APPLICATION NUMBER:

209885Orig1s000

SUMMARY REVIEW
## Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
<th>August 30, 2017</th>
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<tbody>
<tr>
<td>From</td>
<td>Tiffany R Farchione, MD</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<tr>
<td>NDA/BLA # Supplement#</td>
<td>209885</td>
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<tr>
<td>Applicant</td>
<td>Teva Pharmaceuticals, Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>December 30, 2016</td>
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<td>PDUFA Goal Date</td>
<td>August 30, 2017</td>
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<tr>
<td>Proprietary Name / Non-Proprietary Name</td>
<td>Austedo/deutetragenazine</td>
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<tr>
<td>Dosage form(s) / Strength(s)</td>
<td>Tablet/6 mg, 9 mg, and 12 mg</td>
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<tr>
<td>Applicant Proposed Indication(s)/Population(s)</td>
<td>Treatment of Tardive Dyskinesia</td>
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<tr>
<td>Recommendation on Regulatory Action</td>
<td><strong>Approval</strong></td>
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<td>Recommended Indication(s)/Population(s) (if applicable)</td>
<td><strong>Treatment of Tardive Dyskinesia in adults</strong></td>
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</table>
1. Background

Tardive dyskinesia (TD) is a rare but serious iatrogenic disorder caused by treatment with antipsychotic medication. It is characterized by involuntary movements of the tongue, lips, face, or trunk. TD can occur months or years after the start of antipsychotic treatment. Although there are some factors that may make TD more likely, there is no way to predict whether an individual patient will develop this condition. In most cases, it is permanent. Until recently, there were no treatments available; however, one product (valbenazine) was approved for this indication in April, 2017.

Deutetrabenazine (trade name: Austedo; SD-809 during development) is the deuterated form of tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor. Tetrabenazine is approved as Xenazine for the treatment of chorea associated with Huntington’s Disease (HD) under NDA 021894. This application is a 505(b)(2) NDA relying in part on the Xenazine NDA. The TD development program was conducted under IND 120631, and was granted breakthrough therapy designation on November 3, 2015. When this application was submitted, deutetrabenazine was not yet approved for any indication and no other products were approved for the treatment of TD. Thus, this application was granted Priority Review status. Since then, it was approved for the treatment of HD (NDA 208082). Product quality, nonclinical, and clinical pharmacology information for this application is provided via cross-reference to NDA 208082.

Deutetrabenazine is available as 6, 9, or 12 mg tablets. For the treatment of TD, the recommended starting dosage is 12 mg total daily, administered as 6 mg twice a day; the recommended maximum dosage is 48 mg total daily, administered as 24 mg twice a day.

2. Product Quality

No new information.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted and the Applicant did not propose any labeling changes based on nonclinical information. However, the Division of Pediatric and Maternal Health (DPMH; primary reviewer: Catharine Roca, MD) recommended changes to the pregnancy and lactation sections of the approved label. We ultimately did not incorporate these changes, deferring instead to the language that was recently approved by the Division of Neurology Products (DNP). This NDA is a 505(b)(2) to Xenazine and the application does not contain data (animal or human) related to pregnancy or lactation. DNP reviewed the available information and decided to use language found under 201.57(c)(9)(ii)(A)(3) for drugs absorbed systemically by the mother and not contraindicated. Although the current language does not state that breastfeeding is not recommended, it is cautionary in nature.

Of note, DPP approved Ingrezza (valbenazine), another VMAT2 inhibitor, earlier this year which does state that “breastfeeding is not recommended.” However, deutetrabenazine is more
closely related to tetrabenazine than valbenazine, and the Ingrezza application included data that served as the basis for its breastfeeding language.

4. Clinical Pharmacology

The Applicant cross-referenced to NDA for the majority of the clinical pharmacology data supporting this application. A population pharmacokinetic (PopPK) and Exposure-Response (E-R) analysis in TD patients were the only new additions specific to this application. The Office of Clinical Pharmacology (OCP) review team (Gopichand Gottipati, PhD, Kofi Kumi, PhD, Kevin Krudys, PhD, Hao Zhu, PhD) recommends a starting daily dose of 12 mg (as 6 mg twice daily), titration to effect at weekly intervals in increments of 6 mg per day as tolerated, and a maximum total daily dose of 48 mg (as 24 mg twice daily). In their review, the OCP team recommended limiting the maximum daily dose to 36 mg for patients taking concomitant strong CYP2D6 inhibitors.

No new QT information was provided under this NDA. However, the QT Interdisciplinary Review Team (QT-IRT; primary reviewer: Lars Johannesen, PhD) disagreed with the Applicant’s assessment of this product’s cardiac liability. The QT study conducted in support of this application evaluated the potential for QTc prolongation following administration of a single dose of 12 and 24 mg. These doses do not cover therapeutic (up to 24 mg BID) or supratherapeutic (CYP2D6 poor metabolizers or concomitant use with a CYP2D6 inhibitor) concentrations, yet concentration-dependent QTc prolongation was observed in the study. In addition, the concentration-QTc model developed based on the thorough QT study data is based on the sum of the active metabolites, alpha-dihydrotetrazenazine (α-HTBZ) and beta-dihydrotetrazenazine (β-HTBZ). This model assumes that the hERG inhibition by α-HTBZ and β-HTBZ are similar, but no data were submitted to justify this assumption. QT-IRT further notes that the ratio of α-HTBZ and β-HTBZ changes in the presence of a CYP2D6 inhibitor. Thus, QT-IRT concluded that deutetrazenazine alone may not pose a significant cardiac liability; however, there may be a risk for QTc prolongation when it is administered with other QT prolonging medication or CYP2D6 inhibitors, or when administered to patients who are CYP2D6 poor metabolizers.

During labeling negotiations, OCP and QT-IRT reached agreement on the recommendation to assess the QT interval before and after increasing the total deutetrazenazine dosage above 24 mg per day.

5. Clinical Microbiology

No new information.

6. Clinical/Statistical - Efficacy

The TD development program consists of two short-term, double-blind, placebo-controlled efficacy studies and one open-label long-term extension study.
• SD-809-C-18 (C-18): A randomized, double-blind, placebo-controlled, flexible-dose, parallel-group, multicenter study in 58 adult patients with TD, ages 25 to 75. Deutetrabenazine (or matching placebo) was initiated at 12 mg/day then titrated to a maximum total daily dose of 48 mg/day based on dyskinesia control and tolerability (6-week titration period; 6-week maintenance period).

• SD-809-C-23 (C-23): A randomized, double-blind, placebo-controlled, fixed-dose, parallel-group, multicenter study in 221 adult patients with TD, ages 21 to 81. Deutetrabenazine (or matching placebo) was administered at 12, 24, or 36 mg/day (4 weeks dose escalation period starting at 12 mg/day; 8 weeks maintenance).

• SD-809-C-20 (C-20): An open-label, single-arm, multicenter, long-term extension study in 304 adult patients (202 who received deutetrabenazine and 102 patients who received placebo in the parent study). Deutetrabenazine was initiated at 12 mg/day then titrated to a maximum total daily dose of 48 mg/day based on dyskinesia control and tolerability (up to 6 weeks titration; up to 3 years treatment).

For inclusion in these studies, patients were required to have a history of using a dopamine receptor antagonist (DRA) for at least 3 months (or 1 month in patients 60 years of age and older) and a clinical diagnosis of TD with symptoms for at least 3 months prior to screening. The patient’s TD symptoms had to be bothersome to the patient or cause functional impairment. At the screening and baseline visits of Studies C-18 and C-23, both of the following were required:

• Moderate or severe abnormal movements as judged by the investigator based on Item 8 of the Abnormal Involuntary Movement Scale (AIMS)

• A total motor AIMS score of \( \geq 6 \) (based on Items 1 through 7) as assessed by the investigator. Video recordings of the AIMS assessment at screening were reviewed by blinded central raters to confirm eligibility based on items 1 through 7 of the AIMS prior to randomization.

With regard to underlying psychiatric illness, patients were required to be psychiatrically stable with no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for \( \geq 30 \) days before screening (45 days for antidepressants). Patients on long-acting (depot) medications were required to be on stable therapy (dose, frequency) for \( \geq 3 \) months before screening. The protocol also stipulated that the patient’s health care provider be aware of the patient’s participation in the study and that the provider did not anticipate any changes to the patient’s treatment regimen (drug, dose, frequency) in the next 3 months.

Exclusion criteria were related to psychiatric or medical instability, or comorbid conditions that may interfere with study conduct or present safety concerns. Use of any of the following medications within 30 days of screening or baseline was also exclusionary:

• Tetrabenazine (prohibited within 7 days of baseline for Study C-20), reserpine, \( \alpha \)-methyl-p-tyrosine, botulinum toxin (within 3 months of screening in Studies C-18 and C-23 and within 3 months of baseline in Study C-20), and medications with strong
anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
- Metoclopramide, promethazine, or prochlorperazine
- Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamfetamine, etc.) or monoamine oxidase inhibitors
- Levodopa or dopamine agonists

Patients were eligible for enrollment in C-20 after successfully complete either C-18 or C-23.

The primary efficacy endpoint in studies C-18 and C-23 was the change from baseline to Week 12 on the total motor AIMS score (sum of Items 1 through 7). In Study C-23, the primary endpoint was specifically the change in AIMS in the 36 mg/day treatment group; the changes in AIMS in other treatment groups were included in the hierarchy of secondary endpoints. The AIMS is widely used in both clinical and research settings to rate the severity of TD-related abnormal involuntary movements across multiple body regions. The AIMS was assessed at every study visit (including during the extension study, C-20), video recorded, and scored by a blinded central rater.

The Applicant proposed three “key” secondary endpoints for C-18:

- Proportion of subjects who were a treatment success at Week 12 based on the Clinical Global Impression of Change (CGIC)

In the original protocol submission, only the CGIC was listed as a “key” secondary endpoint. The other endpoints were elevated to “key” secondaries in subsequent amendments at a late stage of the trial. Per the statistical review (primary reviewer: Semhar Ogbagaber, PhD), CGIC was the only accepted key secondary endpoint; there was no agreement on the other proposed endpoints.

The primary analysis for the primary and “key” secondary efficacy endpoints in Study C-18 was carried out on the modified Intent-to-Treat population (mITT). The mITT population included patients from the ITT population who received study drug and had at least one centrally-read post-baseline assessment of the AIMS from at least one scheduled post-baseline time point (Weeks 2, 4, 6, 9, and 12).

Deutetrabenazine was statistically significantly superior to placebo in the mean change from baseline in AIMS total score at week 12 (mITT, MMRM), with a least square mean treatment difference to placebo of 1.4 (p-value = 0.0188). Because the blinded central raters did not always review the video AIMS assessments on the day they were conducted, approximately 14% of the patients randomized based on the local rater’s score were not eligible based on the central rater’s score. The Applicant conducted the primary efficacy analysis on the subpopulation excluding those with baseline AIMS score < 6. The result was compatible with
the overall conclusion of the study (p = 0.027). Deutetrabenazine failed to separate from placebo at the 5% level of significance on the first key secondary endpoint, CGIC (p = 0.40).

**Figure 1. LS Mean Change from Baseline in AIMS Score by Treatment and Study Visit (mITT; N=113)**

Source: SD-809-C-18 Clincial Study Report, Figure 11-1, page 127

The Applicant proposed five “key” secondary endpoints for C-23:

- Proportion of subjects who were a treatment success, defined as Much Improved or Very Much Improved based on the CGIC at Week 12 for deutetrabenazine 36 mg/day
- Change in the total motor AIMS score from baseline to Week 12 for deutetrabenazine 24 mg/day
- Proportion of subjects who were a treatment success, based on CGIC at Week 12 for deutetrabenazine 24 mg/day
- Change in the total motor AIMS score from baseline to Week 12 for deutetrabenazine 12 mg/day
- Proportion of subjects who were a treatment success, based on CGIC at Week 12 for deutetrabenazine 12 mg/day

FDA provided advice to the Applicant regarding the testing order of the hierarchical testing procedure. From a regulatory perspective, the advice highlighted the importance of establishing the primary efficacy of the 24 mg/day dose first and then the key secondary endpoint on 36 mg/day next. However, the Sponsor opted to keep the testing order whereby the key secondary endpoint on 36 mg/day preceded the primary efficacy of 24 mg/day.

The primary analysis for the primary and “key” secondary endpoints in Study C-23 was carried out in the mITT population. The mITT population included all randomized subjects with baseline AIMS ≥6 as assessed by central video rating who took at least one dose of study medication and had at least one post-baseline efficacy assessment of the AIMS. The mITT
included total of 222 subjects: 58, 60, 49 and 55 subjects in the placebo, SD-809 12 mg/day, SD-809 24 mg/day and SD-809 36 mg/day treatment groups, respectively.

Deutetrabenazine 36 mg/day was statistically significantly superior to placebo on the mean change from baseline in AIMS total score at Week 12 (mITT, MMRM). The least square mean treatment difference compared to placebo was -1.9 points (p = 0.001). The change from baseline in AIMS total score SD-809 24 mg/day group was nominally statistically significant (p = 0.003), but was specified lower in the hierarchy than the first key secondary endpoint, proportion of patients with treatment success at Week 12 with SD-809 36 mg/day, which was negative (p = 0.059).

Figure 2. LS Mean Change from Baseline (with 95% CI) in AIMS Total Score by Visit (mITT; N=222)

With regard to demographic subgroups, in both studies white patients achieved numerically better response than non-white patients in the deutetrabenazine group compared to placebo. In Study C-23, women and patients who were ≥ 65 years of age had a numerically greater treatment effect. The sample size for the subgroup above age 65 is very small. Of note, all subgroups had numerically greater improvement on deutetrabenazine than on placebo; the study was not powered to assess differences among demographic subgroups.

In exploring the treatment effect in US versus non-US site, the mean improvement in the change from baseline to Week 12 in AIMS total score was greater in the US.

Conclusions on the Substantial Evidence of Effectiveness: The Applicant has substantial provided evidence of effectiveness for deutetrabenazine in the treatment of TD based on two
positive adequate and well-controlled clinical trials. The use of a blinded central rater to assess the primary efficacy endpoint adds a degree of rigor to the trial, reducing inter-rater variability and expectancy bias. In both Study C-18 and C-23, deutetrabenazine was statistically superior to placebo on the primary efficacy endpoint of change from baseline to Week 12 in the total motor AIMS score. In Study C-20, subjects initially treated with placebo received deutetrabenazine, providing additional evidence of continued drug effect.

Of note, Study C-18 was a flexible-dose study with most subjects receiving total daily doses of 36 mg or greater. Although higher doses were found to be ineffective in Study C-18, Study C-23 did not include a 48 mg cohort. Based on Study C-20, it appears that dosing up to 48 mg has been reasonably well-tolerated and effective.

The statistical hierarchy in Study C-23 was problematic. The Applicant tested the proportion of patients with treatment success with deutetrabenazine 36 mg/day as the first key secondary endpoint followed by change from baseline in AIMS total score for deutetrabenazine 24 mg/day. Because of this, the 24 mg/day dose was only nominally statistically significant (p=0.003).

The final product labeling includes the results of all doses in the fixed-dose trial, with only the 36 mg dose identified as statistically significant and no p values presented. The dosage and administration instructions indicate a starting and a maximum dosage, but not a recommended dosage. Titration is based on efficacy and tolerability.

7. Safety

The approved product labeling for HD includes warning language related to clinical worsening and adverse events: depression and suicidality; neuroleptic malignant syndrome (NMS); akathisia, agitation, and restlessness; parkinsonism; sedation and somnolence; QTc prolongation; hyperprolactinemia; and binding to melanin-containing tissues. The currently labeled most common adverse reactions include somnolence, diarrhea, dry mouth, and fatigue (threshold of > 8% and greater than placebo).

The overall safety database for deutetrabenazine includes subject exposures in both the TD and HD programs. However, given that the product is already approved and labeled for HD, the review of this application focused on safety in the TD population.
Table 1. Exposure to Deutetrabenazine in the Clinical Development Program (TD, HD, and Healthy Volunteers)

<table>
<thead>
<tr>
<th>Study</th>
<th>Any SD-809 exposure</th>
<th>≥8 weeks</th>
<th>≥15 weeks</th>
<th>≥28 weeks</th>
<th>≥54 weeks</th>
<th>≥80 weeks</th>
<th>≥93 weeks</th>
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<tbody>
<tr>
<td>Phase 3 in patients with tardive dyskinesia</td>
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<td></td>
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<tr>
<td>SD-809-C-18</td>
<td>58</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD-809-C-23</td>
<td>221</td>
<td>197</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD-809-C-20</td>
<td>304</td>
<td>261</td>
<td>241</td>
<td>201</td>
<td>86</td>
<td>13</td>
<td>2</td>
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<td>Total TD patient exposure to SD-809 (parent study + open-label study)</td>
<td>381</td>
<td>340</td>
<td>278</td>
<td>223</td>
<td>108</td>
<td>21</td>
<td>7</td>
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<tr>
<td>Phase 3 in patients with Huntington’s disease</td>
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<td>SD-809-C-15</td>
<td>45</td>
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<td>SD-809-C-16 (complete response safety update)</td>
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<td>ARC-Rollover</td>
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<td>17</td>
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<td>ARC-Switch</td>
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<td>35</td>
<td>34</td>
<td>33</td>
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<td>12</td>
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<td>Total HD patient exposure</td>
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<td>114</td>
<td>109</td>
<td>99</td>
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<td>Phase 1 (healthy volunteer subjects)</td>
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<tr>
<td>Total healthy volunteer subjects exposure</td>
<td>178</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Total subject exposure to SD-809</td>
<td>680</td>
<td>459</td>
<td>392</td>
<td>332</td>
<td>207</td>
<td>80</td>
<td>36</td>
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</table>

Source: Summary of Clinical Safety—TD, Table 4, page 36

Table 2. Study Drug Exposure in The Tardive Dyskinesia Integrated Safety Dataset

<table>
<thead>
<tr>
<th>Variable Statistic</th>
<th>Placebo (N=131)</th>
<th>SD-809 12 mg (N=74)</th>
<th>SD-809 24 mg (N=73)</th>
<th>SD-809 36 mg (N=74)</th>
<th>SD-809 titration 12-48 mg (N=160)</th>
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<tbody>
<tr>
<td>Weeks treated, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;9 to ≤15 weeks</td>
<td>120 (92)</td>
<td>66 (89)</td>
<td>64 (88)</td>
<td>64 (86)</td>
<td>140 (88)</td>
</tr>
<tr>
<td>Duration of treatment (days)</td>
<td>131</td>
<td>74</td>
<td>73</td>
<td>74</td>
<td>160</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>79.4 (17.54)</td>
<td>79.0 (18.99)</td>
<td>77.5 (19.91)</td>
<td>75.8 (22.13)</td>
<td>88.1 (24.28)</td>
</tr>
<tr>
<td>Median</td>
<td>84.0</td>
<td>84.0</td>
<td>84.0</td>
<td>84.0</td>
<td>105.0</td>
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<tr>
<td>Min, max</td>
<td>3, 102</td>
<td>2, 110</td>
<td>2, 90</td>
<td>5, 87</td>
<td>8, 105</td>
</tr>
</tbody>
</table>

Source: Summary of Clinical Safety—TD, Table 5, page 37

As outlined in the clinical review (primary reviewer: Anandraj Mattai, MD), the TD developmental program appears sufficiently diverse and reflective of the broad population that would be receiving the treatment. Overall, the safety population is typical of the clinical TD population, with the severity and duration of illness, as reflected in time since TD diagnosis and baseline AIMS score, concordant with patients with moderate to severe TD. Patients with significant hepatic or renal dysfunction were excluded from studies; current labeling includes a contraindication for use in patients with hepatic impairment. There were only nine CYP2D6 poor metabolizers in deutetrabenazine titration group, making comparative analyses regarding the importance of this phenotype to the safety of the drug challenging.
However, current labeling includes a dose limitation based on CYP2D6 status (either poor metabolizer or taking strong inhibitor).

With regard to categorization of adverse events (AEs), the primary clinical reviewer noted that verbatim terms appear to be fairly represented by the preferred terms in the AE dataset, with only a few instances of splitting of terms (related to worsening psychiatric illness).

There were six patients who experienced cardiovascular-related death during the development program. Both the primary clinical reviewer and the QT-IRT team expressed concerns that deutetrabenazine may have been a contributing factor in these cases, particularly in those cases involved concomitant use of other drugs known to prolong QTc. Of note, none of the scheduled ECGs obtained prior to the adverse event showed QTc prolongation >480 ms, except for Patient (b) (6) who was treated with sotalol and died from ventricular tachycardia.

With regard to other serious adverse events (SAEs), the proportion of SAEs in the deutetrabenazine treatment groups was similar to that observed in the placebo group. The primary reviewer reviewed the narratives of these cases and felt that most of the SAEs (including a suicide attempt assessed by the investigator to be possibly related to the study drug) did not appear to have a relationship to study drug.

There were four adverse events leading to discontinuation in the placebo group (3.1%) and four in the deutetrabenazine titration group (2.5%). No adverse events leading to discontinuation were reported for more than one patient. In the long-term safety study (C-20), the most common reasons for patient discontinuation in were diarrhea, depression, and anxiety (two patients each).

The following table will be including in labeling to describe the frequency of AEs in the TD program.

**Table 3. Adverse Reactions in 2 Placebo-Controlled Tardive Dyskinesia Studies (Study 1 and Study 2) of 12-week Treatment on AUSTEDO Reported in at least 2% of Patients and Greater than Placebo**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>AUSTEDO (N=279) (%)</th>
<th>Placebo (N=131) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Depression/ Dysthymic disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Akathisia/Agitation/Restlessness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
8. **Advisory Committee Meeting**

The NDA was not presented at an Advisory Committee. This is a 505(b)(2) application with no novel or controversial safety or efficacy issues.

9. **Pediatrics**

A full waiver for pediatric studies was granted. Based on the low prevalence of TD in pediatric patients, the necessary studies would impossible or highly impracticable.

10. **Other Relevant Regulatory Issues**

Three sites were selected for inspection based on enrollment, prior inspections, and impact on the overall study results. The Applicant and the CRO were also inspected. According to the Clinical Inspection Summary from the Office of Scientific Investigations (OSI; primary reviewer: Jenn Sellers, MD, PhD), OSI recommended that one subject at Site 151 (site that impacted the overall efficacy result) be excluded from the efficacy analyses because that subject did not meet the criteria for study inclusion. Excluding this subject did not change the overall results of the study. Although this was not the only issue identified during the site inspections, the data generated by the sites was otherwise acceptable in support of the respective indication. No significant regulatory violations were identified during the Applicant inspection. The CRO inspection revealed a regulatory deviation related to data extraction at the screening visit; OSI concluded that this deviation did not appear to impact the data acceptability.

The Controlled Substance Staff (CSS; primary reviewer: Alicja Lerner, MD, PhD) recommended continuing the post-marketing assessment of AEs suggestive of abuse-potential, with assessments included in the standard Periodic Adverse Drug Experience Reports (PADERS).

We note that no abuse-related PMRs were included in the HD approval, and that no cases of abuse or misuse were reported in clinical trials. In addition, there is no evidence of abuse or misuse of the reference product. The Division declined to issue the PMR.

11. **Labeling**

Labeling was negotiated with the Applicant and agreement was reached on the language in both the Full Prescribing Information and the Medication Guide.

The concerns related to the potential for QT prolongation were addressed in labeling with a recommendation to assess before and after titrating the dosage to 24 mg total daily dose or higher. Because many antipsychotics have the potential to prolong OT, the statement.
was replaced with, “The use of AUSTEDO in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongations.”

Of note, the boxed warning related to suicidal ideation and behavior in patients with HD was not expanded to include the TD population.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
No safety issues necessitating a Risk Evaluation and Management Strategy were identified. The Division of Risk Management (DRISK) also reviewed this application and agree that no REMS is required.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
A postmarketing commitment to for a randomized withdrawal trial to assess the persistence of deutetrabenazine effect in the treatment of TD will be issued. The Applicant will be asked to either perform a new study or conduct a substudy in an ongoing trial in which subjects who have demonstrated an adequate response to deutetrabenazine are randomized to receive placebo or continue their current dose. Data from Study C-20 suggest that continuing deutetrabenazine treatment may maintain the reduction in TD symptoms. However, there was moderate attrition over the course of treatment and the lack of a placebo control raises the possibility that subjects’ knowledge as to whether they are receiving an active treatment might affect TD symptom severity.

13. Recommendation/Benefit-Risk Assessment

Based on evidence of efficacy for a serious and debilitating chronic illness with only one other available treatment in the context of risks that can be reasonably mitigated by labeling, I recommend approval of this product for the treatment of TD. The starting dosage is 6 mg twice a day, with a maximum dosage of 24 mg twice a day. The product labeling will include the common adverse reactions noted here, as well as the language related to monitoring in patients taking concomitant medications that may prolong QT.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIFFANY R FARCHIONE
08/30/2017

MITCHELL V Mathis
08/30/2017