CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208082Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD, Deputy Director, DNP.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208082
Applicant	Teva Pharmaceuticals, Inc.
Date of Submission	October 3, 2016
PDUFA Goal Date	April 3, 2017
Proprietary Name / **Non-Proprietary Name**	Austedo/ Deutetrabenazine (deutetrabenazine)
Dosage Form(s) / Strength(s)	Oral tablets / 6 mg, 9 mg, and 12 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of chorea in patients with Huntington's disease.
Recommended Action	Approval
Recommended Indication/Population(s)	Treatment of chorea in patients with Huntington's disease.

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Stacy Metz
Medical Officer Clinical Review	Ken Bergmann
Clinical Pharmacology Review	Kristina Dimova; Angela Men; Xiaofeng Wang; Atul Bhattaram; Kevin Krudys; Jeffrey Kraft; Christian Grimstein
Statistical Review	Xiangmin Zhang; Kun Jin; Hsien Ming Hung
Pharmacology Toxicology	Chris Toscano; Lois Freed
Chemistry Manufacturing and Controls	Wendy Wilson-Lee; Martha Heimann; Gene Holbert; Sherita McLamore-Hines; Masih Jaigirdar; Don Obenhuber
ONDQA Biopharmaceutics Review	Jing Li; Okpo Eradiri; Angelica Dorantes
CSS	Alicja Lerner; Michael Klein
OSI	Antoine El Hage; Susan Thompson; Kassa Ayalew
OSE/DMEPA	Deborah Myers; Danielle Harris
OSE/DRISK	Jasmine Kumar; Jamie Wilkins Parker
QT/IRT	Moh Jee Ng; Qianyu Dang; Dinko Rekic; Jiang Liu; Michael Li; Norman Stockbridge
OSE PMs	Ermias Zerislasse; Corwin Howard
OSE/DEPI	Lockwood Taylor; Elisa Braver
Cross-Discipline Team Leader	Gerald (Dave) Podskalny

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

e 505(b)(2) application under review is for deutetrabenazine (Austedo), a deuterated form of tetrabenazine, proposed for the treatment of orea associated with Huntington's disease. The applicant proposes using tetrabenazine, which is approved for the same indication, as reference ted drug. This application relies on the tetrabenazine NDA for some pharmacology/toxicology studies that were not conducted by the applicant, cluding a fertility and early embryonic development study, an embryofetal developmental study, a pre- and post-natal development study, and rcinogenicity assessment.

th deutetrabenazine and tetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors. The mechanism of action of utetrabenazine and tetrabenazine on chorea is believed to be related to their effect as reversible depletors of monoamines (e.g., dopamine, otonin, norepinephrine, and histamine) from nerve terminals.

e efficacy of deutetrabenazine was established in a 12-week placebo-controlled study that used a well-accepted measure of chorea, the total ximal chorea (TMC) score. The change from baseline in TMC score was significantly higher (drug-placebo difference of 2.5 points, on a 24-int scale) for deutetrabenazine than for placebo ($p<0.0001$). The meaningfulness of the TMS results was supported by statistically significant fects on the Patient Global Impression of Change and the Clinical Global Impression of Change.

e safety profile of deutetrabenazine is acceptable. There were no unique toxicities identified for deutetrabenazine, as compared with rabenazine. A close examination of the deutetrabenazine safety database was conducted for the safety issues known for tetrabenazine. These ues include sedation and somnolence, akathisia, depression, and suicidality. Notwithstanding the usual limitations of cross-study comparisons, e frequency of these events appears no higher for deutetrabenazine than for tetrabenazine. Absent a head to head comparative study, it is possible to make any definitive conclusions about the comparative safety profile between tetrabenazine and deutetrabenazine, but there are no w safety concerns identified. A QT prolongation signal is known and labeled for tetrabenazine. The TQT study conducted by the applicant did t use sufficiently high concentrations of deutetrabenazine to rule out QT prolongation at supratherapeutic or therapeutic concentrations. As for rabenazine, this can be addressed by labeling.

trabenazine is already marketed for the same indication as that proposed for deutetrabenazine, and deutetrabenazine does offer as only clear vantage over tetrabenazine that, at high end of the dosing range, tetrabenazine must be taken two to three times a day, while deutetrabenazine y be taken just twice a day.

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