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APPLICATION NUMBER:

209885Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209885
Supporting document/s:	1
Applicant's letter date:	12/30/16
CDER stamp date:	12/30/16
Product:	Austedo (SD-809; deutetrabenazine)
Indication:	Treatment of Tardive Dyskinesia (TD)
Applicant:	Teva Pharmaceuticals
Review Division:	Psychiatry Products
Reviewer:	Amy M. Avila, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

This application is a 505(b)(2) NDA for deutetrabenazine (AUSTEDO) for the treatment of tardive dyskinesia. Deutetrabenazine is a deuterated form of tetrabenazine, a drug substance approved under the trade name Xenazine (NDA 21894) for the treatment of chorea associated with Huntington's disease. Austedo (SD-809) was approved for the treatment of chorea associated with Huntington's disease (NDA 208082) on April 3, 2017 under the 505(b)(2) pathway with Xenazine serving as the reference listed drug (RLD). Nonclinical studies were not submitted with the current application. The Applicant cross-referenced NDA 208082 for all nonclinical studies conducted with SD-809 (deutetrabenazine).

1.2 Brief Discussion of Nonclinical Findings

SD-809 (deutetrabenazine) is a deuterated form of tetrabenazine. Two hydrogen atoms on tetrabenazine have been replaced with deuterium atoms in order to slow down the rate of metabolism of the two primary active metabolites of tetrabenazine, α- and β-dihydrotetrabenazine. The pharmacologically active major metabolites of tetrabenazine, α- and β-dihydrotetrabenazine, and the deuterated versions formed from metabolism of deutetrabenazine, d_6-α-dihydrotetrabenazine and d_6-β-dihydrotetrabenazine, are high affinity antagonists of the vesicular monoamine transporter 2 (VMAT2), a protein involved in the transport of neurotransmitters into synaptic vesicles.

Nonclinical studies conducted with SD-809 that supported the approval of Austedo under NDA 208082 included a complete genetic toxicology battery, an embryo-fetal development study in rats with tetrabenazine as a comparator, and a 3-month repeat-dose toxicity study in rats with tetrabenazine as a comparator. According to the nonclinical reviews for NDA 208082, no adverse findings were identified that were unique to SD-809, relative to tetrabenazine, in those pivotal toxicology studies. NDA 208082 was a 505(b)(2) application, with the Applicant relying in part on the Agency's previous findings of safety for the reference listed drug, Xenazine. No additional nonclinical studies with SD-809, besides those cross-referenced in approved NDA 208082, were required by the Division of Psychiatry Products to support the approval of SD-809 (Austedo) for the indication of tardive dyskinesia (NDA 209885).

1.3 Recommendations

1.3.1 Approvability: This application is recommended for approval from a Pharmacology/Toxicology perspective for the indication of tardive dyskinesia.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling

At the time this review was finalized, labeling negotiations were ongoing with the Applicant. The Applicant did not propose any changes to the nonclinical sections of the

approved label for Austedo (NDA 208082) (sections 8.1, 8.2, 8.3, and 13.1). However, the Division of Pediatric and Maternal Health (DPMH) was consulted by the Division to review the pregnancy and lactation labeling sections of the label. DPMH recommended some changes to the approved label for sections 8.1, 8.2, and 8.3 (refer to DPMH consult review for details). At the time this review was finalized, internal discussions regarding possible to changes to the pregnancy and lactation sections of the label (8.1, 8.2, and 8.3) were ongoing.

2 Drug Information

2.1 Drug

CAS Registry Number: 1392826-25-3

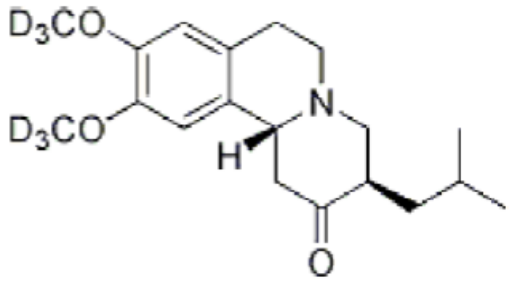
Generic Name: deutetrabenazine

Code Name: SD-809, d6-tetrabenazine, d6-TBZ

Chemical Name: (RR, SS)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d3)-3-(2-methylpropyl)-2Hbenzo[a]quinolizin-2-one

Molecular Formula/Molecular Weight: $C_{19}H_{21}D_6NO_3$ / 323.46
Note: D = Deuterium

Structure or Biochemical Description:



Pharmacologic Class: Vesicular monoamine transporter 2 (VMAT2) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 120631: treatment of tardive dyskinesia
NDA 208082: approved on April 3, 2017 for the treatment of chorea associated with Huntington's disease

2.3 Drug Formulation

Tablets: 6 mg, 9 mg, and 12 mg

2.4 Comments on Novel Excipients

NA

2.5 Comments on Impurities/Degradants of Concern

Nonclinical studies were conducted to evaluate the safety of impurities under NDA 208082. Results did not reveal any health risk to the patient population.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with tardive dyskinesia
Dosing regimen: starting dose of 12 mg/day titrated to a maximum dose of 48 mg/day, administered twice a day (BID).

2.7 Regulatory Background

A pre-NDA meeting was held on November 3, 2016.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted to this application. NDA 208082 was cross-referenced for all nonclinical data. NDA 208082 was approved on April 3, 2017 for the treatment of chorea associated with Huntington's disease.

3.3 Previous Reviews Referenced

Refer to nonclinical reviews for NDA 208082 by Dr. Christopher Toscano for a complete review of all nonclinical studies with SD-809 (deutetrabenazine).

11 Integrated Summary and Safety Evaluation

The binding affinities to the vesicular monoamine transporter 2 (VMAT2) were similar between the deuterated and non-deuterated major active metabolites of tetrabenazine and deutetrabenazine. Additionally, deuteration of the α- and β-dihydrotetrabenazine did not have any significant impact on binding to off-target receptors, including alpha-1 alpha-2 adrenergic receptors, dopamine D1 and D2 receptors, non-selective opioid, serotonin, and sigma receptors. These data suggest that deuteration of tetrabenazine has little or no impact on the pharmacology of the drug. The deuterated and non-deuterated forms of α- and β-dihydrotetrabenazine metabolites inhibited the hERG channel less than 50% at concentrations of 10 μM when tested in an in vitro assay. No in vivo cardiovascular or respiratory safety pharmacology studies were conducted with SD-809; however a functional observational battery was included in the 3-month repeat-dose toxicity study in rats.

In rodents, equal doses of SD-809 and tetrabenazine resulted in comparable half-lives and roughly similar (< 2-fold greater) AUC values for the α- and β-dihydrotetrabenazine metabolites formed from SD-809 as compared to tetrabenazine. This is in contrast to humans, in which deuterium substitution of tetrabenainze results in an increase in the half-lives of α- and β-dihydrotetrabenazine, and about two-fold increases in AUC values. This difference in PK between rodents and humans may be due to differences in CYP enzymes. The distribution of [^{14}C]-SD-809 or [^{14}C]-tetrabenazine-related radioactivity in

tissues did not differ significantly between the two compounds when administered to male rats, with the greatest concentrations of radioactivity observed in the uveal tract and the gastrointestinal tract. The excretion of radioactivity was also similar for both compounds in rats, with the majority of radioactivity excreted in feces. The Division of Neurology products determined during the review of NDA 208082, initial submission and resubmission, that the M1 (SD-1021) and M4 (SD-1028) metabolites of SD-809 are not major human metabolites, but rather minor metabolites.

A non-GLP 14-day repeat-dose toxicity and toxicokinetic study was conducted in male Sprague-Dawley rats administered SD-809 at dose levels of 0, 15, 30, and 50 mg/kg/day (administered BID) or 50 mg/kg/day tetrabenazine (administered BID). The NOAEL was < 15 mg/kg/day (7.5 mg/kg/ BID) due to CNS-related clinical signs including tremors, flattened body, and palpebral closure, decreased body weight gain, and decreased white blood cell parameters at all doses of SD-809 or tetrabenazine. In the pivotal GLP 3-month repeat-dose toxicity and toxicokinetic study, Sprague-Dawley male and female rats were administered SD-809 at dose levels of 0, 5, 10, and 30 mg/kg/day (administered BID) or 30 mg/kg/day tetrabenazine (administered BID) by oral gavage. CNS-related clinical signs including twitching, partial closure of eyes, and increased activity were observed in a dose-dependent manner in males at all doses of SD-809 and with tetrabenazine. Partial closure of the eyes and increased activity was observed in females at 10 and 30 mg/kg/day for SD-809 and for tetrabenazine. Tremors were observed at the ≥10 mg/kg/day SD-809 and tetrabenazine for males and for females at the high dose of SD-809 and for tetrabenazine. In addition, handling-induced convulsions were observed in 1 male each at the high dose for SD-809 and for tetrabenazine. The frequency and incidence of clinical signs were comparable at the high dose of SD-809 to tetrabeanzine. A decrease in absolute body weight was observed in males at all doses of SD-809 and with tetrabenazine. White blood cell parameters were decreased for high dose males and for males treated with tetrabenazine. Dose-dependent decreased uterus weights and increased mammary gland hyperplasia was observed in females at all dose levels of SD-809 and with tetrabenazine. The overall NOAEL was determined to be less than 5 mg/kg/day SD-809 for both males and females. However, there were no unique toxicities due to SD-809 in either males or females compared to tetrabenazine. Additionally, exposure to α- and β-dihydrotetrabenazine was similar in rats administered SD-809 or tetrabenazine.

SD-809 was evaluated in a complete genetic toxicology battery, including an in vitro Ames assay, chromosomal aberration assay, and an in vivo micronucleus assay conducted in mice using tetrabenazine as a comparator. In addition, in vitro bacterial reverse mutation assays and in vitro chromosomal aberration assays were conducted with the deuterated and non-deuterated α- and β-dihydrotetrabenazine metabolites. All genetic toxicology studies with SD-809 and the deuterated and non-deuterated α- and β-dihydrotetrabenazine metabolites were negative.

SD-809 was assessed for its effects on embryo-fetal development in a GLP study in pregnant rats. SD-809 was administered to pregnant Sprague-Dawley rats by oral gavage at dose levels of 0, 5, 10, and 30 mg/kg/day (administered BID) from gestation

day 6 to 17. A separate group of rats were administered tetrabenazine at a dose of 30 mg/kg/day (administered BID) as a comparator. The maternal NOAEL was determined to be 10 mg/kg/day based on decreased body weight gain at higher doses. No embryo-fetal development NOAEL was determined for SD-809 (<5 mg/kg/day) due to a dose-dependent increase in the incidence of 7th cervical rib. However, this finding also occurred with tetrabenazine indicating that this is not a unique toxicity to SD-809. There were no drug-related external or visceral malformations or variations, or skeletal malformations.

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/s/

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08/03/2017

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