APPLICATION NUMBER:

208082Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Division of Risk Management (DRISK)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

<table>
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<th>NDA</th>
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<td>PDUFA Goal Date</td>
<td>April 3, 2017</td>
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<td>OSE RCM #</td>
<td>2015-1301, 2015-1298</td>
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<td>Reviewer Name(s)</td>
<td>Yasmeen Abou-Sayed, PharmD</td>
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<td>Team Leader</td>
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<td>Deputy Division Director (Acting)</td>
<td>Jamie Wilkins Parker, PharmD</td>
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<tr>
<td>Review Completion Date</td>
<td>April 3, 2017</td>
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<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td>Established Name</td>
<td>Deutetrabenazine</td>
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<td>Trade Name</td>
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<tr>
<td>Name of Applicant</td>
<td>Teva</td>
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<tr>
<td>Therapeutic Class</td>
<td>VMAT2 inhibitor</td>
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<tr>
<td>Formulation(s)</td>
<td>Oral tablet as 6 mg, 9 mg, and 12 mg</td>
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<tr>
<td>Dosing Regimen</td>
<td>6 mg initially, to be titrated up by 6 mg increments weekly up to max daily dose of 48 mg</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Austedo (deutetrabenazine) is necessary to ensure the benefits outweigh its risks. Teva Pharmaceuticals, Inc. (Teva) submitted a New Drug Application (NDA) 208082 under the 505(b)(2) regulatory pathway for deutetrabenazine with the proposed indication for the treatment of chorea associated with Huntington’s Disease (HD). The risks associated with deutetrabenazine include depression, suicidality, and drug-drug interactions. The applicant did not submit a REMS with this application but did propose routine pharmacovigilance.

DRISK believes that a REMS is not needed to ensure the benefits of deutetrabenazine outweigh its risks. In general, healthcare providers who treat HD should be familiar with the heightened risk of depression and suicidality, and drug-drug interactions associated with deutetrabenazine, as the RLD, Xenazine (NDA 021894) was approved with a REMS which addressed these risks. The REMS for Xenazine was released on August 25, 2015, because the Agency determined the Communication Plan had been completed and the REMS had met its goals.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Austedo (deutetrabenazine) is necessary to ensure the benefits outweigh its risks. Teva submitted a New Drug Application (NDA 208082) under the 505(b)(2) regulatory pathway for deutetrabenazine with the proposed indication for the treatment of chorea associated with Huntington’s Disease (HD). This application is under review in the Division of Neurology Products (DNP), with reference made to Xenazine (tetrabenazine/NDA 21894). Although deutetrabenazine is referencing Xenazine under the 505(b)(2) pathway, it is being reviewed under the Program as it is a deuterated form of tetrabenazine, and therefore a New Molecular Entity. The applicant did not submit a REMS with this application but proposed to conduct routine pharmacovigilance to ensure timely collection, processing, follow-up, analysis, and reporting of all adverse events in accordance with pharmacovigilance regulatory requirements.

2 Background

2.1 PRODUCT INFORMATION
Deutetrabenazine, a new molecular entity (NME)a, is a vesicular monoamine transporter 2 (VMAT2) inhibitor proposed for the treatment of chorea associated with Huntington’s disease. By selectively inhibiting VMAT2 in the central nervous system (CNS), deutetrabenazine depletes presynaptic monoamines, including dopamine, and decreases chorea in patients with HD. It is structurally related to Xenazine (tetrabenazine), which is the only approved therapy for this indication in this class, and is the

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a FDAAA factor (F): Whether the drug is a new molecular entity.
referenced listed drug for this application. Xenazine was approved in 2008 with a REMS to address the risk of depression and suicidality, as well as the risk of drug-drug interactions. The REMS consisted of a communication plan and timetable for assessments. It was released in August of 2015 after the completion of all communication plan activities and assessments demonstrated that the REMS had met its goals.

Deutetrabenazine undergoes rapid and extensive hepatic metabolism by carbonyl reductase, and the resulting metabolites potently inhibit VMAT2 in the CNS. Cytochrome P450 2D6 (CYP2D6) is the principal metabolizer of the active metabolites. The structure of deutetrabenazine, when compared to tetrabenazine, allows for a slower rate of metabolism by CYP2D6, which allows for comparable systemic exposure with lower doses and lower peak concentrations. This also can lead to a reduction in the impact of CYP2D6 impairment, whether from concomitant medication use or genetics, and provide increased metabolic stability compared to tetrabenazine, and therefore reduced drug to drug interactions.

Deutetrabenazine is proposed as 6mg, 9mg, and 12mg oral tablets and is to be administered as a chronic therapy. The dosing is to be initiated on an outpatient basis at 6 mg daily, and should be titrated up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea. Doses of 12 mg daily and higher should be divided in two doses. Doses should be administered with meals, and should be swallowed whole. The maximum recommended daily dose is 48 mg (maximum 24 mg in a single dose). In poor CYP2D6 metabolizers or for patients taking strong CYP2D6 inhibitors, the maximum daily dose is 36 mg (maximum 18 mg in a single dose). Deutetrabenazine received orphan drug designation on November 5, 2014. It is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

11/05/2014: Orphan-drug designation granted for deutetrabenazine.

05/29/2015: Deutetrabenazine, NDA 208082, submission for the treatment of chorea associated with Huntington’s Disease received.

05/27/2016: Complete Response letter sent to the applicant due to clinical pharmacology, non-clinical and product quality deficiencies.

10/03/2016: Resubmission of Complete Response received from Applicant.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

\(^b\) FDAAA factor (D): The expected or actual duration of treatment with the drug.
Huntington’s disease (HD) is a rare genetically inherited degenerative disorder of the brain. About 30,000 people in the US are affected and HD is considered an “orphan disease”. It is inherited by receiving an abnormal gene that can come from either parent. The child of an affected parent has a 50-50 chance of inheriting the disease. While the classic sign of the disorder is chorea, involuntary and uncontrollable dance-like movements of the face and limbs, the illness is characterized by progressive motor, behavioral and psychiatric disturbances, and dementia. The onset of the illness is generally between the ages of 30 and 50, progressing to death within 15 to 20 years.

Chorea is a hallmark of HD that interferes with daily functioning and can pose a significant risk of injury. It can cause gait instability and poor postural control, increasing the risk of serious injury due to falls or flailing into objects.

Suicidal ideation and behavior is more common in patients with HD than in the general population. Completed suicides in the HD population have been reported to be as high as 13%, while the general population’s suicide rate is below 1%, with suicidal ideation reported in up to 19% of HD patients. Dysphagia is also a component of HD, and it can lead to aspiration pneumonia, weight loss, and behavioral problems. Because increased involuntary motor activity is driven by central dopamine dysregulation, inhibiting vesicular monoamine transporter, type 2 (VMAT2) reduces dopaminergic neurotransmission and provides a therapeutic option for controlling chorea in patients with HD.

3.2 Description of Current Treatment Options
In some cases, chorea can be managed with nonpharmacological options, such as providing a calm, predictable environment, and using assistive devices such as padded reclining chairs and bed padding. When pharmacologic therapy is warranted, the only currently approved medication for the treatment of chorea in HD is tetrabenazine.

Other pharmacologic options for chorea include neuroleptics, due to the blockade of dopamine transmission. Typical neuroleptics used are haloperidol, fluphenazine, and chlorpromazine. Atypical neuroleptics which have been used to treat chorea in HD include olanzapine, risperidone, clozapine, and aripiprazole. Amantadine can be considered for use in those who cannot tolerate tetrabenazine or the neuroleptics mentioned above. Benzodiazepines may be used intermittently when there is transient worsening of chorea in stressful situations.

4 Benefit Assessment
The clinical development program for deutetrabenazine is composed of two studies, SD-809-C-15 (First-HD) which focused on efficacy and safety, and SD-809-C-16 (ARC-HD) which is an on-going unblinded, open-label, single-arm long term safety and tolerability study which informed the safety population. The

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^c FDAAA factor (A): The estimated size of the population likely to use the drug involved.

d FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
A pivotal trial, First-HD, supporting this application consisted of a randomized double-blind, placebo-controlled parallel group study which evaluated the use of deutetrabenazine in 90 adult subjects (deutetrabenazine group n = 45, placebo group n = 45) with chorea associated with HD. The subjects were randomly chosen to be treated with total daily doses of deutetrabenazine ranging from 6 to 48 mg over the course of 12 weeks. The primary efficacy endpoint was change in Total Maximal Chorea\(^e\) (TMC) score from baseline to maintenance therapy. The deutetrabenazine treatment group had a highly statistically significant reduction in TMC (p<0.0001), with subjects achieving a 4.4 unit reduction in TMC compared to a 1.9 unit reduction in the placebo group.

Key secondary endpoints included the Patient Global Impression of Change and Clinical Global Impression of Change. Global Impression of Change was defined as the proportion of patients who perceived themselves as Much Improved or Very Much Improved using a Pearson’s chi-square test. At the end of treatment therapy 51.1% of the deutetrabenazine patients compared to 20% of the placebo treated group reported Much or Very Much Improved (p = 0.0020). Similar results were seen with the Clinical Global Impression of Change reported by site investigators that found 42.2% (19) of the deutetrabenazine subjects Much or Very Much Improved compared to 13.3% (6) in the placebo group (p-value 0.0022). Other secondary efficacy endpoints were analyzed, however “the clinical team determined that they were not statistically significant and held less value due to the unknown metric qualities of the outcomes measures and statistical vulnerability due to the multiplicity of analyses performed”.

Based upon the results of the deutetrabenazine clinical development program, the Division of Neurology Products has concluded that evidence of efficacy of deutetrabenazine as treatment of chorea associated with Huntington’s Disease, has been established.\(^f\)

5 Risk Assessment & Safe-Use Conditions

The safety analysis for deutetrabenazine includes data from the pivotal efficacy trial, First-HD, and study ARC-HD.

A total of 299 subjects have received deutetrabenazine, including 121 subjects with chorea associated with HD, and 178 healthy adult volunteers. The most common adverse reactions observed in greater than 8% of deutetrabenazine-treated patients were somnolence, diarrhea, dry mouth, and fatigue.

There was one report of death in the deutetrabenazine clinical program. In ARC-HD, one subject died due to sudden cardiac death, which was determined to by the investigator to be unlikely related to deutetrabenazine, and agreed upon by the clinical reviewer. Serious adverse events to be detailed

\(^e\) Total Maximal Chorea is a subscale of the Unified Huntington disease Rating Scale that was developed by the Huntington Study Group as a clinical rating scale to assess four domains of clinical performance and capacity in Huntington’s disease: motor function, cognitive function, behavioral abnormalities and functional capacity.

\(^f\) FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
further include events of depression and suicidality, drug-drug interactions and discussion of potential QT prolongation.  

5.1 DEPRESSION AND SUICIDALITY
Depression is more common in the HD population than the general population. A majority of subjects in First-HD (74%) had a history of depression, with 57.7% of subjects using an antidepressant medication at baseline. Approximately 15% of the study population had a lifetime history of suicidal ideation. Depression in First-HD was evaluated through use of the Hospital Anxiety and Depression Scale-Depression Subscale (HADS-D), and suicidality was evaluated through use of the Columbia Suicide Severity Rating Scale (C-SSRS). There was no evidence of an increase in the incidence of depression over time in either the deutetrabenazine or placebo group based on the HADS-D scores. The same outcome was seen in ARC-HD, where depression incidence did not increase in treatment subjects through week 80. However, the clinical reviewer notes in his review that the adverse event data sets showed five patients with previous histories of depression that reported increased symptoms, including one who reported suicidal ideation.

5.2 DRUG-DRUG INTERACTIONS
The safety data from both deutetrabenazine studies (First-HD, ARC-HD) indicates a similar incidence of adverse events in subjects who were using a concomitant strong CYP2D6 inhibitor compared with those who were not. A total of 8 subjects in the First-HD deutetrabenazine treatment group were using a strong CYP2D6 inhibitor at baseline. Among those 8 subjects, all reported AE’s were of mild to moderate severity, and none of the subjects experienced a serious adverse event. The following table illustrates the incidence of AE’s in subjects using a strong CYP2D6 inhibitor versus those who are not:

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8 FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

h The Hospital Anxiety and Depression Scale is one of the most widely used instruments to assess and monitor the severity of symptoms of anxiety and depression. The depression subscale separates that aspect from the anxiety portion.

i The Columbia Suicide Severity Rating Scale is a suicidal ideation rating scale created to evaluate suicidality in subject ages 12 and up. It identifies behaviors which may be indicative of an individual’s intent to commit suicide.
The clinical reviewer’s analysis of the data concluded that the overall summary of adverse events was similar in subjects who were using a strong CYP2D6 inhibitor versus those who were not using a strong CYP2D6 inhibitor at baseline.

A total of 16 subjects in ARC-HD were using a strong CYP2D6 inhibitor at baseline, versus 64 deutetramenazine treatment subjects not using a strong CYP2D6 inhibitor at baseline. There were no notable differences in the overall adverse event profile in subjects who were versus those who were not using a strong CYP2D6 inhibitor at baseline. The AE’s of interest reported are as follows:

<table>
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<th>Preferred Term</th>
<th>Baseline use of strong CYP2D6 inhibitor</th>
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<tr>
<td></td>
<td>Yes (n=16)</td>
</tr>
<tr>
<td></td>
<td>No (n=64)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Irritability</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
</tr>
<tr>
<td>Contusion</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>1 (2.7) *</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
</tr>
</tbody>
</table>

With the exception of 1 adverse event of severe intensity (1 subject experienced worsening chorea and withdrew from the study), all adverse events in the subjects in ARC-HD who were using a strong CYP2D6 inhibitor at baseline were of mild or moderate severity. Because 1 subject did experience a serious adverse event likely caused by a drug-drug interaction, DNP in the last review cycle, agreed upon a cap of 36 mg/day (18 mg bid) for individuals concomitantly taking a strong CYP2D6 inhibitor.
The structure of deutetrabenazine, when compared to tetrabenazine, allows for a slower rate of metabolism by CYP2D6. This reduces the impact of CYP2D6 inhibition, whether from concomitant medication use or genetics, and therefore reduced drug to drug interactions.

With tetrabenazine, patients who require doses greater than 50 mg per day should be genotyped for CYP2D6 – with poor metabolizers capped at a maximum single dose of 25 mg and max daily dose of 50 mg. The REMS approved for tetrabenazine in 2008 required the sponsor, Valeant Pharmaceuticals, to inform healthcare professionals (HCPs) about the need to slowly titrate the dose, perform CYP2D6 testing on patients requiring doses over 50 mg daily, and to cap the daily dose in poor metabolizers to 50 mg daily. Based on the 6-year assessment report submitted November 13, 2014, in which survey results indicated respondents were aware of the risks associated with dosing and CYP2D6 inhibitors, the REMS was released on August 25, 2015.6

5.3 QT PROLONGATION
A Thorough QT (TQT) Prolongation study was performed in healthy volunteers using a single-dose deutetrabenazine of 12 mg and 24 mg. This led to maximum, time-matched, placebo-adjusted, average increases from baseline QTcF interval of 2.8 ms and 4.5 ms, respectively. The sponsor and the Agency agree this is not a significant effect on QT prolongation and therefore has no clinical impact. The FDA Interdisciplinary Review Team (IRT) that analyzed the data believes the study is limited based on the challenge dose selected, and does not account for higher daily doses which are in the therapeautic range, nor does it account for situations where CYP2D6 metabolism may be impaired. Therefore, the opinion of the IRT review team, as well as the clinical reviewer, is that the language which exists in the current Xenazine label should be retained: “Effects at higher exposures to either XENAZINE or its metabolites have not been evaluated.”

5.4 EXPECTED POSTMARKET USE
Deutetrabenazine is likely to be prescribed by neurologists and movement disorder specialists, who are familiar with the management of Huntington’s Disease. Prescribers should be familiar with the potential risks associated with deutetrabenazine as they are similar, to those of the RLD, Xenazine, which was subject to a REMS which has been released due to completion of the communication plan and assessments which demonstrated it had met its goals. It is expected that the drug will be used in both an in-patient and out-patient setting. Patients with early stage Huntington’s disease marked by low cognitive and physical impairment are likely to self-medicate, taking the tablets by mouth as directed by their healthcare provider. Advanced disease progression leads to behavioral, cognitive and physical impairment that will likely necessitate dispensation and/or administration of deutetrabenazine under the supervision of a caregiver, and ongoing management by a neurologist and/or movement disorder specialist.

6 Risk Management Activities Proposed by the Applicant
The Applicant did not propose any risk management activities for deutetrabenazine beyond routine pharmacovigilance and labeling.

7 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of deutetrabenazine on the basis of the efficacy and safety information currently available.

DRISK believes a REMS is not necessary for deutetrabenazine at this time. Per the clinical reviewer, while no direct comparison was studied between deutetrabenazine and tetrabenazine, the safety concerns which initially warranted a REMS for tetrabenazine are of less concern with deutetrabenazine. With regards to depression and suicidality, and increased drug-drug interactions based on the CYP2D6 pathway, deutetrabenazine overall has a similar profile when compared to tetrabenazine, but with fewer events in the deutetrabenazine development program. Deutetrabenazine does not show a clinically significant increase in depression and suicidality when compared to placebo, and it is not possible to know if the events of depression (n=27) and suicidality (n=6) seen in ARC-HD are an increased risk from deutetrabenazine, given the background rate of affective disorder in HD. With regards to CYP2D6 interactions, the metabolic profile of deutetrabenazine reduces the rate at which the drug is metabolized by CYP2D6, when compared to tetrabenazine. The reduced rate of metabolism reduces the likelihood drug toxicity due to drug interactions or in patients who are poor CYP2D6 metabolizers. While Xenazine (tetrabenazine) was approved with a REMS in 2008 to address these two risks and due to completion of communication plan activities, the REMS was subsequently released in 2015. Therefore, DRISK believes the product labeling can sufficiently convey the risks associated with deutetrabenazine, via a boxed warning for depression and suicidality and a warning for drug-drug interactions, as well as a medication guide. No new, novel, or previously undescribed adverse drug reactions have been described that would warrant a REMS at this time, and the prescribing population for deutetrabenazine is likely to be the same as that of Xenazine.

8 Conclusion & Recommendations

Based on the available data, DRISK believes a REMS is not necessary to ensure the benefits of deutetrabenazine outweigh the risks. In general, healthcare providers who treat Huntington’s disease are familiar with the heightened risk of depression and suicidality that initially prompted a REMS with Xenazine and are aware of the importance of patient monitoring during titration and continued therapy to detect treatment-emergent depression and suicidal behavior or ideation, given the high background incidence of affective disorders in the HD population. The Division of Neurology Products should notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can then be reevaluated.

9 Materials Reviewed

The following is a list of materials informing this review:

10 Appendices

10.1 REFERENCES


5 Suchowersky O. Huntington Disease: Management. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 31, 2017.)


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/s/

YASMEEN I ABOU-SAYED
04/03/2017

JAMIE C WILKINS PARKER
04/03/2017
Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  

DEFERRAL OF RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date: May 2, 2016
Reviewer: Jasminder Kumar, Pharm.D.  
Risk Management Analyst  
Division of Risk Management (DRISK)

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division Director: Cynthia LaCivita, Pharm.D.
Subject: Defer comment on DRISK evaluation of the need for a REMS for deutetrabenazine
Drug Name: Austedo (deutetrabenazine)
Therapeutic class and Dosage Form: vesicular monoamine transporter 2 (VMAT2) inhibitor, oral tablets
Application Type/Number: NDA 208082
Applicant/sponsor: Teva Pharmaceuticals, Inc.
OSE RCM #: 2015-1301

*** This document contains proprietary and confidential information that should not be released to the public. ***
This memo is to defer the Division of Risk Management’s (DRISK) review of the need for a risk evaluation and mitigation strategy (REMS) for Austedo (deutetrabenazine), NDA 208082.

A 505(b)(2) application for deutetrabenazine was received by the Division of Neurology Products (DNP) Teva Pharmaceuticals, Inc. on May 29, 2015, with the proposed indication for the treatment of chorea associated with Huntington’s disease. The submission did not include a REMS, but did include a risk management plan consisting of routine and enhanced pharmacovigilance.

The Supervisory Pharmacologist has made the following recommendation for regulatory action based on the submission:

*Without an adequate understanding of the in vivo metabolic profile in humans, it is not possible to determine if all major circulating metabolites have been adequately evaluated in the appropriate nonclinical studies... However, the OCBP team has concluded that the sponsor has not adequately characterized the in vivo metabolic profile of SD-809 in humans. Without this information, the adequacy of the nonclinical data cannot be determined. The need for additional nonclinical data will depend on the new human mass balance data being collected by the sponsor (cf. Memorandum of Teleconference Minutes, March 23, 2016). This issue should be addressed prior to approval.*

In addition, the Pharmacology/Toxicology reviewer stated the following:

*Based on the available information provided by the sponsor for circulating metabolites in humans dosed with SD-809, there is concern regarding the variability in reported levels of SD-809 metabolites and that the level of circulating metabolites may have been underestimated...If the Clinical Pharmacology review team finds that the currently available human data on SD-809-related metabolites are inadequate, then, due to the lack of nonclinical data on circulating metabolites, it will not be possible to make a determination if the sponsor has successfully bridged to the nonclinical data available for the RLD, a critical element for the approval of Austedo under 505(b)(2).*

Therefore, an evaluation of the need for REMS for deutetrabenazine will be undertaken by DRISK after the Applicant addresses the deficiencies identified by the Supervisory Pharmacologist and the Pharmacology/Toxicology reviewer. Please send DRISK a new consult request at such time. This memo serves to close the existing consult request to DRISK for deutetrabenzaine under NDA 208082.

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1 Freed, LM. DNP Nonclinical Memorandum for Austedo (NDA 208082), dated March 31, 2016.

2 Toscano, CD. Pharmacology/Toxicology Review for Austedo (NDA 208082), dated February 4, 2016.
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/s/

JASMINDER N KUMAR
05/02/2016

JAMIE C WILKINS PARKER
05/02/2016