505(b)(2) NDA that relies on tetrabenazine for its pharmacology/toxicology studies, including a fertility and early embryonic development study, an embryofetal developmental study, a pre- and post-natal development study, and assessment of carcinogenicity. Deutetrabenazine’s effectiveness in Huntington’s disease was demonstrated in a new controlled trial.

The efficacy of deutetrabenazine was established in a 12-week placebo-controlled study that used a well-accepted measure of chorea, the total maximal chorea (TMC) score, as the 1° endpoint. The change from baseline in TMC score was significantly higher (a drug-placebo difference of 2.5 points on a 24-point scale) for deutetrabenazine than for placebo (\( p < 0.0001 \)). These results were supported by statistically significant effects on 2° outcome measures: the Patient Global Impression of Change and the Clinical Global Impression of Change. Deutetrabenazine’s only known advantage over tetrabenazine is the need for less frequent dosing (BID instead of TID) at the higher end of the dosing range. No doubt there will be individuals who, having had an inadequate response to tetrabenazine, will switch to deutetrabenazine in search of better efficacy. *There is no basis for believing that the two products differ with respect to efficacy*; moreover, an attempt to show superiority of deutetrabenazine to tetrabenazine would seem futile.

The deutetrabenazine safety database was closely examined with consideration of tetrabenazine’s known adverse effects. These include sedation and somnolence, akathisia, depression, and suicidality. Notwithstanding the recognized limitations of cross-study comparisons, the frequencies of these events appear similar for the two drugs. Huntington’s Disease (HD) is an orphan disease, and the safety database was therefore small. Given the size of the database and lack of a head-to-head study, it is impossible to reach any definitive conclusions regarding comparative safety, but there are no obvious new safety concerns. A QT prolongation signal is known and labeled for tetrabenazine. The TQT study conducted by the applicant did not reach sufficiently high deutetrabenazine exposures to rule out QT prolongation at supratherapeutic concentrations that would likely occur in patients who are CYP2D6 poor metabolizers, as well as patients taking CYP2D6 inhibitors. As was the case for tetrabenazine, this will be addressed in labeling. The possibility that deuteration leads to specific safety issues seems remote. Presumably, if such toxicity exists at all, its manifestations would be rare and would not have been detected in a development program of this size.

The benefit-risk calculus is straightforward here: the potential benefit for patients is a reduction in symptoms; the potential harms are manifested as symptoms. Aside from the risk of suicide, the risks seem reversible. Thus, individual patients can make their own decisions with respect to initiating and, if desired, discontinuing the drug.
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<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<td><strong>Analysis of Condition</strong></td>
<td>Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. HD has an estimated prevalence of 5/100,000 in the US. HD is an orphan disease. The affected gene codes for a cytosine-adenine-guanine (CAG) repeat expansion that produces abnormal Huntingtin protein. Patients with a CAG repeat length $\geq 37$ become symptomatic. The length of the CAG repeat influences the severity of the disease and the age of onset (longer is worse). The disease is characterized by progressive dementia, motor impairment, and psychiatric symptoms, beginning most often between 30 and 50 years of age. Death usually occurs within 20 years of symptom onset.</td>
<td>HD is a serious and profoundly disabling disorder. HD essentially represents a death sentence. There is currently no treatment that is known to delay the progression of the disease.</td>
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<td><strong>Current Treatment Options</strong></td>
<td>Tetrabenazine is the only drug approved for the treatment of HD, specifically, for the treatment of chorea associated with HD. Tetrabenazine may cause side effects, including sedation, worsening depression, suicidality and drug-induced Parkinsonism. Antidepressants and antipsychotics are used to treat the psychiatric and behavioral aspects of HD.</td>
<td>Tetrabenazine is the only available treatment for patients with HD. The drug has no effect on the progression of the disease, but is indicated to reduce chorea.</td>
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<td><strong>Benefit</strong></td>
<td>Benefit was established in a mostly US, multicenter, randomized, double-blind, placebo-controlled study in 90 patients (Study C-15). The study used a well-accepted measure of chorea as the 1st outcome measure: the Total Maximal Chorea (TMC) score. There was a statistically significant difference between deutetrabenazine and placebo for the primary endpoint (difference in score change from baseline of -2.5, $p&lt;0.0001$). This effect size was similar to that seen with tetrabenazine. The meaningfulness of the benefit of deutetrabenazine to patients was supported by statistically significant improvements on 2nd endpoints: the Patient Global Impression of Change and the Clinical Global Impression of Change, compared with placebo.</td>
<td>There is substantial evidence for the efficacy of deutetrabenazine. The treatment effect appears similar to that of tetrabenazine, which is approved for the treatment of chorea in HD patients.</td>
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2. Background

Huntington’s disease (HD) is a genetic neurodegenerative disorder characterized by progressive dementia, motor impairment, and psychiatric symptoms. Patients with the adult form of the disease typically become symptomatic between 30 and 50 years of age, with death ensuing 15 to 20 years after symptom onset. The Huntingtin gene is located on the short arm of chromosome 4, and inheritance is autosomal dominant. The gene mutation codes for a cytosine-adenine-guanine (CAG) triplet repeat that produces abnormal huntingtin protein. Patients with a CAG repeat length of 37 or more become symptomatic. Despite discovery of the genetic basis of the disease some 24 years ago, no treatment is known to affect its inexorable progression. Prevalence is estimated at 5/100,000 in the US. HD was the subject of a public patient-focused drug development meeting at FDA on September 22, 2015. Patients made it clear that although tetrabenazine can be helpful, they are hoping for the availability of a drug that will prevent progression of the disease.

Tetrabenazine is the only approved treatment for HD. Initially approved in 2008, the drug is indicated for the treatment of chorea associated with Huntington’s disease, but does not affect disease progression. Deutetrabenazine is a deuterated form of tetrabenazine that is proposed for the same indication: treatment of chorea associated with Huntington’s disease.

Tetrabenazine and deutetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors. Their anti-chorea effects are believed to be mediated by decreased uptake of monoamines into synaptic vesicles with depletion of monoamine stores (e.g., dopamine, serotonin, norepinephrine, and histamine).

The NDA is a 505(b)(2) submission, with tetrabenazine (NDA 21894) as the Reference Listed Drug (RLD). Clinical development was conducted under IND 112975. This application relies on IND 112975.
on the RLD for various pharmacology-toxicology studies, including a fertility and early embryonic development study, a pre- and postnatal development study, and assessment of carcinogenic potential. There was, however, a new randomized placebo-controlled effectiveness study to demonstrate efficacy of deutetrabenazine in HD.

Deutetrabenazine has not been approved in any country, and has orphan drug designation.

The clinical pharmacology studies in the original submission were not adequate to determine whether all of deutetrabenazine’s major human metabolites had been identified. Specifically, there was concern that levels of the M1 and M4 metabolites exceeded the regulatory threshold of 10% of total drug-related material. We are now satisfied, however, that these metabolites do not exceed the 10% threshold, such that all relevant metabolites have been characterized and adequately studied.

3. Product Quality

I concur with the conclusions reached by the Office of Pharmaceutical Quality regarding the acceptability of the manufacturing of the drug product and drug substance. The deficiencies identified in the first cycle have been resolved. Manufacturing site inspections were acceptable, and there are no outstanding product quality issues. Sufficient data have been presented to support a 32-month expiry.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer: the original pharm/tox issues that precluded approval have been resolved. The original submission lacked sufficient information to confirm that the major human metabolites were comparable between tetrabenazine and deutetrabenazine. This comparison was necessary to determine whether the safety of tetrabenazine supported that of deutetrabenazine. The resubmission sufficiently clarified the human metabolite profiles; no new major metabolites (>10% of drug-related materials) have been identified, such that reliance on the tetrabenazine data is appropriate.

5. Clinical Pharmacology

Deutetrabenazine is a deuterated form of tetrabenazine in which the two O-linked methyl groups of the tetrabenazine molecule have been replaced by two trideuteromethyl groups.
Pharmacokinetics of deutetrabenazine (and of tetrabenazine): Refer to the original review.

Bridging of deutetrabenazine to tetrabenazine: Bridging is a critical issue that is well covered by the reviews of clinical pharmacology, biopharmaceutics, the CDTL, and the Deputy Division Director.

This 505(b)(2) application relies, in part, on FDA’s prior finding of safety and efficacy for tetrabenazine. Thus, an adequate PK bridge has to be provided to the tetrabenazine NDA. In particular, it is critical to know how levels of metabolites compare for the two drugs, and whether there are major metabolites unique to deutetrabenazine.

In the first review cycle, there was concern whether the in vivo metabolic profile of deutetrabenazine had been adequately characterized; specifically, whether levels of the M1 and M4 metabolites exceeded 10% of total drug-related material, which would have categorized them as major metabolites.

The reviewers have determined that M4 levels are about 6% of total drug-related exposure, and M1 levels are approximately 10%. Thus, reliance on the tetrabenazine data to support the deutetrabenazine 505(b)(2) application is scientifically supported and justified, and there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Considering the similarities between tetrabenazine and deutetrabenazine, the division agreed to rely on a single efficacy study for deutetrabenazine.
The clinical study is well described in the original reviews of Drs. Bergmann, Zhang, Podskalny, and Bastings, and summarized in my original memo of May 26, 2016.

The review team had considered placing a figure in labeling showing the cumulative distribution of responses in the study, similar to the figure shown in tetrabenazine labeling. I believe, however, it would be more clear to show a histogram of the distribution of responses. Figure 2 shows the distribution in the change in total maximal chorea score from baseline to maintenance, and a version of this figure will be provided in Section 14 of labeling.

![Figure 2: Distribution of the Change in Total Maximal Chorea Scores](image)

8. Safety

Please refer to my original Office Director Summary Review for a discussion of the safety of deutetrabenazine. The applicant included a safety update with this new submission, but there are no new issues. Deutetrabenazine appears to have a safety profile similar to that of tetrabenazine, with no unique issues identified.
9. Advisory Committee Meeting

The NDA was not presented to the Peripheral and Central Nervous System Drugs Advisory Committee. This is a 505(b)(2) application without novel or controversial safety or efficacy issues.

10. Pediatrics

Deutetrabenazine is an orphan drug, and therefore, no pediatric obligations exist.

11. Other Relevant Regulatory Issues

Controlled Substances Staff (CSS): Tetrabenazine is not a scheduled drug. Although the issue was not a reason for the Complete Response action in the first cycle review, the CSS reviewer noted that neither abuse potential nor dependence were evaluated in the preclinical/clinical studies, and suggested evaluation of withdrawal and rebound symptoms at the end of study SD-809-C-15 ARC HD, which is ongoing.

Subsequent to our Complete Response action, the applicant was not able to conduct this assessment because the study is still ongoing; however, they noted the following:

“During the clinical development of SD-809, abrupt discontinuation did not produce adverse events. This observation suggests that SD-809 does not produce a withdrawal syndrome. A search for events relating to drug abuse, drug dependence and drug withdrawal, as well as euphoric mood, was conducted using standardized MedDRA query (SMQ) terms; no such adverse events were found in Studies SD-809-C-15 and SD-809-C-16 (Complete Response Safety Update, Section 8.6). The studies in the SD-809 clinical development program did not reveal any tendency for drug-seeking behavior. Moreover, Xenazine® (tetrabenazine) is neither a controlled substance nor has abuse been reported from the postmarketing experience.”

CSS continues to have concerns (the applicant did not submit any new data). CSS stresses that the deutetrabenazine appeared to produce rebound in ~20% of patients during the first week of withdrawal, as well as tolerance that began on Week 9 of treatment. Their original review drew attention to a number of scales that showed worsening during washout.

The clinical review team and Dr. Bastings remain unimpressed by the nature of the adverse events reported. Dr. Bastings also notes that tetrabenazine is not known to have such effects, and he believes there is no need for further assessment of withdrawal or rebound for deutetrabenazine.

I agree with the Division on this issue. I cannot find explicit data in the original CSS review to support the concept that some 20% of patients experienced symptoms of rebound. Moreover, because patients were not blinded to washout (i.e., they knew they were discontinuing their...
study drug), I believe the data obtained during the washout period must be interpreted with caution.

The applicant still plans to assess adverse events after drug withdrawal in the ongoing study. (I think that if it were important to gain more certainty about withdrawal and/or rebound, we would suggest a randomized [double-blind] withdrawal phase.) But I, like Dr. Bastings, take reassurance from the fact that these issues have not been reported for tetrabenazine, despite almost a decade of marketing experience, and see no reason to request a formal post-marketing commitment.

12. Labeling

Labeling has been negotiated with the applicant. Originally, we were considering a cumulative distribution plot for the 1° endpoint, similar to the figure in the tetrabenazine labeling. But I believe that a histogram showing the range of responses in patients randomized to deutetramazine and placebo will be more comprehensible and helpful, and such a figure will be placed in Section 14.

13. Postmarketing

I agree with Dr. Bastings and see no reason for a REMS or for any postmarketing requirements or commitments.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
04/03/2017