

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209885Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209885 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)
Proprietary Name: Austedo Established/Proper Name: deutetrabenazine Dosage Form: Tablet		Applicant: Teva Branded Pharmaceutical Products R&D, Inc. Agent for Applicant (if applicable):
RPM: Sarah Seung		Division: Division of Psychiatry Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		For ALL 505(b)(2) applications, two months prior to EVERY action: - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity (notify CDER OND IO) Date of check: 7/12/17 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>8/30/17</u>		☒ AP ☐ TA ☐ CR
Previous actions (specify type and date for each action taken)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority

Chemical classification (new NDAs only): vesicular monoamine transporter 2 (VMAT2) inhibitor
(confirm chemical classification at time of approval)

- | | |
|--|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☒ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval: 8/30/17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name	Grant Letter: 3/15/17 Reviews: 1/10/17, 3/14/17
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: ☐ None 8/30/17 DMEPA: ☐ None 6/30/17 DMPP/PLT (DRISK): ☐ None 6/27/17 OPDP: ☐ None 6/28/17, 8/3/17 SEALD: ☒ None CSS: ☐ None 8/7/17 Product Quality ☐ None 7/26/17 Other: ☐ None DPMH (PLLR) 6/2/17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	2/24/17
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) 8/7/17
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>8/16/17</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☐ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Grant: 11/3/15 Intent to Rescind: 8/2/17
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	11/2/15
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <u>MPC SharePoint Site</u>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Multiple IRs sent
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Medical Policy Council Meeting Minutes 11/2/15 T-con Memo: 2/15/17
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 11/3/16
EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A 4/18/17
Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A 6/20/17
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 8/30/17
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None one (1)
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	8/7/17
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	In Clinical Review: 8/7/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☐ None QT-IRT: 5/22/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☐ N/A 8/28/17 not a controlled substance
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☐ None CSS: 8/28/17 REMS: 8/30/17
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☐ None requested 3/9/16
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☐ None 8/2/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 8/10/17
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 8/3/2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☐ None 7/26/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	In Integrated Quality Assessment: 7/26/17
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☐ Acceptable ☐ Withhold recommendation ☒ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

Seung, Sarah

From: Seung, Sarah
Sent: Tuesday, August 29, 2017 4:36 PM
To: 'David Truong'
Subject: RE: Labeling Final Comments: NDA 209885 Austedo for TD

Hi David,

We now have agreed upon labeling for the prescribing information (PI) and medication guide (MG). Please submit a clean copy of the agreed upon labeling and a tracked changes version (comparing the previously approved labeling and the agreed upon label) of the PI & MG in word and pdf formats to the NDA and to me via email by tomorrow morning (Wednesday, August 30, 2017).

Regards,
Sarah

From: David Truong [<mailto:David.Truong@tevapharm.com>]
Sent: Tuesday, August 29, 2017 2:38 PM
To: Seung, Sarah
Subject: RE: Labeling Final Comments: NDA 209885 Austedo for TD

Hi Sarah,

Please find attached the label with FDA comments accepted and Teva's acceptances are also tracked in the comments. Minor editorial changes were made and tracked. Please note that some of the formatting were corrected and were not tracked. I have also included a pdf version to retain formatting. Please let me know if there are any questions.

davidTRUONG, PharmD, MS | Global Regulatory Affairs | Mobile: (858) 239-5050 | david.truong@tevapharm.com

From: Seung, Sarah [<mailto:Sarah.Seung@fda.hhs.gov>]
Sent: Tuesday, August 29, 2017 8:54 AM
To: David Truong
Subject: Labeling Final Comments: NDA 209885 Austedo for TD

Hi David,

Please see the attached prescribing information (PI) regarding your NDA 209885 Austedo that was submitted on December 30, 2016. We are providing our final set of comments.

Requested changes are tracked and/or enclosed in comments. Please accept all tracked changes, and use this as the base document. Track all proposed edits and respond to our comments as "Accept" or provide an explanation for proposing new text/not accepting our request. Please submit your revised PI as an annotated Word document. It should be noted, however, that given the PDUFA due date of tomorrow, it is doubtful that any substantial changes would be accepted.

Comments regarding the Medication Guide will be forthcoming in a separate email.

Please respond via email on or before 3:00pm (EST) today (Tuesday, August 29, 2017).

Regards,
Sarah

*Sarah Seung, PharmD
CDR, US Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171
Silver Spring, MD 20993
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov*



Seung, Sarah

From: David Truong <David.Truong@tevapharm.com>
Sent: Tuesday, August 29, 2017 4:27 PM
To: Seung, Sarah
Subject: RE: Medication Guide Final Comments: NDA 209885 Austedo for TD
Attachments: NDA209885Austedo Med-Guide 8-29-17 Teva Response .docx; NDA209885Austedo Med-Guide 8-29-17 Teva Response .pdf

Hi Sarah,

Please find attached the Medication Guide with FDA's comments accepted. Teva's acceptances are tracked in the comments section. A minor editorial change was made and tracked. Please note that of the formatting of the bullets were corrected and not tracked. I have also included a pdf version to retain formatting. Please let me know if there are any questions.

Best regards,

David

davidTRUONG, PharmD, MS | Global Regulatory Affairs | Mobile: (858) 239-5050 | david.truong@tevapharm.com

From: Seung, Sarah [<mailto:Sarah.Seung@fda.hhs.gov>]
Sent: Tuesday, August 29, 2017 12:41 PM
To: David Truong
Subject: Medication Guide Final Comments: NDA 209885 Austedo for TD

Hi David,

Attached is our final comments on the Medication Guide (MG) for your NDA 209885 Austedo. Requested changes are tracked with explanations enclosed in comments. Please accept all tracked changes, and use this as the base document. Track all proposed edits and respond to our comments as "Accept" or provide an explanation for proposing new text/not accepting our request. Please submit your revised MG as an annotated Word document. It should be noted, however, that given the PDUFA due date of tomorrow, it is doubtful that any substantial changes would be accepted.

Please respond via email on or before **6:00pm on Tuesday, August 29, 2017**.

Regards,
Sarah

*Sarah Seung, PharmD
CDR, US Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171
Silver Spring, MD 20993*

Phone: 240.402.3879

Email: sarah.seung@fda.hhs.gov



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
08/30/2017

PAUL A DAVID
08/30/2017

Seung, Sarah

From: Holovac, Mary Ann
Sent: Tuesday, August 08, 2017 11:48 AM
To: Seung, Sarah
Cc: Locicero, Colleen L; Sharma, Khushboo; Goldstein, Beth A (Duvall); Holovac, Mary Ann
Subject: NDA 209885 - cleared for action

Sarah,

We discussed the subject application at Monday's 505(b)(2) clearance meeting. The application is cleared for action from a 505(b)(2) perspective.

Please make the following changes to the draft assessment before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the resubmission arrives so that we can add it anew to our clearance queue.

- *Q3: Please delete the bridge information provided on the assessment and replace it with the following: The bridge was established with the original 208082 NDA. As there is no new reliance, the bridge does not need to be re-established for this NDA for a new indication.*
- *Q11c bottom: List Austedo NDA 208082 as a pharmaceutical equivalent.*

Please let me know if you have any questions.

Mary Ann

From: Seung, Sarah
Sent: Thursday, July 27, 2017 10:11 AM
To: Holovac, Mary Ann
Subject: RE: draft 505(b)(2) assessment for NDA 209885

Hi Mary Ann,

It was rejected as a O-2 NDA because it was not submitted at the same time as the original NDA (208082). After NDA 208082 was approved on 4/3/17, this NDA (209885) became a Type 9 NDA.

Thanks,
Sarah

From: Holovac, Mary Ann
Sent: Thursday, July 27, 2017 8:25 AM
To: Seung, Sarah
Subject: RE: draft 505(b)(2) assessment for NDA 209885

Thank you Sarah for the quick reply.

Although not relevant to 505(b)(2) do you know why the original-2 NDA was rejected and given a separate number? If you don't recall off the top of your head don't worry about it. It seemed odd to me.

Mary Ann

From: Seung, Sarah
Sent: Wednesday, July 26, 2017 4:40 PM
To: Holovac, Mary Ann
Subject: Re: draft 505(b)(2) assessment for NDA 209885

Hi Mary Ann,

Yes that is correct. There is no new reliance for this NDA.

Thank you!
Sarah

From: Holovac, Mary Ann <Maryann.Holovac@fda.hhs.gov>
Date: July 26, 2017 at 4:22:34 PM EDT
To: Seung, Sarah <Sarah.Seung@fda.hhs.gov>
Subject: FW: draft 505(b)(2) assessment for NDA 209885

Hi Sarah,

I am looking at the subject NDA in preparation for 505(b)(2) committee review. Everything appears to be in order. Can you confirm there is no NEW RELIANCE for this NDA? It appears the new NDA is relying only upon the same information the original NDA relied upon, i.e. the Xenazine NDA, correct? Just want to double check as I may be asked.

Thank you.
Mary Ann

From: CDER OND IO (Mailbox)
Sent: Friday, June 30, 2017 7:33 AM
To: Holovac, Mary Ann
Subject: FW: draft 505(b)(2) assessment for NDA 209885

Hello Mary Ann,

This is for you.

Jewell

From: Seung, Sarah
Sent: Thursday, June 29, 2017 5:40 PM
To: CDER OND IO (Mailbox)
Subject: draft 505(b)(2) assessment for NDA 209885

Good afternoon,

Please find attached the draft 505(b)(2) Assessment for NDA 209885.

The planned action date is 8/30/17.
Heading towards APPROVAL.

Thank you,
Sarah

Sarah H. Seung, PharmD
CDR, US Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
FDA/CDER/OND/ODEI
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov



IND 120631

**INTENT TO RESCIND –
BREAKTHROUGH THERAPY DESIGNATION**

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs
41 Moores Road
Frazer, PA 19355

Dear Dr. Truong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SD-809 (deutetrabenazine).

We also refer to our November 3, 2015 letter granting Breakthrough Therapy designation to SD-809 (deutetrabenazine) for Tardive Dyskinesia. We are notifying you of our intent to rescind this Breakthrough Therapy designation because the criteria for designation are no longer being met for the following reason: Ingrezza (valbenazine) capsules, approved for the treatment of Tardive Dyskinesia, is for the same indication as your breakthrough designation and, therefore, the designated drug no longer shows substantial improvement over available therapy.

You have 60 days to provide additional data and justification to support continuing Breakthrough Therapy designation for SD-809 (deutetrabenazine) for Tardive Dyskinesia and/or request a meeting with the FDA to discuss the Breakthrough Therapy designation for this drug. Please contact the Regulatory Health Project Manager within 60 days to discuss how you plan to respond to our intent to rescind this designation.

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>)

If you have any questions, contact Sarah Seung, Regulatory Project Manager, at (240)402-3879 or sarah.seung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
08/02/2017

Seung, Sarah

From: Seung, Sarah
Sent: Friday, July 07, 2017 8:01 PM
To: 'david.truong@tevapharm.com'
Subject: Labeling Comments 1: NDA 209885 Austedo for TD
Attachments: NDA209885 deutetrabenazine 050117 draft for sponsor 7-7-17.docx

Hi David,

Please see the attached prescribing information (PI) regarding your NDA 209885 Austedo that was submitted on December 30, 2016. We are providing our initial comments. Please note several sections are under review. Requested changes are tracked and/or enclosed in comments. Please accept all tracked changes, and use this as the base document. Track all proposed edits and respond to our comments as "Accept" or provide an explanation for proposing new text/not accepting our request. Please submit your revised PI as an annotated Word document.

We note that your May 1, 2017 proposed labeling submission did not contain updated Carton and Container labels. Please provide updated Carton and Container labels.

Comments regarding the Medication Guide will be forthcoming in a separate email.

Please respond via email on or before **Friday, July 14, 2017**.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Sarah

*Sarah Seung, PharmD
CDR, US Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171*

Silver Spring, MD 20993

Phone: 240.402.3879

Email: sarah.seung@fda.hhs.gov



25 Page(s) of Draft Labeling have been
Withheld in Full as b4 (CCI/TS) immediately
following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH H Seung
07/07/2017

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☒ Full Waiver ☐ Partial Waiver ☐ Pediatric Assessment ☐ Deferral/Pediatric Plan

BLA/NDA#: NDA 209885

PRODUCT PROPRIETARY NAME: Austedo

ESTABLISHED/GENERIC NAME: Deutetrabenazine

APPLICANT/SPONSOR: Teva Branded Pharmaceutical Products R&D, Inc.

PREVIOUSLY APPROVED INDICATION/S:

(1) *Treatment of chorea associated with Huntington's disease (under NDA 208082)*

(2) _____

(3) _____

(4) _____

PROPOSED INDICATION/S:

(1) *Treatment of tardive dyskinesia* _____

(2) _____

(3) _____

(4) _____

BLA/NDA STAMP DATE: December 30, 2016

PDUFA GOAL DATE: August 30, 2017

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ ***active ingredient(s) (includes new combination);*** ☒ ***indication(s);*** ☐ ***dosage form;*** ☐ ***dosing regimen;*** or ☐ ***route of administration?***

Did the sponsor submit an Agreed iPSP? Yes ☒ ***No*** ☐

Are there any changes to the Agreed iPSP that are different than the sponsor's current pediatric plan? Yes ☐ ***No*** ☒

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ☐ ***No*** ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- ☐ *Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- ☒ *Pediatric Record (in DARRTS)*

- 1 Pediatric age group(s) to be waived. 0-17 years old
- 2 Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)

- ☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- ☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- ☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- ☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. **(This reason is for Partial Waivers Only)**

3 Provide justification for Waiver: The necessary studies are highly impracticable due to the low prevalence and incidence of TD among pediatric patients.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

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/s/

SARAH H Seung
06/27/2017

Seung, Sarah

From: Seung, Sarah
Sent: Thursday, June 08, 2017 3:49 PM
To: 'david.truong@tevapharm.com'
Subject: CSS Information Request: NDA 209885 Deutetrabenazine

Hi David,

This communication is in reference to your NDA 209885 for deutetrabenazine. Reference is also made to our Information Request (IR) dated March 7, 2017 and to your response dated March 15, 2017. We have the following follow-up IR from the Controlled Substance Staff.

1. How many patients completed the study SD-809-C-20 at the time of NDA submission, Mod 2.7.4.6.7 page 97, seems to indicate that 34 patients completed study. This would suggest that the discontinuation data provided in IR to CSS questions summary 15.25, page 33/80, is from these 34 patients, is this correct?
2. Provide accountability data as pill count, that is numbers of pills missing or not accounted for, for all three studies and for Austedo and placebo separately.

Please submit the response to this IR officially to NDA 209885 as soon as possible but no later than COB June 15, 2017.

Regards,
Sarah

*Sarah Seung, PharmD
CDR, US Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171
Silver Spring, MD 20993
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov*



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/s/

SARAH H Seung
06/08/2017

Lee, Danbi

From: Lee, Danbi
Sent: Friday, May 05, 2017 8:21 AM
To: david.truong@tevapharm.com
Cc: Lee, Danbi; Seung, Sarah
Subject: NDA 209885; deutetrabenazine QT IR
Attachments: Highlights of ClinPharm and Cardiac Safety_20150923.docx

Good morning Dr. Truong,

Reference is made to your 120-day safety update submitted on May 1, 2017. Please fill out the attached Highlights of Clin/Pharm and Cardiac Safety table and send it back as soon as possible but no later than Tuesday May 9, 2017.

As always, please submit officially to the IND and send me a courtesy copy.

Thank you,
Danbi

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

DANBI LEE
05/05/2017

Lee, Danbi

From: Lee, Danbi
Sent: Wednesday, May 03, 2017 4:41 PM
To: 'david.truong@tevapharm.com'
Cc: Seung, Sarah
Subject: NDA 209885; deutetrabenazine for TD

Dr. Truong,

I am sending this information request on behalf of Sarah Seung.

Reference is made to Figure 4 of your labeling draft. Figure 4 shows distribution with respect to percent of patients with specified magnitude of AIM Total score improvement at the end of week 12 for Study 1 (or Study 23 in the NDA).

Please clarify the number of subjects missing in the plot. At baseline, the number of subjects were: 58 (placebo), 60 (12 mg), 49 (24 mg), 55 (36 mg). At week 12, subjects who completed the study were: 56 (Placebo), 53 (12 mg), 45 (24 mg), 52 (36 mg). The number of subjects who were missing should be 2 (Placebo), 7 (12 mg), 4 (24 mg), 3 (36 mg). However, these numbers do not seem to agree with what is presented in Figure 4. Please attach SAS code used to produce the figure.

In order to ensure timely review of this application, please respond by 4 PM this Friday, May 5, 2017. As always, please submit officially to the IND and send me a courtesy copy via email.

Thank you,

Danbi Lee, Pharm.D.

Regulatory Project Manager

Division of Psychiatry Products

Food and Drug Administration

10903 New Hampshire Ave.

Bldg 22, Room 4133

Silver Spring, MD 20993

Phone: 240-402-8986

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/s/

DANBI LEE
05/03/2017



NDA 209885

MID-CYCLE COMMUNICATION

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs
3333 North Torrey Pines Court, Suite 400
La Jolla, CA 92037

Dear Dr. Truong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg

We also refer to the teleconference between representatives of your firm and the FDA on April 18, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, contact Sarah Seung, Regulatory Project Manager at (240) 402-3879 or sarah.seung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MID-CYCLE COMMUNICATION

Meeting Date and Time: April 18, 2017
1:00 PM (EST) to 2:00 PM (EST)

Application Number: 209885
Product Name: Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg
Indication: Treatment of Tardive Dyskinesia
Applicant Name: Teva Branded Pharmaceutical Products R&D, Inc.

Meeting Chair: Mitchell Mathis, MD
Meeting Recorder: Sarah Seung, PharmD

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Anandraj Mattai, MD	Clinical Reviewer, DPP
Daniel Lee, MD	Clinical Reviewer, DPP
Hao Zhu, PhD	Team Leader, Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Reviewer, OCP
Gopichand Gottipati, PhD	Pharmacometrics Reviewer, OCP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
Peiling Yang, PhD	Biometrics Team Leader
Semhar Ogbagaber, PhD	Biometrics Reviewer
Loretta Holmes, BSN, PharmD	Safety Evaluator, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology (OSE)
Leah Hart, PharmD	Acting Team Leader, Division of Risk Management, OSE
Alycia Anderson, CCRP	Safety Regulatory Project Manager, OSE
Catherine Roca, MD	Medical Officer, Division of Pediatric and Maternal Health (DPMH)
Jane Liedtka, MD	Acting Team Lead, DPMH
Aline M. Moukhtara, RN, MPH	Regulatory Review Officer, Office of Prescription Drug Promotion
Martin S. Rusinowitz, MD	Senior Medical Reviewer, Controlled Substance Staff
Sarah Seung, PharmD	Regulatory Project Manager, DPP

APPLICANT ATTENDEES

Dennis Ahern, Senior Director	Global Regulatory Affairs
Margaret Bradbury, PhD	Senior Director, Non-Clinical Development
Donna Cox, PhD, Director	Clinical Pharmacology

Matthew Davis, PhD
David Stamler, MD
David Truong, PharmD, MS

Director, Biostatistics
Vice-President, Clinical Development
Senior Manager, Global Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified at this time.

3.0 INFORMATION REQUESTS

No information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The applicant was updated on the following milestone dates for deutetrabenazine:

- Late-Cycle Meeting is scheduled for June 20, 2017.
- We plan to communicate proposed labeling and if necessary, any postmarketing commitment requests by June 30, 2017 if major deficiencies are not identified during the review.

- We plan to take an action by the August 30, 2017 PDUFA date.

7.0 OTHER DISCUSSION

The applicant provided an update on the following items:

- The 120-day safety update will be submitted at the end of April. They have ongoing data from both the Huntington's Disease (HD) and Tardive Dyskinesia (TD) patient populations. They did not detect any no new safety signal.
- A revised labeling will be submitted at the end of April. They are updating the labeling with the approved NDA 208082 Austedo for HD labeling. In addition, they plan to revise portions of the labeling based the approved NDA 209241 Ingrezza labeling.

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/s/

MITCHELL V Mathis
04/26/2017

Seung, Sarah

From: Seung, Sarah
Sent: Thursday, March 30, 2017 1:02 PM
To: 'David Truong'
Subject: RE: Urgent Information Request: NDA 209885 Deutetrabenazine for TD

Hi David,

Please see the clarification on point 2 below (added in black font):

2. Please provide the information of the entity which performed the central reading: the name, address, contact information

Regards,
Sarah

From: David Truong [<mailto:David.Truong@tevapharm.com>]
Sent: Thursday, March 30, 2017 12:41 PM
To: Seung, Sarah
Subject: RE: Urgent Information Request: NDA 209885 Deutetrabenazine for TD

Hi Sarah,

Thank you for the email. Can you clarify for point 2, does OSI want the information for each central rater involved in the studies?

david**TRUONG**, PharmD, MS | Global Regulatory Affairs | 3333 N. Torrey Pines Court, Suite 400 | La Jolla, CA 92037 | Telephone: (858) 875-5897 | Mobile: (858) 239-5050 | david.truong@tevapharm.com

From: Seung, Sarah [<mailto:Sarah.Seung@fda.hhs.gov>]
Sent: Thursday, March 30, 2017 9:35 AM
To: David Truong
Subject: Urgent Information Request: NDA 209885 Deutetrabenazine for TD
Importance: High

Hi David,

We have the following urgent information request:

Please refer to your New Drug Application (NDA #209885, IND#:120631), deutetrabenazine, Austedo for the indication of tardive dyskinesia, submitted on 30Dec2016.

OSI just learned from the site CI inspections that the AIMS scores assessed by blinded video rating are not available at site for verification. We have the following 2 requests:

1. Please send all central AIMS scores assessed by blinded video rating for site Steven Macina, D.O. (Site #108), Michael McManus (Site #110) and Lili Meisamy (Site #151) for both studies SD-809-C-18 and SD-809-C-23 in 3 separate PDF files
2. Please provide the information of the central reading, name, address, contact information

Please respond by **today 30 March 2017**. If you cannot, please provide rationale.

Regards,

Sarah H. Seung, PharmD
CDR, US Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
FDA/CDER/OND/ODEI
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov

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/s/

SARAH H Seung
03/30/2017



NDA 209885

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Teva Branded Pharmaceutical Products R&D, Inc.
3333 North Torrey Pines Court
Suite 400
La Jolla, CA 92037

ATTENTION: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs

Dear Dr. Truong:

Please refer to your New Drug Application (NDA) dated and received December 30, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Deutetrabenazine Tablets, 6 mg, 9 mg and 12 mg.

We also refer to your correspondence dated and received January 12, 2017, requesting review of your proposed proprietary name, Austedo.

We have completed our review of the proposed proprietary name, Austedo and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 12, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Alycia Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4270. For any other information regarding this application, contact Sarah Seung, Regulatory Project Manager in the Office of New Drugs, at (240) 402-3879.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/15/2017

Seung, Sarah

From: Seung, Sarah
Sent: Tuesday, March 07, 2017 6:00 PM
To: 'david.truong@tevapharm.com'
Subject: NDA 209885 Deutetrabenazine - Information Request - Controlled Substance Staff

Hi David,

We have the following Information Request (IR) from the Controlled Substance Staff.

In order to better evaluate dependence, withdrawal and rebound the sponsor should provide:

- all adverse events which occurred during the discontinuation period
- reports of any cases of drug misuse, diversion, and overdose and a summary of drug accountability for all studies (or information where it can be located, since there is no ISS)
- comparison of the baseline values and follow-up visits for all scales used to evaluate drug efficacy and related adverse events for the studies # SD-809-C-18, # SD-809-C-23 and # SD-809-C-20 separately, which will include:
 - o AIMS-Abnormal Involuntary Movement Scale
 - o BARS-Barnes Akathisia Rating Scale
 - o CDQ-24-Craniocervical Dystonia Questionnaire
 - o CGIC-Clinical Global Impression of Change
 - o C-SSRS-Columbia-Suicide Severity Rating Scale
 - o ESS-Epworth Sleepiness Scale
 - o HADS-Hospital Anxiety and Depression Scale
 - o MoCA-Montreal Cognitive Assessment
 - o PGIC-Patient Global Impression of Change
 - o UPDRS-Unified Parkinson's Disease Rating Scale.

Please submit the response to this IR officially to NDA 209885 by **COB March 14, 2017**.

Regards,
Sarah

*Sarah Seung, Pharm.D.
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171
Silver Spring, MD 20993
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov*



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/s/

SARAH H Seung
03/07/2017



NDA 209885

**INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION**

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs
3333 North Torrey Pines Court, Suite 400
La Jolla, CA 92037

Dear Dr. Truong:

Please refer to your New Drug Application (NDA) dated December 30, 2016, received December 30, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg.

We also refer to your amendments dated February 17, 2017 and February 23, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

- 1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

- 2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendments dated February 17, 2017 and February 23, 2017.

If you have any questions, contact me at (240) 402-3879 or sarah.seung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sarah Seung, PharmD
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SARAH H Seung
03/02/2017



NDA 209885

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs
3333 North Torrey Pines Court, Suite 400
La Jolla, CA 92037

Dear Dr. Truong:

Please refer to your New Drug Application (NDA) dated December 30, 2016, received December 30, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 30, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 30, 2017. In addition, the planned date for our internal mid-cycle review meeting is April 4, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

If your 505(b)(2) application relies on FDA’s finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the “paragraph IV acknowledgment letter” described in 21 CFR 314.52(b) and the “postmark” is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark

on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issue and have the following labeling comment:

1. A horizontal line must separate the Table of Contents from the Full Prescribing Information.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 10, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Sarah Seung, Regulatory Project Manager, at (240) 402-3879 or sarah.seung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
02/24/2017

Seung, Sarah

From: Seung, Sarah
Sent: Thursday, February 16, 2017 1:32 PM
To: 'david.truong@tevapharm.com'
Subject: Information Request: NDA 209885 Deutetrabenazine

Hi David,

This is in reference to your NDA 209885 for deutetrabenazine for the treatment of tardive dyskinesia. The review team has the following Information Request:

For Population PK and Exposure-Response Reports (Report CP-16-07 and Report CP-16-11) please submit the datasets, model codes and output files in specific formats listed below:

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariate model, final model and validation model. These files should be submitted as ASCII files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Please submit the response officially to the NDA by **COB Thursday, February 23, 2017** and notify me with an email when you submit the response.

Regards,

*Sarah Seung, Pharm.D.
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171
Silver Spring, MD 20993
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov*



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/s/

SARAH H Seung
02/16/2017

MEMORANDUM OF TELECONFERENCE

TELECONFERENCE DATE: February 13, 2017
TIME: 9:30am-10:00am
APPLICATION: NDA 209885
DRUG NAME: Austedo (deutetrabenazine)
APPLICANT NAME: Teva Branded Pharmaceutical Products R&D, Inc.
TYPE OF MEETING: Teleconference

MEETING CHAIR: Sarah Seung, PharmD
MEETING RECORDER: Sarah Seung, PharmD

FDA ATTENDEES:

Douglas Warfield, PhD	Associate Director of Biomedical Informatics, Division of Psychiatry Products (DPP)
Anandraj Mattai, MD	Clinical Reviewer, DPP
Sarah Seung, PharmD	Regulatory Project Manager, DPP

EXTERNAL CONSTITUENT ATTENDEES:

Dennis Ahern	Senior Director, Global Regulatory Affairs
Matthew Davis, PhD	Director, Biostatistics
Christine Schulteis	Senior Director, Global Regulatory Affairs
David Stamler	Vice President, Clinical Development
David Truong	Senior Manager, Global Regulatory Affairs

BACKGROUND:

On February 9, 2017, the Division sent the following information request (IR) to the Applicant via email:

Your ISE and ISS analysis data subject listings (ADSL) for NDA 209885 contain duplicated unique subject identifiers (USUBJID) which do not conform to the CDISC ADaM standard. This is problematic and prevents review of the integrated summary of efficacy and safety of your application. The datasets provided conform to the FDA's Study Data Technical Conformance Guidance (pg.10); however, where the subject participated in more than one study, the results for each study must be represented in additional variables within the same USUBJID row of data, so duplicates of the USUBJID are not created. Please correct using the CDISC ADaM standardized variables (TR[xx], TRT[xx], etc.) and resubmit ISS/ISE for NDA209885. Please also submit the programs used for ISS/ISE for NDA209885.

On February 10, 2017, the Applicant requested a teleconference to discuss the information request. The Applicant provided the following explanation and proposal for revising the ISS/ISE via email:

The analysis data model version 2.1 states in the introduction/purpose section that “The design of analysis datasets is generally driven by the scientific and medical objectives of the clinical trial” and focuses the implementation of ADaM on the individual trial level. The issue of ADaM application to integrated analyses is not specifically covered in the model or implementation guide, and the CDISC specific rules for this are currently ambiguous. In addition, the “CDER Common Data Standards Issues Document” provides guidance on integrated analyses for the DM SDTM domain (which is analogous in SDTM to ADSL) stating “Integrated summaries may contain more than one record per unique subject in the case that an individual subject was enrolled in more than one study”.

In addition, a draft guidance has been released by CDISC outlining ADaM data structures for integration. Please see attached. Section 2.3 in the draft guidance states “In some cases, it may be helpful to maintain more than one record for that subject <who participated in more than one trial> in the integrated ADSL in order to preserve traceability back to the original source data or to facilitate various analyses or pooling schemes”. In addition, Section 4.2, in the description of the ADSL domain, states “The largest difference in the integrated ADSL datasets compared to the study-level ADSL dataset is that there can be multiple records per subject when any subject participates in more than one study that is used for analyses. For example, if a subject participates in a double-blind study followed by an extension study, there can be three records in the integrated ADSL: one for the double-blind study, one for the extension study and one for the subject’s entire experience”. In addition in the same paragraph they state “When the extension data is analyzed separately for some subjects (e.g. only extension data is included in an analysis for subjects who took placebo in the core study), multiple records in ADSL are required”. The resulting dataset structure in section 4.1 states “one record per subject, per study/studies, per analysis category”. As we are analyzing the double-blind studies separately than the extension, these examples provided in the guidance directly apply to our submission.

It is important to note that in the integrated analyses we analyze subjects in two separate treatment columns in many areas. For the integrated summary of safety, patients who received placebo in the double-blind study are summarized both in the placebo treatment arm (using the data captured during the double-blind phase), and also in the SD-809 Titration arm (using their first 15 weeks of treatment from the open-label period). In addition, the SD-809 titration analysis in the integrated summary of efficacy combines the titrated data from SD-809 treated patients in SD-809-C-18 with the first 15 weeks of treatment from study SD-809-C-20 for patients originally receiving placebo in the double blind phase. The construction of the datasets with two records per subject in ADSL for subjects who were enrolled both into a double-blind study and the open-label study facilitates the analysis of the integrated data in this regard.

In this case, we followed the same line of logic to include one record in ADSL per patient per study they were enrolled in, and therefore the combination of STUDYID and USUBJID in ADSL in the integrated summaries of safety and efficacy can be used to merge with the appropriate records in the BDS domains for results that came from the double blind studies (SD-809-C-18 or SD-809-C-23) or the long-term safety study (SD-809-C-20). The define.XML and study data reviewers guides for the integrated datasets describe the details of combining the ADSL and BDS results. Teva has used this strategy of integrated ADaM datasets in previous NDA submissions that were accepted by FDA without issue.

Based on this additional explanation of the ADaM datasets and description of how to identify STUDYID and USUBJID records in ADSL, Teva proposes to revise the ADSL datasets in the ISS and ISE submissions to include the additional required variables in the draft integrated ADaM guidance, which includes the following variables: STUDIES, ANALCAT, UADSLFL, NUMSTUDY. Teva will submit the SAS programs for ISS and ISE ADaM datasets as requested.

Would this proposal be acceptable to address the review team's request?

MEETING OBJECTIVES:

The object of the teleconference was to provide comments to the Applicant regarding their explanation and proposal.

DISCUSSION POINTS:

The Division conveyed the following comments to the Applicant:

1. The CDER Common Data Standards Issues Document referenced is obsolete and was superseded by the FDA's Study Data Technical Conformance Guidance (first published January 2014) and referenced in the Division's information request email.
2. The FDA Study Data Standards Resources For Industry includes the Data Standards Catalog. The FDA does not support "draft" versions of any CDISC standards.
3. The Applicant should not expect the Agency's prior acceptance of a previously submitted and reviewed application's study data (for a different NDA) using similar methodologies/standardization, etc., given that it does not have any bearing on the acceptance of this current application; especially when clear discrepancies are present.

DECISIONS (AGREEMENTS) REACHED:

The Division informed the Applicant that their proposed changes are acceptable.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

There were no unresolved issues or issues requiring further discussion.

ACTION ITEMS:

The Applicant will submit the requested information as requested in the Agency's February 9, 2017 information request by February, 17, 2017.

ATTACHMENTS/HANDOUTS:

There were no attachments or handouts.

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/s/

SARAH H Seung
02/15/2017

Seung, Sarah

From: Seung, Sarah
Sent: Thursday, February 09, 2017 2:37 PM
To: 'david.truong@tevapharm.com'
Subject: Information Request: NDA 209885

Importance: High

Hi David,

This communication is in reference to your NDA 209885 for deutetrabenazine for the treatment of tardive dyskinesia.

We have the following information request:

Your ISE and ISS analysis data subject listings (ADSL) for NDA209885 contain duplicated unique subject identifiers (USUBJID); which does not conform to the CDISC ADaM standard. This is problematic and prevents review of the integrated summary of efficacy and safety of your application. The datasets provided conform to the FDA's Study Data Technical Conformance Guidance (pg.10); however, where the subject participated in more than one study, the results for each study must be represented in additional variables within the same USUBJID row of data, so duplicates of the USUBJID are not created. Please correct using the CDISC ADaM standardized variables (TR[xx], TRT[xx], etc.) and resubmit ISS/ISE for NDA209885. Please also submit the programs used for ISS/ISE for NDA209885.

Please note that this is a potential filing issue. Submit the response officially to the NDA by **COB Friday, February 17, 2017**. Please email me when you submit the response so I can alert the review team right away.

Regards,
Sarah

*Sarah Seung, Pharm.D.
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Psychiatry Products
Office of New Drugs
Food and Drug Administration
10903 New Hampshire Ave
Bldg 22, Room 4171
Silver Spring, MD 20993
Phone: 240.402.3879
Email: sarah.seung@fda.hhs.gov*



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/s/

SARAH H Seung
02/09/2017



NDA 209885

NDA ACKNOWLEDGMENT

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs
3333 North Torrey Pines Court, Suite 400
La Jolla, CA 92037

Dear Dr. Truong:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg

Date of Application: December 30, 2016

Date of Receipt: December 30, 2016

Our Reference Number: NDA 209885

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 28, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact me at (240) 402-3879 or sarah.seung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sarah Seung, PharmD
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SARAH H Seung
01/19/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120631

MEETING MINUTES

Teva Pharmaceuticals, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Regulatory Affairs
3333 North Torrey Pines Court
La Jolla, CA 92037

Dear Dr. Truong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SD-809 (deutetrabenazine).

We also refer to the meeting between representatives of your firm and the FDA on November 3, 2016. The purpose of the meeting was to discuss the proposed deutetrabenazine NDA content.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Martin Yoon, Regulatory Project Manager at (240) 402-3911 or martin.yoon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, November 3, 2016 from 11:00 AM – 12:00 PM (EST)
Meeting Location: White Oak Building 22, Room 1415

Application Number: IND 120631
Product Name: SD-809 (deutetrabenazine)
Indication: Tardive Dyskinesia
Sponsor/Applicant Name: Teva Pharmaceuticals, Inc.

Meeting Chair: Mitchell Mathis, MD
Meeting Recorder: Martin Yoon

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Jasmine Gatti, MD	Clinical Team Leader, DPP
Bernard Fischer, MD	Clinical Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, DPP
Peiling Yang, PhD	Biometrics Team Leader
Jinglin Zhong, PhD	Biometrics Reviewer
Paul David, RPh	Chief Project Management Staff, DPP
Martin Yoon, PharmD	Regulatory Project Manager, DPP
Sarah Seung, PharmD	Regulatory Project Manager, DPP

SPONSOR ATTENDEES

Dennis Ahern, MS	Senior Director, Global Regulatory Affairs
Leonard Alansky, RPh	Global Regulatory CMC
Margaret Bradbury, PhD	Senior Director, Research and Development
David Chapman, PhD	Senior Director, Project Champion
Donna Cox, PhD	Director, Clinical Pharmacology
Matthew Davis, PhD	Associate Director, Biostatistics
Jouko Isojarvi, MD, PhD	Senior Director, Clinical Development
Jim Kerr	Senior Director, CMC, Discovery & Product Development

(b) (4)

David Stamler, MD
David Truong, PharmD, MS

Vice President, Clinical Development
Senior Manager, Global Regulatory Affairs

1.0 BACKGROUND

Deutetrabenazine (SD-809) is a deuterium-substituted form of tetrabenazine under development by Teva Pharmaceuticals for chorea associated with Huntington's disease (NDA 208082), tics associated with Tourette's syndrome (IND 127692), and tardive dyskinesia (IND 120631). The Division of Neurology Products issued a Complete Response to NDA 208082 on May 27, 2016, based on the need to further characterize metabolites M1 and M4. IND 127692 was placed on clinical hold based on insufficient clinical and nonclinical data on all human metabolites and the appropriateness of the rat for the juvenile toxicity study. The tardive dyskinesia (TD) program was granted Breakthrough Therapy Designation November 3, 2015, based on improvement from baseline to Week 12 in TD symptoms as assessed by the Abnormal Involuntary Movement Scale (AIMS). The Sponsor expects to submit an NDA for tardive dyskinesia prior to the end of 2016.

Tetrabenazine is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor approved by FDA in 2008 as Xenazine (Valeant Pharmaceuticals) for treatment of chorea associated with Huntington's disease. It is also approved in Canada for tardive dyskinesia and Tourette's syndrome. Tetrabenazine has multiple metabolites including the active metabolites α -dihydro-tetrabenazine (HTBZ) and β -HTBZ. These active metabolites are rapidly metabolized via CYP2D6; therefore, tetrabenazine is taken three times per day. High initial C_{max} coupled with rapid metabolism leads to sizable variability in blood levels and, Teva believes, poor tolerability. Additionally, CYP2D6 polymorphisms can have large impacts on α - and β -HTBZ plasma concentrations.

The Sponsor believes that substitution of deuterium for hydrogen in the tetrabenazine methoxy groups leads to slower α - and β -HTBZ metabolism without affecting metabolism of the parent compound or impact to VMAT2 binding. Deutetrabenazine yields increased exposure to the active metabolites with a lower C_{max} compared to an equivalent dose of tetrabenazine. This allows for twice-per-day dosing, lower doses, and, the Sponsor asserts, improved tolerability.

A total of 178 subjects have been exposed to deutetrabenazine in Phase 1 studies. Phase 2 and 3 studies are detailed in Table 1. below.

Table 1. Deutetrabenazine Phase 2 and 3 studies.

Study	Exposed to SD-809	Description	Status
Huntington's Disease			
SD-809-C-15	127	RCT Placebo & Tetrabenazine	Completed
SD-809-C-16	82 (Rollover) ^a 37 (Switch)	Open-Label Long-Term Safety	Ongoing
Tourette's Syndrome			
SD-809-C-17	23	Pilot Study	Completed

Tardive Dyskinesia			
SD-809-C-18	58	RCT (12 weeks)	Completed (Analysis Ongoing)
SD-809-C-23	221	RCT (12 weeks)	Ongoing
SD-809-C-20	308 ^b	Open-Label (108 weeks) Long-Term Safety	Ongoing

^aPrevious exposure in SD-809-C-15.

^bPrevious exposure in 207 of these individuals from studies SD-809-C-18 and C-23.

The objectives of this meeting are:

1. To reach agreement on the filing plan for the proposed NDA.
2. To reach agreement that the results from the two completed Phase 3 randomized, placebo-controlled safety and efficacy studies and the safety database for the SD-809 TD development program are sufficient to support review of the planned TD NDA.
3. To reach agreement that the clinical pharmacology program submitted in NDA 208082 is sufficient to support review of the planned TD NDA.
4. To reach agreement that the nonclinical program submitted in NDA 208082 is sufficient to support review of the planned TD NDA.
5. To reach agreement that the quality information submitted in NDA 208082 is sufficient to support review of the planned TD NDA.
6. To reach agreement on the placement of written portions of the integrated summaries of efficacy and safety in the NDA.

2. DISCUSSION

2.1. REGULATORY – NDA FILING PLAN

Question 1: Teva proposes the following content for the TD NDA:

- Module 1- This module will contain those elements required under 21CFR §314 and presented in Electronic Common Technical Document (eCTD) format. In addition, Teva will include a reviewer's guide that will provide additional context and a point of orientation for each of the modules of the NDA.
- Module 2- TD NDA:
 - Module 2.2 (CTD Introduction); TD specific document
 - Module 2.3 (Quality Overall Summary); The current CMC information for SD-809 is under review by DNP (NDA 208082) and no new information has been developed for the TD NDA. Therefore, a copy of 2.3 from NDA 208082 will be included for reference.
 - Module 2.4 (Nonclinical Overview); The current nonclinical information for SD-809 is under review by DNP (NDA 208082) and no new information has been developed for the TD NDA. Therefore, a copy of 2.4 from NDA 208082 will be included for reference.
 - Module 2.6 (Nonclinical Written and Tabulated Summaries); The current nonclinical information for SD-809 is under review by DNP (NDA 208082) and no new information has been developed for the TD NDA. Therefore, a copy of 2.6 from NDA 208082 will be included for reference.

- Module 2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods); The current information for SD-809 is under review by DNP (NDA 208082) and no new information has been developed for the TD NDA. Therefore, a copy of 2.7.1 from NDA 208082 will be included for reference.
- Module 2.7.2 (Summary of Clinical Pharmacology Studies); The current information for SD-809 is under review by DNP (NDA 208082); a copy will be included for reference. In addition, a Population PK Model specifically for TD will be included for review in this NDA.
- Module 2.7.3 (Summary of Clinical Efficacy); This module will be TD specific and will be included for review in this NDA.
- Module 2.7.4 (Summary of Clinical Safety); This module will include integrated TD and HD patient data and will be included for review in this NDA.
- Module 2.7.5 (References); This module will be specific for the TD NDA.
- Module 2.7.6 (Synopsis of Individual Studies); This module will include all clinical studies.
- Module 3- This module is currently being reviewed by DNP under NDA 208082 and provided in the proposed NDA for TD as reference.
- Module 4- This module is currently being reviewed by DNP under NDA 208082 and provided in the proposed NDA for TD as reference.
- Module 5- This module will be classified into 3 categories:
 - TD specific Module 5 sections are: 5.3 (Clinical Study Reports and Related Information) and 5.4 (Literature References) and includes:
 - Study reports and related information for studies SD-809-C-18, SD-809-C-20, SD-809-C-23 (case report forms for patients that died, experienced a serious adverse event, or discontinued prematurely due to an adverse event), analysis datasets (ADaM), and tabulations (SDTM).
 - 5.3.3.5 (Population PK Study Reports and Related Information) – Study Report CP-16-07
 - 5.3.5.3 (Integrated Summary of Efficacy) – Including related datasets
 - Sections currently being reviewed by DNP under NDA 208082 and provided in the proposed NDA for TD as reference are: 5.3.1.1 (Bioavailability Study Reports and Related Information), 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies), 5.3.2.2 (Reports of Hepatic Metabolism and Drug Interaction Studies), 5.3.3.1 (Healthy Subject PK and Initial Tolerability Study Reports and Related Information), 5.3.3.2 (Patient PK and Initial Tolerability Study Reports and Related Information), 5.3.3.3 (Intrinsic Factor PK Study Reports and Related Information), 5.3.4.1 (Healthy Subject PD and PK/PD Study Reports and Related Information).
 - Sections that will contain information germane to both the TD and HD programs:
 - 5.2 (Tabular listing of all clinical studies), 5.3.5.3 (Integrated Summary of Safety, including related datasets)

Appreciating that the ultimate decision regarding review procedures is FDA's responsibility, is the FDA willing to grant Teva's request for the cross-referencing proposed above?

FDA Response to Question 1: *The plan to cross-reference appears reasonable. However, the adequacy of the information contained in the cross-referenced sections will be a matter of review.*

Teva Response to Comment 1: Teva appreciates the comments from the FDA regarding cross-referencing as it acknowledges the significant overlap in supporting data for the HD NDA (NDA 208082) and TD NDA (NDA 209885) that is independent of indication. Teva would like to discuss the review process of the TD NDA as it relates to the agreement to cross-reference the ongoing review of HD NDA. As a function of the statute, TD NDA will technically be submitted as a New Molecular Entity (NME) NDA due to the ongoing review of the HD NDA. Upon the approval of HD NDA (Class 2 resubmission with a PDUFA goal date of 03 April 2017), the TD NDA will no longer be classified as NME (i.e., 4 months after the targeted December 2016 submission). Given that the TD NDA will technically be an 'NME' NDA for a short period of time, and that the unique areas for review of the TD NDA are restricted to clinical efficacy and safety data, Teva would like to discuss opportunities to simplify FDA's review of the TD NDA:

- Relative timelines regarding action dates and labeling discussion for the HD and TD NDAs: Teva will present our understanding of timelines regarding action dates and labeling discussion.
- Labeling review for both the HD and TD NDAs: We plan to have a single package insert for both indications (b) (4)
[REDACTED] TD specific language will be inserted and highlighted for the reviewers' convenience. If labeling discussion for the HD NDA begins before filing of the TD NDA in December 2016, we plan to re-submit the package insert to reflect the changes and agreements already made for the HD NDA to help the TD NDA reviewers to focus only on the TD sections of the label.

(b) (4)

2.2. CLINICAL PHARMACOLOGY

Question 2: Does FDA agree that the completed clinical pharmacology program for SD-809 being reviewed by DNP under NDA208082 can be cross-referenced to support review of the TD NDA?

FDA Response to Question 2: *See our response to Question 1.*

Discussion: *No further discussion.*

2.3. NONCLINICAL

Question 3: Does FDA agree that the completed nonclinical program for SD-809 being reviewed by DNP under NDA208082 can be cross-referenced to support review of the TD NDA?

FDA Response to Question 3: *See our response to Question 1.*

Discussion: *No further discussion.*

2.4. CMC

Question 4: Does FDA agree that the completed quality information for SD-809 being reviewed by DNP under NDA208082 can be cross-referenced to support review of the TD NDA?

FDA Response to Question 4: *See our response to Question 1.*

Discussion: *No further discussion.*

2.5. CLINICAL

Question 5: Does FDA agree that the efficacy results from the 2 pivotal studies are sufficient to support review of the TD NDA?

FDA Response to Question 5: *On face, the results as described appear to be sufficient to support an NDA submission for the tardive dyskinesia indication.*

Discussion: *No further discussion.*

Question 6: In addition to the exposure to SD-809 in TD patients, the TD NDA will also reference the safety database for SD-809 in patients with Huntington's disease from NDA 208082. Does FDA agree that these combined data provide sufficient safety information for review of the TD NDA?

FDA Response to Question 6: *In principle, we have no objection to referencing safety data from the Huntington's disease program in the tardive dyskinesia NDA as long as the data are presented separately. Based on the details provided, you estimate total combined HD and TD exposures of approximately 680 with over 300 exposures of 6 months and over 200 exposures of 12 months. These numbers appear acceptable to the Division, but the adequacy of submitted safety information is ultimately a matter of review.*

Teva Response to Comment 6: In the Summary of Clinical Safety, Teva plans to present detailed safety information for the TD population and a summary of safety data from the HD population. Details on the HD safety data will be provided by submitting the narrative portion of the Complete Response Safety Update (submitted to the HD NDA on 03 Oct 2016), but not the corresponding tables, figures, listings, and datasets, in Module 5 of the TD NDA. Does the FDA agree with the proposed plan?

(b) (4)

2.6. REGULATORY

Question 7: Teva proposes that Sections 2.7.3, Summary of Clinical Efficacy, and Section 2.7.4, Summary of Clinical Safety, will be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively, while still concise enough to conform to the page limitations of Section 2.7. In accordance with FDA guidance regarding the location of the ISS and ISE within an NDA, Section 5.3.5.3 would include only the tables, figures, and listings supporting the integrated summaries of efficacy and safety.

Does FDA agree that this approach is acceptable?

FDA Response to Question 7: Yes, this appears acceptable.

Discussion: No further discussion.

Question 8: Based on the planned NDA submission date of December 2016, Teva plans to provide a 120-day safety update in April 2017. The update will include updated, cumulative safety and exposure data from the ongoing open-label studies: SD-809-C-16 (HD) study (cutoff date of 30 September 2016) and SD-809-C-20 (TD) study (cutoff of 30 December 2016). Teva proposes to (b) (4) serious adverse events, and discontinuations due to adverse events.

Can the FDA confirm the adequacy of the updated safety information?

FDA Response to Question 8: No, (b) (4) However, summaries of other serious adverse events and discontinuations due to adverse events are acceptable.

Teva Response to Comment 8: Teva will provide case report forms for all subject deaths.

Discussion: No further discussion.

Question 9: While Teva understands referral of a drug to an FDA Advisory Committee is required for NCEs, for planning purposes, does FDA believe that there would be a reason (e.g., novel indication) to present SD-809 at an advisory committee meeting?

FDA Response to Question 9: *At this time, we believe an Advisory Committee is likely.*

Teva Response to Comment 9: In the context of our discussion of review timelines in Comment 1, we would like to discuss the timing of the Advisory Committee.

(b) (4)

Question 10: Since Teva plans to submit the TD NDA (end of December 2016) while the HD NDA (208082) is under final review (estimated PDUFA April 2017), Teva proposes we conduct an Applicant Orientation meeting with the review team assigned to the NDA. The value of the meeting will be to acclimate the Agency to the content, format, and any nuance inherent in the TD NDA relative to NDA 208082. Would the Agency be open to holding this meeting?

FDA Response to Question 10: *The Division appreciates the offer of an orientation meeting. We will contact you if we believe such a meeting is needed. You may also consider including a reviewer guide in the NDA submission.*

Teva Comment to Comment 10: Teva will provide a reviewer's guide in the TD NDA submission.

Discussion: *No further discussion.*

Additional Comments: For each trial used to support an efficacy claim, please include the following items in your NDA submission:

- (a) all raw as well as derived variables in .xpt format,
- (b) the executable SAS programs for primary and sensitivity analyses of endpoints intended to be described in the labeling,
- (c) the executable SAS programs by means of which the derived variables were produced from the raw variables,
- (d) all the meeting minutes of Independent Data Monitoring Committee (IDMC) and letters sent from IDMC to the sponsor, and
- (e) a list of serial numbers and submission dates for all protocols, all protocol amendments, and any statistical amendments (including Statistical Analysis Plans) submitted to all relevant INDs.

Teva Response to Additional Comments:

Referencing additional comment (b), Teva plans to provide the executable SAS programs for the AIMS primary endpoint, CGIC secondary endpoint and the corresponding sensitivity analyses for studies SD-809-C-18 and SD-809-C-23. Does the FDA agree?

Referencing additional comment (c), Teva would like to confirm if FDA is requesting executable SAS programs for ADaM datasets for studies SD-809-C-18 and SD-809-C-23.

Are there specific dataset programs that the FDA would like Teva to provide?

For the executable SAS programs, it will be helpful to know the version of SAS and the Operating System that SAS is running on at FDA in order to ensure compatibility.

Referencing additional comment (e), regarding our SD-809-C-20 protocol and Statistical Analysis Plan (SAP) submissions. Please see the Table below. Does FDA have any comments regarding these submissions?

Submission Document	Date	Sequence Number
ISS SAP	26 August 2016	IND 120631, SN 0034
ISE SAP	26 August 2016	IND 120631, SN 0034
SD-809-C-20 SAP	26 August 2016	IND 120631, SN 0034
SD-809-C-20 Protocol amendment	30 September 2016	IND 120631, SN 0038

Discussion: *A few clarifications were made. We reminded the Sponsor to also include the required macros or data sets that would be needed in a different SAS program, and encouraged the Sponsor to provide more detailed SAS code (e.g., derivation of the region variable, modal/mean dose). We may ask for more information during the future NDA review.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and Teva does not believe a REMS is necessary.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

Other Points of Discussion with the Sponsor:

The Sponsor wished to clarify a review timeline in the event that their drug was approved for HD after submission of the NDA for TD. If it were approved for HD, the drug would no longer be an

NME. We clarified that if the NDA for HD were approved within the first 60 days after submission of the NDA for TD, it may be possible to convert the submission from an NDA to a supplement. However, this was extremely unlikely given the PDUFA date for the HD indication is April 3, 2017 and the Sponsor plans to submit the TD NDA in late December. Review timelines are fixed at submission and it would be unlikely the TD review timeline could be altered even if the HD indication were approved.

The Division acknowledged receipt of the Sponsor's iPSP. However, it was submitted in an incorrect format and so formal feedback to the Sponsor has been delayed. The Division will recognize the original submission date and endeavor to reach an agreed iPSP with the Sponsor prior to their filing of the TD NDA.

The Division clarified that labeling changes in response to the HD NDA review would not be considered a 'late submission' when submitted to the TD NDA.

(b) (4)

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U>

[CM360507.pdf](#). In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission

[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

7.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In

your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

8.0 Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials

used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

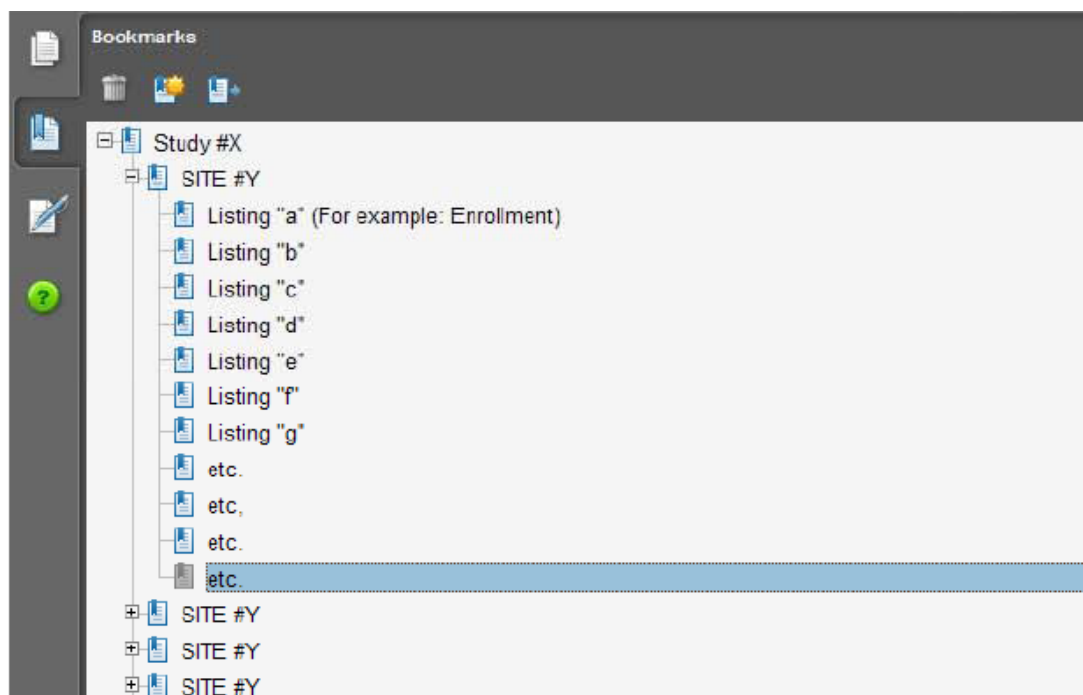
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format

- previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

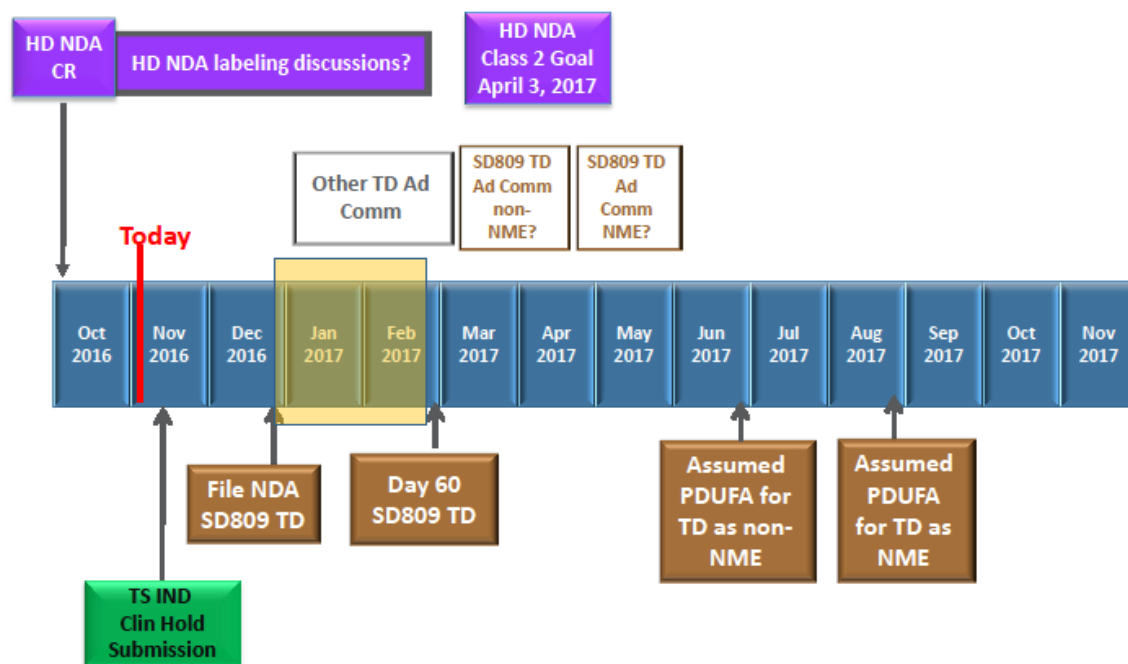
FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

9.0 ATTACHMENTS AND HANDOUTS

The following timeline was provided by the sponsor and discussed at the meeting.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
12/03/2016

CDER Medical Policy Council
Decisions/Action Items – Breakthrough Therapy Designation Requests
November 2, 2015

Council Members:

John Jenkins, OND
Richard Moscicki, CDER
Robert Temple, CDER
Sandra Benton, Executive Secretary

Attendees:

Tiffany Farchione, OND/ODEI/DPP	Miranda Raggio, OND
Zahra Hanaizi, EMA Fellow	Leonard Sacks, OMP
Sabine Haubenreisser, EMA Liaison to FDA	Sharonjit Sagoo, OND/ODEI/DPP
Sandra Kweder, OND	Ellis Unger, OND/ODEI
Mitchell Mathis, OND/ODEI/DPP	Jing Zhang, OND/ODEI/DPP

Topic: To discuss the breakthrough therapy (BT) designation request for Teva's IND 120,631, SD-809 (Deutetrabenazine) for the treatment of (b) (4) tardive dyskinesia (TD).
Background is attached.

Discussion: DPP requested that this BT request be reviewed by the Council via email; DPP recommended granting the request. A Council member asked for the meeting.

The Council questioned the magnitude of the effect seen in the current BT request for IND 120,631 compared to a previous request granted BT.¹ Both sponsors used the Abnormal Involuntary Movement Scale (AIMS) as the endpoint for the studies to support BT. However, DPP noted that the BT request granted previously had modified scoring instructions. It is unclear whether that may have inflated the effect. Both of these products are in development and there is no approved therapy to treat TD.

The Council does not believe that a drug that shows any effect, no matter how small, in a serious and life threatening disease with no approved therapy is an automatic pass to granting the BT request. The Council asked DPP whether this one meets "the bar" for granting BT? The Council noted table 2 on page 11 of the sponsor submission, showing a $\geq 10\%$ improvement from baseline to week 12 with SD-809 over placebo.

DPP noted that this is only preliminary data. TD is a serious, often disabling hyperkinetic movement disorder caused by medications that block dopamine receptors (e.g., antipsychotics, antiemetics). Patients can develop serious forms of the disease where they have troubling eating and functioning. In this disease, patients may not show "very much improved" or "much improved." A high bar is unrealistic. A 10, 20, or 30% improvement over placebo can be seen as a breakthrough for this disease. Any improvement can be beneficial.

¹ Under IND 111591, NBI-98854 (Neurocrine Biosciences), another vesicular monoamine transporter 2 (VMAT2) inhibitor, is being developed for the treatment of neuroleptic-induced tardive dyskinesia. Breakthrough therapy designation was granted on 10/28/14.

The Council noted that there is an approved version of this product that health care practitioners can prescribe off-label. The question arose as to whether this molecule is very different from tetrabenazine, an approved drug that has been used off-label to treat this condition. The Division noted that the addition of deuterium may not importantly affect its biological mode of action, although it could alter the pharmacokinetics of the drug. DPP noted that this may mean that less drug can be given to patients with the possibility of reducing serious adverse events.

(b) (4)

The Council agreed with DPP's recommendation to grant BT for this request. The Council asked if the development program would be modified. DPP noted that both BT requests for TD have traditional phase 3 trials ongoing. The council reminded DPP to monitor the programs in case the programs either need to be revised if indeed a BT drug or to rescind the BT if the promise is not shown.

Recommendation: The Council recommended granting the breakthrough therapy designation request from Teva for its IND 120,631, SD-809 (Deutetrabenazine) for the treatment of (b) (4) tardive dyskinesia (TD).

Attachment: Background Document

Draft: S Benton 11/2/2015
R/D: E Unger 11/3/2015
Final: S Benton 11/18/2015

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	120, 631 (Seq 12)
Request Receipt Date	September 04, 2015
Product	SD-809 (Deutetrabenazine)
Indication	Treatment of (b) (4) Tardive Dyskinesia (TD).
Drug Class/Mechanism of Action	Vesicular Monoamine Transporter 2 (VMAT2) Inhibitor
Sponsor	Teva
ODE/Division	OND-I/Division of Psychiatric Products (DPP)
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	October 30, 2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

(b) (4) tardive dyskinesia (TD)

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? ☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

- Consideration of Breakthrough Therapy Criteria:**

- Is the condition serious/life-threatening¹? ☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics"
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
- Only animal/nonclinical data submitted as evidence ☐
 - Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

- Provide below a brief description of the deficiencies for each box checked above in Section 3b:

Not applicable

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

- Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics”
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

- **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

SD-809 (deutetrabenazine) is a selective deuterium substituted, stable, non-radioactive, isotopic form of tetrabenazine which has previously been approved for the treatment of chorea associated with Huntington's disease (NDA 021, 894; Valeant Pharmaceuticals; 08-15-2008). It is a vesicular monoamine transporter 2 (VMAT2) inhibitor structurally related to tetrabenazine, with two trideuteromethoxy groups (-OCD₃) installed at the 9- and 10-positions of the molecule. VMAT2 is a membrane protein which transports neurotransmitters (e.g. dopamine, norepinephrine, serotonin, and histamine) from cellular cytosol into synaptic vesicles. The circulating active metabolites of tetrabenazine, α -HTBZ and β -HTBZ, are principally metabolized by CYP2D6. Tetrabenazine also carries a Warning/Precaution for QT prolongation and the safety profile of tetrabenazine includes risks of depression, suicidality, akathisia, Parkinsonism, and dysphagia (Xenazine Prescribing Information, 2015). As a consequence of deuterium placement in SD-809, the rate at which CYP2D6 breaks down the α -HTBZ and β -HTBZ metabolites is attenuated relative to that of Tetrabenazine resulting in longer half-lives of circulating active metabolites (total [α + β]-HTBZ) and reduced metabolic variability and provides the basis for the SD-809 development strategy: to achieve comparable systemic exposure (area under the concentration-time curve [AUC]) with lower doses and lower peak concentrations (C_{max}) compared with tetrabenazine and to reduce the impact of CYP2D6 impairment, whether from concomitant medication use or genetics.

Information regarding the disease and intended population for the proposed indication.

Tardive dyskinesia (TD) is a serious, often disabling hyperkinetic movement disorder caused by medications that block dopamine receptors (e.g., antipsychotics, anti-emetics). TD is strongly associated with use of typical or atypical antipsychotic medications and occurs usually after prolonged exposure; however, it may also occur with short-term exposure. Antipsychotics are used for treating serious psychiatric conditions, such as schizophrenia, and there are usually no alternatives to treatment with this pharmacologic class. The clinical manifestations of TD include chorea, athetosis, dystonia, akathisia, stereotyped behaviors, and occasionally, tremors. Symptoms most commonly consist of oral-buccal-lingual masticatory movements characterized by repetitive jaw, face, and lingual movements and may involve puffing of the cheeks, lip-smacking, puckering, and pursing. Other body regions including the trunk and upper and lower extremities can also be affected. Severe cases can be associated with difficulty speaking, chewing, and swallowing, and with tongue mutilation.

TD can be differentiated from acute movement disorders that may occur within the same patient groups, e.g. akathisia, acute dystonia, parkinsonism. Acute movement disorders resulting from exposure to dopamine antagonists are commonly called extrapyramidal syndromes (EPS).

Withdrawal dyskinesias may also occur when treatment with dopamine antagonists is decreased or withdrawn. They are often refractory to all therapeutic modalities. In addition to the prototypic orofacial dyskinesia, tardive syndromes also include a spectrum of hyperkinesia occurring during or after prolonged treatment with dopamine antagonists.

Study Population

The study population in the two, randomized double blind trials [the completed study, Study SD-809-C-18 (flexible dose, 6-24 mg bid; 117 subjects: 58 SD 809, 59 Placebo); and, the on-going study, SD-809-C-23 (fixed dose, 12 mg, 24 mg, 36 mg bid or placebo; 92/200, 69 SD-809)] and the long-term, open label trial, SD-809-C-20, (6-24 mg bid; 126 with 115 on-going) are patients 18-75 years of age. These patients have moderate to severe drug-induced TD, as defined by having symptoms that are bothersome or cause functional impairment of ≥ 3 months duration and have used a dopamine receptor antagonist for at least 3 months (or 1 month in subjects ≥ 60 years of age). Investigator- determined moderate-severe abnormal movements [Abnormal Involuntary Movement Scale: AIMS, Item 8 and total motor AIMS score ≥ 6 (based on Items 1-7)] must be present at Screening and Baseline. These patients are psychiatrically stable and meet various other Inclusion and none of the Exclusion Criteria identified in the protocols. [Copies of these scales are included the Appendix of this Review Template.]

Disease mechanism (if known) and natural history (if the disease is uncommon)

TD is associated with the use of antipsychotics (e.g. for treating schizophrenia, schizoaffective disorder or bipolar disorder) for extended periods. TD may also occur in vulnerable individuals (e.g. fetal alcohol syndrome, developmental disorders, other brain disorders) after receiving only 1 dose. Development of TD has been associated with polymorphisms of the dopamine receptor D2 (DRD2) gene, TaqI A and TaqI B and associated haplotypes, the dopamine receptor D3 (DRD3) gene, the dopamine transporter (DAT) gene, and the manganese superoxide dismutase (MnSOD) gene. Dopamine transporter dysfunction has been hypothesized to play a role, but has not been confirmed.

- **Information related to endpoints used in the available clinical data:**

- a. **Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.**

Primary endpoint for Study SD-809-C-18 and Study SD-809-C-23: The change in AIMS scores (Items 1 through 7) from Baseline to Week 12, as assessed by blinded central video rating.

Key Secondary Endpoints for Study SD-809-C-18: 1) the proportion of subjects who are a treatment success at Week 12, based on the Clinical Global Impression of Change (CGIC). A treatment success is defined as Much Improved or Very Much Improved on the CGIC at the Week 12 visit. The CGIC is a 7- point Likert Scale, ranging from very much worse to very much improved. 2) Change in the modified Craniocervical Dystonia Questionnaire (CDQ-24) from Baseline to Week 12.

Key Secondary Endpoints for Study SD-809-C-23: same as in Study SD-809-C-18, except that the CDQ-24 is not identified as a key secondary endpoint.

In the completed flexible dose study, SD-809-C-18, Teva reports that treatment with SD-809 resulted in a statistically significant reduction in the AIMS score. Subjects receiving SD-809 achieved a least squares (LS) mean 3.0-unit reduction in AIMS score, compared with a 1.6-unit reduction in subjects receiving placebo, for a treatment effect of 1.4 units ($p=0.0188$). Analysis of AIMS responders by percent improvement from Baseline to endpoint showed that the treatment effect favored SD-809 versus placebo and these effects were statistically significant for each category of response

up to $\geq 30\%$ improvement from Baseline. Sponsors Table 1 and 2 are copied into the Appendix of this Template. For the key secondary endpoint of CGIC, the difference between treatment groups was not statistically significant.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:**

An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.

Treatment of TD is a novel indication and the Division has not yet formally endorsed any measurement as an accepted primary efficacy endpoint measure. AIMS is a commonly used instrument in clinical practice and medical research for measuring TD symptoms. Therefore, the Division has no objection in allowing the sponsor to use AIMS as the primary efficacy measure in this program. The Division has allowed modified AIMS as the primary efficacy endpoint in another IND (IND 111591) for similar indication and this IND had been granted Breakthrough designation.

Because of the novelty of the indication, it is very likely the NDA will need to be presented in an Advisory Committee meeting. The final acceptance of this efficacy measure and the clinical meaningfulness of the effect size would need to be discussed at the AC meeting.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.**

None

- A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

There are currently no available therapies which are approved for the treatment of TD.

- In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Tetrabenazine is approved in the treatment of chorea associated with Huntington's disease. It is not currently approved for the indication of TD. There is off-label use of tetrabenazine for the treatment of TD.

Avoidance of treatment with the offending medications is the only definitive method of prevention of TD. However, avoidance of antipsychotic medications in patients with underlying schizophrenia or active psychosis is often impractical. The Sponsor states that an evidence-based

recommendations from the American Academy of Neurology (Bhidayasiri et al., 2013), suggest that clonazepam, ginkgo biloba, amantadine, and tetrabenazine may be considered as treatment options based on available data. The utility of these agents is uncertain given the lack of well-controlled trials demonstrating their efficacy or safety for the treatment of TD.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Under IND 111591, NBI-98854 (Neurocrine Biosciences), another vesicular monoamine transporter 2 (VMAT2) inhibitor, is being developed for the treatment of neuroleptic-induced tardive dyskinesia. Breakthrough therapy designation was granted on 10/28/14.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

See Table 3 in Appendix.

- b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

We consider the data provided from study SD-809-C-18 to be preliminary. We have not yet reviewed the full data package. Based on the summary of the study report provided by the sponsor, the study is positive. Patients receiving SD-809 achieved a least squares (LS) mean 3.0-unit reduction in AIMS score, compared with a 1.6-unit reduction in patients receiving placebo, for a treatment effect of 1.4 units ($p=0.0188$). Analysis of AIMS responders by percent improvement from Baseline showed that the treatment effect favored SD-809 versus placebo for all degrees of response and these effects were statistically significant for each category of response up to $\geq 30\%$ improvement from Baseline (see attached Table 1 and 2 from the sponsor).

This study was a flexible dose study. The Division would like to see a fixed dose, randomized, placebo-controlled study that can substantiate the treatment effect as well as demonstrate a dose-response relationship if there is one. Additionally, the global functional assessment, CGI-C, did not separate from the placebo in study SD-809-C-18 and so an assessment of functional improvement should be included in the next study.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

As indicated above

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Serious Adverse Events in SD-809-C-18:

There were four SD-809 subjects and six placebo subjects with Serious Adverse Events (SAE's). SAEs occurring in SD-809 subjects included pneumonia, substance-induced mania, exacerbation of schizophrenia, and diagnostic hospitalization. All of these events resolved. SAE's in placebo subjects included heroin overdose, jaw fracture following a bicycle accident, jaw abscess, chronic obstructive pulmonary disease, pneumonia, and laryngeal hypertrophy.

One SD-809 subject was withdrawn from the study due to an AE of confusional state (possibly related to study drug). This event resolved after discontinuation of the study drug. Two placebo subjects were withdrawn from the study due to AEs of chest pain and overdose (unrelated).

Most Common Adverse Events in SD-809-C-18:

In the SD-809 group, somnolence, headache, fatigue, and insomnia were common. Among these, only somnolence and insomnia occurred in more subjects treated with SD-809 than with placebo. Akathisia was observed in 3 subjects treated with SD-809 and no placebo subjects. Dry mouth was reported in 6 placebo subjects and 2 SD-809 subjects.

One subject in each treatment group experienced AEs of depression or depressed mood. One subject in the placebo group experienced suicidal ideation.

There were no meaningful differences between SD-809 and placebo from Baseline to Week 12 in the following safety scales: 1) the Unified Parkinson's Disease Rating Scale [UPDRS (parkinsonism)], Montreal Cognitive Assessment [MoCA (cognitive function)], Epworth Sleepiness Scale [ESS (somnolence)], Barnes Akathisia Rating Scale [BARS (akathisia)], and Hospital Anxiety and Depression Scale [HADS (anxiety and depression)]. In addition to these scales, suicidality was evaluated with the C-SSRS. Post-baseline suicidal ideation or behavior occurred in 3 subjects (5.2%) in the placebo group and no subjects in the SD-809 group.

Sponsor reports no notable findings with SD-809 from vital signs, 12-lead ECGs, hematology, blood chemistry, or urinalysis.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

TD is a serious, and often disabling condition. There is no available treatment at this time, and so TD is an unmet medical need. SD-809 had demonstrated preliminary, promising efficacy in the treatment of TD in study SD-809-C-18.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

There are two additional Phase 3 studies that are on-going. One study is a 12-week, fixed dose (12, 24 and 24 mg BID), randomized, double blind, parallel design efficacy and safety study. The other study is an open-label longer term safety study. The division will continue to provide guidance and give feedback in a timely manner when the sponsor requests it. As we mentioned earlier, it is likely we will bring this NDA to an Advisory Committee because of the novel indication.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: Glenn Mannheim, MD {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

Appendix

Table 1. Primary Endpoint: Change from Baseline to Week 12 in Abnormal Involuntary Movement Scale (mITT Population; N=113)

	SD-809 (N=56)	Placebo (N=57)	Treatment Effect (SD-809 – Placebo)	p-value ^a
Baseline AIMS Score, mean (SD)	9.7 (4.14)	9.6 (3.78)	--	--
Change in AIMS from Baseline to Week 12 ^b LS Mean (SE)	-3.0 (0.45)	-1.6 (0.46)	-1.4 (0.60)	0.0188

^a Based on a linear mixed model for repeated measurements with change from baseline in AIMS score as the dependent variable, fixed effects for treatment, time point (Weeks 2, 4, 6, 9, 12), treatment by time point interaction, dopamine receptor antagonist status, and baseline AIMS as a covariate. Subject is a random effect. An unstructured covariance model is used. The Satterthwaite method is used to compute the denominator degrees of freedom for the F test and LS means estimates. The p-value is based on the F test.

^b Change from Baseline to Week 12 as assessed by a central rater.

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; LS, least squares; mITT, modified Intent-to-Treat; SE, standard error.

Table 2. Abnormal Involuntary Movement Scale Responders by Percent Improvement at Week 12 (mITT Population with Non-Responder Imputation; N=113)

AIMS Response Level	SD-809 (N=56) n (%)	Placebo (N=57) n (%)	p-value ^a
Percent Improvement from Baseline to Week 12			
≥10%	39 (69.6)	24 (42.1)	0.0032
≥20%	28 (50.0)	17 (29.8)	0.0285
≥30%	26 (46.4)	14 (24.6)	0.0151
≥40%	18 (32.1)	13 (22.8)	0.2661
≥50%	13 (23.2)	10 (17.5)	0.4541
≥60%	11 (19.6)	5 (8.8)	0.0975
≥70%	6 (10.7)	1 (1.8)	0.0608*
≥80%	5 (8.9)	1 (1.8)	0.1134*
≥90%	2 (3.6)	1 (1.8)	0.6183*

Notes: Based on centrally read AIMS Score (sum of Items 1-7). Four SD-809 subjects and 6 placebo subjects with missing data at Week 12 were imputed as non-responders.

^aStatistic based on small cell counts, defined as any expected cell count < 5, is flagged with an asterisk. The p-value is from Pearson's chi-square test (Fisher's exact test is used for small cell counts).

Table 3. Summary of Phase 3 Clinical Program of SD-809

Study ID	Study title	Study design	Trial Endpoints	Dosing regimen	Study population	Planned enrollment	Subject exposure	Results
Tardive Dyskinesia								
SD-809-C-18 ^b (ARM-TD) (EudraCT 2014-001890- 15)	A Randomized, Blind, Placebo-Controlled Study of SD-809 (deutetra-benazine) for the Treatment of Moderate to Severe Tardive Dyskinesia	Randomized, Double- Blind, Placebo- Controlled Study. Titration to stable study drug dose over 6 weeks; treatment period of 12 weeks; 1- week washout, and follow up telephone call 4 weeks after last dose (if subject did not roll over into C-20 long- term safety study).	Primary: change in Abnormal Involuntary Movements Scale (AIMS) (Items 1 through 7) from Baseline to Week 12, blinded central video rating Key Secondary: 1) Clinical Global Impression of Change (<i>CGIC</i>) at wk 12 Modified Craniocervical Dystonia Questionnaire (<i>CDQ-24</i>) , Baseline to Week 12	Starting dose SD-809 12 mg (6 mg bid) or placebo; weekly increments of 6 mg/day. Maximum total daily dose of SD-809 is 48 mg (24 mg bid) or placebo.	Male and female subjects, 18- 75 years, moderate to severe drug-induced TD (bothersome symptoms or functional impairment $\geq$ 3 months), use of a dopamine receptor antagonist for at least 3 months (or 1 month in subjects $\geq$ 60 years of age), and Baseline Investigator determined moderate-severe abnormal movements [Abnormal Involuntary Movement Scale: AIMS, Item 8 and total motor AIMS score $\geq$ 6 (based on Items 1-7)], who is psychiatrically stable, and meet other Criteria.	117 subjects randomized (1:1):58- SD-809; 59-placebo Completed 05/21/2015	58 subjects	Stat sig reduction in AIMS. Subjects on SD-809 achieved a least squares (LS) mean 3.0-unit reduction in AIMS score, compared with a 1.6-unit reduction in subjects receiving placebo, for a treatment effect of 1.4 units ($p=0.0188$). Key sec endpoints (<i>CGIC</i> ; <i>CDQ-24</i>)-neg.

Study ID	Study title	Study design	Trial Endpoints	Dosing regimen	Study population	Planned enrollment	Subject exposure	Results
SD-809-C-23 (AIM-TD) (EudraCT 2014-003135- 19)	A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetra- benazine) for the Treatment of Moderate to Severe Tardive Dyskinesia	Randomized, double-blind, placebo-controlled, parallel-group study. 4-week dose escalation period; 8-week maintenance period; 1-week washout and follow up telephone call 4 weeks after last dose (for subjects not participating in the C-20 long term safety study).	Primary: change in Abnormal Involuntary Movements Scale (AIMS) (Items 1 through 7) from Baseline to Week 12, blinded central video rating Key Secondary: 1) Clinical Global Impression of Change (CGIC) at wk 12	Subjects will be randomly assigned in a 1:1:1:1 ratio to receive 1 of 3 fixed-dose regimens of SD-809 (12 mg, 24 mg or 36 mg) or placebo.	Male and female subjects, 18-75 years, moderate to severe drug-induced TD (bothersome symptoms or functional impairment $\geq$ 3 months), use of a dopamine receptor antagonist for at least 3 months (or 1 month in subjects $\geq$ 60 years of age), and Baseline Investigator determined moderate-severe abnormal movements [Abnormal Involuntary Movement Scale: AIMS, Item 8 and total motor AIMS score $\geq$ 6 (based on Items 1-7)], who is psychiatrically stable, and meet other Criteria.	200 subjects (50/tx arm)	92 subjects enrolled as of 16 July 2015; Approximately 69 are exposed to SD-809 ^c	None
SD-809-C-20 (EudraCT 2014-001891- 73)	An Open-Label, Long-Term Safety Study of SD-809 (deutetra-benazine) for the Treatment of Moderate to Severe Tardive Dyskinesia	Open-label, single-arm study. Titration to stable study drug dose over 6 weeks; long term treatment period of up to 52 weeks; Drug discontinuation at week 54; 1-week washout, and follow up telephone call 4 weeks after last dose.	Safety	Starting dose SD-809 12 mg (6 mg bid); weekly increments of 6 mg/day. Maximum total daily dose of SD-809 is 48 mg (24 mg bid).	Male and female adult subjects with moderate to severe drug-induced TD who have completed study SD-809-C-18 or SD-809-C-23		126 subjects were enrolled; As of the cutoff date, 115 subjects are ongoing on	None

Abnormal Involuntary Movements Scale (AIMS)

AIMS Examination Procedure^d

Either before or after completing the Examination Procedure, observe the patient unobtrusively at rest (e.g., in the waiting room).

The chair to be used in this examination should be a hard, firm one without arms.

1. Ask the patient whether there is anything in his or her mouth (i.e., gum, candy, etc.) and, if so, to remove it.
2. Ask about the *current* condition of his/her teeth. Ask if he/she wears dentures. Do teeth or dentures bother the patient *now*.
3. Ask whether he/she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they *currently* bother the patient or interfere with his/her activities.
4. Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)
5. Ask the patient to sit with hands hanging unsupported. If male, between his legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)
6. Ask the patient to open mouth. (Observe tongue at rest within the mouth.) Do this twice.
7. Ask the patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.
8. Ask the patient to tap thumb with each finger as rapidly as possible for 10 to 15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements.)
9. Flex and extend the patient's left and right arms (one at a time).
10. Ask the patient to stand up. (Observe in profile. Observe all body areas again, hips included.)
11. Ask patient to extend both arms out in front, palms down. (Observe trunk, legs, and mouth.)
12. Have patient walk a few paces, turn, and walk back to the chair. (Observe hands and gait.) Do this twice.

^d Guy W. AIMS: ECDEU Assessment Manual for Psychopharmacology. Washington, DC: Government Printing Office; 1976.

Abnormal Involuntary Movement Scale (AIMS)

Summary of Scoring Criteria

Scoring Criteria for Items 1 through 7	
Score	Description
0 – Not present	Abnormal movements are not observed. Some movements may be observed but are not considered abnormal.
1 – Minimal, may be extreme normal	Abnormal movements occur infrequently and/or are difficult to detect
2 – Mild	Abnormal movements occur infrequently and are easy to detect
3 – Moderate	Abnormal movements occur frequently and are easy to detect
4 – Severe	Abnormal movements occur almost continuously and/or of extreme intensity

Complete Examination Procedures before making ratings. Rate highest severity observed in category I, II, III		Rater	
		Date	
I. FACIAL & ORAL MOVEMENTS	1. Muscles of Facial Expression e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	
	2. Lips and Perioral Area e.g. puckering, pouting, smacking	0 1 2 3 4	
	3. Jaw Biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement, Darting in and out of mouth	0 1 2 3 4	
II. EXTREMITY MOVEMENTS	5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)	0 1 2 3 4	
	6. Lower (legs, knees, ankles, toes) Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot)	0 1 2 3 4	
III. TRUNK MOVEMENTS	7. Neck, shoulders and hips Rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	
IV. GLOBAL JUDGEMENT	8. Severity of abnormal movements None, normal = 0 Minimal = 1 Mild = 2 Moderate = 3 Severe = 4	0 1 2 3 4	
	9. Incapacitation due to abnormal movements None, normal = 0 Minimal = 1 Mild = 2 Moderate = 3 Severe = 4	0 1 2 3 4	
	10. Patient's awareness of abnormal movements. Rate only patient's report: No Awareness = 0 Aware, no distress = 1 Aware, mild distress = 2 Aware, moderate distress = 3 Aware, severe distress = 4	0 1 2 3 4	
V. DENTAL STATUS	11. Current problems with teeth and/or dentures	YES	NO
	12. Does patient usually wear dentures?	YES	NO

Clinical Global Impression of Change (CGIC)

With respect to the subject's tardive dyskinesia, how would you describe the subject now compared to immediately before starting study drug:	
-3	Very Much Worse
-2	Much Worse
-1	Minimally Worse
0	Not Changed
1	Minimally Improved
2	Much Improved
3	Very Much Improved

Modified Craniocervical Dystonia Questionnaire (CDQ-24)

Because of your abnormal movements, how often have you experienced the following in the past two weeks? Please mark one answer per question and try to answer each question.

1. Have you had problems reading or watching TV?
(never/occasionally/sometimes/often/always)
2. Has it been difficult for you to do things you like to do—for example, leisure activities?
(never/occasionally/sometimes/often/always)
3. Has it been difficult for you to control your abnormal movements when you were nervous or under stress? (never/occasionally/sometimes/often/always)
4. Have you suffered from pain/discomfort in the mouth, tongue, face, head, or neck region?
(never/occasionally/sometimes/often/always)
5. Have you been prevented from falling asleep by pain/discomfort or abnormal movements?
(never/occasionally/sometimes/often/always)
6. Has it been difficult for you to do fine work with your fingers—for example, writing, threading a needle? (never/occasionally/sometimes/often/always)
7. Have you avoided situations where many people were present—for example, social events?
(never/occasionally/sometimes/often/always)
8. Have your abnormal movements made you feel uneasy in public?
(never/occasionally/sometimes/often/always)
9. Have you felt the need to conceal your abnormal movements from other people?
(never/occasionally/sometimes/often/always)
10. Have you worried about how other people react to you?
(never/occasionally/sometimes/often/always)
11. Have you worried about your future? (never/occasionally/sometimes/often/always)
12. Have you felt afraid? (never/occasionally/sometimes/often/always)
13. Have you felt down or depressed? (never/occasionally/sometimes/often/always)
14. Have you been sad or on the verge of tears? (never/occasionally/sometimes/often/always)
15. Have you felt annoyed or bitter? (never/occasionally/sometimes/often/always)
16. Have you felt isolated or lonely because of your abnormal movements?
(never/occasionally/sometimes/often/always)
17. Have you had problems with close friends or your family due to your abnormal movements? (never/occasionally/sometimes/often/always)
18. Have you felt unsure or tense with new people?
(never/occasionally/sometimes/often/always)
19. Has it been difficult for you to keep up with the demands of your job or home life? (not at all/slightly/moderately/severely/very severely)
– Are you employed: yes/no
20. Have you experienced difficulty as a motorist or pedestrian? (not at all/slightly/moderately/severely/very severely)
21. Have you felt hindered by pain/discomfort in the mouth, tongue, face, head or neck region?
(not at all/slightly/moderately/severely/very severely)
22. Have you felt you didn't look so good? (not at all/slightly/moderately/severely/very severely)
23. Have your abnormal movements had a negative effect on your family life? (not at all/slightly/moderately/severely/very severely)
24. Have your abnormal movements negatively affected the relationship with your partner?
(not at all/slightly/moderately/severely/very severely)
– Do you have a partner: yes/no

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/s/

SANDRA J BENTON
11/18/2015

MITCHELL V Mathis
11/18/2015



IND 120631

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Teva Pharmaceuticals, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Regulatory Affairs
3333 North Torrey Pines Court
La Jolla, CA 92037

Dear Dr. Truong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SD-809 (deutetrabenazine).

We also refer to your September 4, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that SD-809 (deutetrabenazine) for Tardive Dyskinesia meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of SD-809 (deutetrabenazine) for Tardive Dyskinesia to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*³ for procedures on requesting a meeting. If you feel

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

²

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for SD-809 (deutetrabenazine) for Tardive Dyskinesia is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Sharonjit Sagoo, Pharm.D., Regulatory Project Manager, at (301) 796-0431.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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/s/

MITCHELL V Mathis
11/03/2015

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 209885

LATE-CYCLE MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: David Truong, PharmD, MS
Senior Manager, Global Regulatory Affairs
3333 North Torrey Pines Court, Suite 400
La Jolla, CA 92037

Dear Dr. Truong:

Please refer to your New Drug Application (NDA) dated December 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 20, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sarah Seung, Regulatory Project Manager at (240) 402-3879.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 20, 2017
1:00 PM to 2:00 PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1315
Application Number: 209885
Product Name: Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg
Applicant Name: Teva Branded Pharmaceutical Products R&D, Inc.
Meeting Chair: Mitchell Mathis, MD
Meeting Recorder: Sarah Seung, PharmD

FDA ATTENDEES

Mitchell Mathis, MD	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, MD	Deputy Director, DPP
Jean Kim, MD	Clinical Team Leader (Acting), DPP
Anandraj Mattai, MD	Clinical Reviewer, DPP
Hao Zhu, PhD	Team Leader, Office of Clinical Pharmacology (OCP)
Kevin Krudys, PhD	Team Leader, Division of Pharmacometrics, OCP
Gopichand Gottipati, PhD	Reviewer, Division of Pharmacometrics, OCP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Amy Avila, PhD	Pharmacology/Toxicology Reviewer, DPP
Peiling Yang, PhD	Biometrics Team Leader
Lars Johannesen	QT-IRT Reviewer, QT Interdisciplinary Review team
Leah Hart, PharmD	Acting Team Leader, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE)
Theresa Ng, PharmD, BCPS	Risk Management Analyst (RMA), DRISK, OSE
Alycia Anderson, CCRP	Regulatory Health Project Manager, OSE
Noah Nevo, PharmD, BCPP	Safety Evaluator, Division of Pharmacovigilance I (DPV I)
Sarah Seung, PharmD	Regulatory Project Manager, DPP

APPLICANT ATTENDEES

David Chapman, PhD	Project Champion
Donna Cox, PhD	Director, Clinical Pharmacology
Matthew Davis, PhD	Director, Biostatistics
Douglas Harnish, PhD	Vice President, Global Regulatory Affairs
Walter Hong, MD	Senior Director, Clinical Development
Micha Levi	Director, Pharmacometrics
Christine Schulteis, PhD	Senior Director, Global Regulatory Affairs

(b) (4)

David Truong, PharmD, MS, Senior Manager, Regulatory Affairs

(b) (4)

Susan Franks, MS, Senior Vice President Global Regulatory Affairs

1.0 BACKGROUND

NDA 209885 was submitted on December 30, 2016 for Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg.

Proposed indication(s): Treatment of Tardive Dyskinesia

PDUFA goal date: August 30, 2017

FDA issued a Background Package in preparation for this meeting on June 9, 2017.

2.0 DISCUSSION

1. Introductory Comments

Discussion: *The Division explained the purpose and objectives of the Late-Cycle Meeting and informed Teva that the application has not yet been fully reviewed by the signatory authority and Cross-Discipline Team Leader (CDTL); therefore, the final regulatory decision for the application will not be addressed at the meeting.*

2. Discussion of Substantive Review Issues

Clinical

Significance of cardiac liability in the context of QT prolongation.

- Implications regarding labeling

Discussion: *The Division reiterated concerns outlined in the Background Package regarding cardiac liability of SD-809 in the context of its propensity to prolong the QT interval. Particular attention was placed on deficiencies related to the design of the thorough QT Study as well the inadequate assumptions based on the QTc model submitted (i.e., alpha and beta HTBZ are equal contributing factors to QT prolongation). Given these limitations, the Division noted it was difficult to justify modification of the label to remove language regarding the clinical significance of SD-809 mediated QT prolongation.*

The Applicant recognized these limitations but asserted SD-809 had no clinically significant cardiac liability based on their aggregate review of the safety data. Dr. William White, an external cardiovascular consultant, noted the small number of cardiac adverse events that occurred during the course of the study. There were only a handful of

patients that had increases in QT (versus baseline) that exceeded 480 msec. Furthermore, upon review of individual ECGs, Dr. White thought some of the QT increases were artifact. His analysis of the deaths that occurred in the clinical development program did not point specifically to increases in QT prolongation as a putative contributing factor. He noted that many of the individuals had significant comorbid medical conditions that could have been the primary cause of death.

Despite the newly submitted cardiac data, the Division was not sufficiently convinced that it would be safe to administer SD-809 in certain populations without an adequate warning regarding the risks of QT prolongation. This was especially evident in subjects taking CYP2D6 inhibitors, who are CYP2D6 poor metabolizers, or who use other medications that can prolong the QT interval. As genotyping is not common in clinical practice, there were concerns that such individuals could be exposed to differentially high levels of study drug and consequently be vulnerable to large increases in QT interval. The Division thought the current labeling language regarding QT prolongation in Section 5 should stand with a modification that would permit co-administration of antipsychotic medications.

Finally, the Applicant asked about other data that could be submitted to help alleviate DPP's concerns about this issue. The Division mentioned that such data may be submitted in the future but would not be included in this review cycle.

Statistical

Secondary Endpoints: the key secondary endpoint, CGIC, in the hierarchical testing was not met.

Discussion: *The Applicant acknowledged and agreed that the secondary endpoint failed based on the pre-specified sequence. The Applicant shared that they conducted sensitivity analyses using odds ratio and believe that there is an effect on CGIC. In their opinion, the effect on CGIC would be helpful to clinicians.*

(b) (4)

(b) (4)

3. Information Requests

None – We submitted several Information Requests in the course of the review and there are no outstanding requests to discuss at this time.

Discussion: *No further discussion.*

4. Postmarketing Requirements/Postmarketing Commitments

Clinical

- **Additional evidence for treatment durability and persistence:** The long-term treatment period in Study C-20 provides some evidence suggesting that continuing SD-

809 treatment may maintain the reduction in TD symptoms. However, there was moderate attrition over the course of treatment and the lack of a placebo control raises the possibility that subjects' knowledge as to whether they are receiving an active treatment might affect TD symptom severity. (b) (4)



5. Review Plans

- Internal labeling discussions are ongoing.
- We plan to complete our review and take action by the August 30, 2017 PDUFA goal date.

Discussion: *No further discussion.*

6. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL); therefore, this meeting did not address the final regulatory decision for the application.

Discussion: *No further discussion.*

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/s/

MITCHELL V Mathis
07/17/2017