# CENTER FOR DRUG EVALUATION AND RESEARCH

***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)**

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|---|---|
| **Application Type** | NDA |
| **Application Number** | 208082 |
| **PDUFA Goal Date** | April 3, 2017 |
| **OSE RCM #** | 2015-1301, 2015-1298 |
| | |
| **Reviewer Name(s)** | Yasmeen Abou-Sayed, PharmD |
| **Team Leader** | Donella Fitzgerald, PharmD |
| **Deputy Division Director (Acting)** | Jamie Wilkins Parker, PharmD |
| **Review Completion Date** | April 3, 2017 |
| **Subject** | Evaluation of Need for a REMS |
| | |
| **Established Name** | Deutetrabenazine |
| **Trade Name** | Austedo |
| **Name of Applicant** | Teva |
| **Therapeutic Class** | VMAT2 inhibitor |
| **Formulation(s)** | Oral tablet as 6 mg, 9 mg, and 12 mg |
| **Dosing Regimen** | 6 mg initially, to be titrated up by 6 mg increments weekly up to max daily dose of 48 mg |

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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

[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.[b] 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.

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