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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

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

Material Reviewed/Consulted - Action Package, including:	
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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, α- and β-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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	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 ≥ 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.	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.
Current Treatment Options	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.	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.
Benefit	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 1° 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, $p<0.0001$). 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 2° endpoints: the Patient Global Impression of Change and the Clinical Global Impression of Change, compared with placebo.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	Deutetrabenazine has a safety profile similar to that of tetrabenazine. Adverse effects include sedation/somnolence, depression and suicidality, parkinsonism, akathisia, restlessness, and cognitive decline. It may be difficult to differentiate between adverse reactions and progression of the underlying disease, which could be problematic for prescribers and patients. The labeling recommends periodic reassessment of the need for the drug, and withdrawal, if necessary, to determine whether symptoms are drug-related or a manifestation of the underlying disease.	The potential harms of the drug are, by and large, reversible and manageable, with the exception of suicide.
Risk Management	As is the case for tetrabenazine, the risks associated with deutetrabenazine can be managed by labeling. Routine pharmacovigilance is recommended.	Labeling will include a Boxed Warning for increased risk for suicidality and depression in patients with HD, as per the labeling for tetrabenazine. There will also be a Medication Guide to highlight the need for vigilance for the emergence of depression, suicidal thoughts, and suicidal actions.

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

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