APPLICATION NUMBER:

209885Orig1s000

OTHER REVIEW(S)
REGULATORY PROJECT MANAGER
LABELING REVIEW

Drug Name/NDA: Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg/NDA 209885
Applicant: Teva Branded Pharmaceutical Products R&D, Inc.
Indication: Treatment of tardive dyskinesia

Pending Supplements:

<table>
<thead>
<tr>
<th>NDA</th>
<th>Supplement #</th>
<th>Dated</th>
<th>Provides for</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>208082</td>
<td>Type 1</td>
<td>5/29/15</td>
<td>Original NDA. Austedo (deutetrabenazine) for the treatment of chorea associated with Huntington’s disease</td>
<td>Approved 4/3/17</td>
</tr>
<tr>
<td>209885</td>
<td>Type 9</td>
<td>12/30/16</td>
<td>Original Type 9 NDA. Austedo (deutetrabenazine) for the treatment of tardive dyskinesia</td>
<td>Pending</td>
</tr>
</tbody>
</table>

BACKGROUND

- Teva submitted multiple original NDAs for Austedo. Both NDAs 208082 (managed by DNP) and 209885 (managed by DPP) were considered Type 1 (original new molecular entity) applications. Given that NDA 208082 was approved first, the sponsor had the choice of changing NDA 209885 from a Type 1 NDA to either a Type 9 or Type 10 NDA. The difference being that a Type 9 NDA is one in which the sponsor does not intend to market the product under a separate label, and the NDA is “administratively closed” after approval. A Type 10 NDA is one in which the sponsor intends to market the product under a separate label. Teva informed the Agency that they wanted to have a single label for both the chorea and tardive dyskinesia indications. As such, NDA 209885 will be administratively closed upon approval, and all subsequent labeling revisions will be managed under DNP’s NDA 208082.
- NDA 209885 was submitted under “The Program” as a priority designation review subject to a 10 month PDUFA clock. Although the NDA type has changed, DPP was informed by senior management to maintain the original PDUFA clock as well as retain “The Program” qualities such as the mid-cycle and late-cycle meetings with the sponsor.
- This Type 9 application, NDA 209885, Austedo (deutetrabenazine) for the treatment of tardive dyskinesia, was submitted on 12/30/16.
- Austedo (deutetrabenazine) for the treatment of chorea associated with Huntington’s disease was submitted on 5/29/15 under NDA 208082 and was approved on 4/3/17.
- The last approved labeling, for comparison purposes, was NDA 208082, which was approved on 4/3/17.
- This review will only encompass pending application NDA 209885, which was submitted on 12/30/16.

REVIEW

NDA 209885
Dated: 12/30/16 (Review Designation – Priority)
Amendment Dates: 3/10/17, 5/1/17, 7/14/17, 8/1/17, 8/30/17
Reviewed by:
Tiffany Farchione, Deputy/CDTL, Division of Psychiatry (DPP) (8/30/17)
Anandraj Mattai, Clinical Reviewer, DPP (Date 8/7/17)
Semhar Ogbagaber, Biometrics Reviewer, Division of Biometrics I (Date 8/2/17)
Gopichand Gottipati, Office of Clinical Pharmacology Integrated Review (Dated 8/10/17)
Catherine Roca, Medical Officer, Material Heath Division of Pediatric and Material Health (DPMH) (Date 6/2/17)
Shawna Hutchins, Patient Labeling Reviewer, Division of Medical Policy Programs (DMPP) (Date 6/27/17)
Christine Bradshaw, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP) (Date 6/28/17 & 8/3/17)
Loretta Holmes, Reviewer, Division of Medication Error Prevention and Analysis (DMEPA) (Date 7/5/17)

This application provides for a new indication of treatment of tardive dyskinesia and proposes the following changes to the approved NDA 208082 label:
• Revision to Boxed Warning in HL and in FPI.
• Revision to Recent Major Changes, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, and Adverse Reactions in HL.
• Revision to Section 1 and subsection 2.1 to add the new indication.
• Revision to subsection 2.1 to add QT interval assessment.
• Reordering of subsections in Sections 4, 5, and 7 in order of decreasing severity.
• Revision to Sections 4 and 5 to differentiate between the two patient populations of Huntington’s disease and tardive dyskinesia
• Revision to Section 4 to update the list of contraindicated medications.
• Revision to subsection 5.3.
• Reordering of the line listings at the beginning of Section 6.
• Addition of adverse reactions data from clinical trials in tardive dyskinesia in subsection 6.1.
• Revisions to subsection 7.2.
• Revisions to subsections 12.1 and 12.2.
• Addition of subsection 14.2 entitled “Tardive Dyskinesia.”
• Revisions to Section 17.
• Addition of patents & registered trademark for Austedo.
• Multiple revisions throughout the Medication Guide.

DISCUSSION

• The review team recommends approval for this pending new drug application.
• It should be noted that all of the labeling revisions were discussed and agreed upon with DNP given that DNP will assume management of the label once DPP’s NDA has been approved.
• When compared to the last approved labeling (Agency’s approval letter dated 4/3/2017 for NDA 208082), this application only provides for the labeling changes noted above and delineated in the attached annotated labeling.
• The review team and the applicant reached labeling agreement. See attached emails dated 8/29/17.

CONCLUSIONS

1. This application only provides for the revisions as stated above when compared to the last approved labeling for NDA 208082 (approval letter dated 4/3/17).
2. I recommend that an approval letter be issued for this pending new drug application.

{See appended electronic signature page}

Sarah Seung, PharmD

{See appended electronic signature page}

Paul David, RPh
Chief, Project Management Staff

Attachment: annotated labeling & labeling e-mail agreement
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

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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

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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

Reference ID: 4146577
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

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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
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
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #: NDA 209885
Product Name: Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12mg
PMR/PMC Description: PMC 3236-1
To better assess the persistence of deutetrabenazine treatment for TD, perform a new trial or conduct a substudy in a currently ongoing trial in which subjects who have demonstrated an adequate response to deutetrabenazine are randomized to receive placebo or continue their current dose.

PMR/PMC Schedule Milestones:
- Final Protocol Submission: 01/31/2018
- Study/Trial Completion: 01/31/2021
- Final Report Submission: 01/31/2022
- Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   [ ] Unmet need
   [ ] Life-threatening condition
   [ ] Long-term data needed
   [ ] Only feasible to conduct post-approval
   [x] Prior clinical experience indicates safety
   [ ] Small subpopulation affected
   [ ] Theoretical concern
   [ ] Other

   The rationale for this issue was developed following analyses of clinical studies submitted with the NDA. The issue is not critical for efficacy/safety to support initial approval but may provide useful information that can be included in future labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
The rationale for this PMC is based on data from Study C-20 that suggests 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. A randomized withdrawal period in a post-marketing study will address the persistence of deutetrabenazine treatment for TD after cessation of treatment.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
   If not a PMR, skip to 4.

   Which regulation?
   □ Accelerated Approval (subpart H/E)  
   □ Animal Efficacy Rule  
   □ Pediatric Research Equity Act  
   □ FDAAA required safety study/clinical trial

   If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
   □ Assess a known serious risk related to the use of the drug?
   □ Assess signals of serious risk related to the use of the drug?
   □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
   □ Analysis of spontaneous postmarketing adverse events?  
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

   □ Analysis using pharmacovigilance system?  
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

   □ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
     Do not select the above study/clinical trial type if: a study will not be sufficient to identify or assess a serious risk

   □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   Randomized withdrawal trial. Subjects who have demonstrated an adequate response to deutetrabenazine treatment for reduction in tardive dyskinesia symptoms will be randomized to continue their current dose vs. placebo, and tardive dyskinesia symptoms will be assessed for recurrence.
Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

*Continuation of Question 4*

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed
PMR/PMC Development Coordinator:

☐ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________
(signature line for BLAs)
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

MARC B STONE
08/30/2017
## 505(b)(2) ASSESSMENT

### Application Information

<table>
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<tr>
<th>NDA #</th>
<th>NDA Supplement #: S-</th>
<th>Efficacy Supplement Type SE-</th>
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<tbody>
<tr>
<td>209885</td>
<td></td>
<td></td>
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</tbody>
</table>

Proprietary Name: Austedo  
Established/Proper Name: deutetrabenazine  
Dosage Form: Tablet  
Strengths: 6 mg, 9 mg, and 12 mg  
Applicant: Teva Branded Pharmaceutical Products R&D, Inc.

Date of Receipt: 12/30/2016  
PDUFA Goal Date: 8/30/2017  
Action Goal Date (if different):  
RPM: Sarah Seung  
Proposed Indication(s): Treatment of tardive dyskinesia

### GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

   YES ☐  NO ☒

If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.
2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

<table>
<thead>
<tr>
<th>Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)</th>
<th>Information relied-upon (e.g., specific sections of the application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 021894 “Xenazine”</td>
<td>FDA’s previous finding of efficacy, labeling section “12.3 Pharmacokinetics – Distribution,”</td>
</tr>
</tbody>
</table>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature. *(See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.)*

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.

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the

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3For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicity studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.
For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s).

For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

If the application cannot be approved as labeled without the published literature?

YES ☐ NO ☒

If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) listed drug product?

YES ☐ NO ☒

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☒
RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application rely on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

   YES ☑ NO ☐

   If “NO,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(#s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

<table>
<thead>
<tr>
<th>Name of Listed Drug</th>
<th>NDA #</th>
<th>Did applicant specify reliance on the product? (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenazine (tetrabenazine) Tablets, 12.5 mg and 25 mg</td>
<td>021894</td>
<td>Y</td>
</tr>
</tbody>
</table>

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

   N/A ☑ YES ☐ NO ☐

   If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.

   If “NO”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:

   a) Approved in a 505(b)(2) application?

      YES ☑ NO ☐

      If “YES”, please list which drug(s).

      Name of drug(s) approved in a 505(b)(2) application:

   b) Approved by the DESI process?

      YES ☑ NO ☐

      If “YES”, please list which drug(s).

      Name of drug(s) approved via the DESI process:

   c) Described in a final OTC drug monograph?

      YES ☑ NO ☐

      If “YES”, please list which drug(s).
Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing? ☐ YES ☒ NO

If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

☐ YES ☒ NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

Proposed product is a different active ingredient, potency and provides for a new indication (i.e., treatment of tardive dyskinesia).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

☐ YES ☒ NO
If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☒

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☐ NO ☒

If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all
of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Austedo NDA 208082

### PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed [X] Proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES [ ] NO [ ]

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- [ ] No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

- [X] 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

- [ ] 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

- [ ] 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

- [ ] 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). If Paragraph IV certification was submitted, proceed to question #15.

- [ ] 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR
314.50(i)(1)(i)(A)(4) above). If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.


☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ONLY for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If “NO”, please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If “NO”, please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided.

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval
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
08/29/2017
MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 25, 2017

To: Mitchell V. Mathis, M.D.
Division of Psychiatry Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Martin Rusinowitz, M.D., Medical Officer
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: NDA 209885/IND 120631
Name: AustedoTM, (deutetragenazine, SD-809, d6-tetabenazine)
Indication: Treatment of Tardive Dyskinesia
Dosage: 6-mg, 9-mg, and 12-mg tablets
Proposed dosage: to be administered with food, from 12 mg to 48 mg BID
Sponsor: Teva Pharmaceuticals, Inc.

Materials reviewed:
• NDA is in EDR Dec 30, 2016
• Sponsor’s response to CSS information request for an additional data
  on abuse, misuse and overdose, March 15, 2017, Seq. 0007.

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I. BACKGROUND

This memorandum responds to a consult request from the Division of Psychiatry Products (DPP) to evaluate the abuse potential of Austedo (deutetragenazine) NDA 209885. NDA 209885 was submitted as a 505(b)(2) NDA for the treatment of tardive dyskinesia and references Xenazine
Austedo (deutetrabenazine) NDA 209885

(tetrabenazine) (NDA 21894) as the listed drug. Austedo (SD-809SD-809, deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2)\(^1\) inhibitor which is structurally related to tetrabenazine.

The Sponsor is developing Austedo (SD-809SD-809, deutetrabenazine; d6-tetrabenazine) as a treatment for tardive dyskinesia (TD).

Tardive dyskinesia (TD) is a neurological disorder characterized by repetitive, involuntary, purposeless movements. It emerges after the long-term use of neuroleptic medications for psychiatric, gastrointestinal, and neurological disorders. TD may include grimacing, tongue protrusion, lip smacking, puckering, pursing and rapid eye blinking. Rapid movements of the arms, legs, and trunk may also occur. The disorder generally persists even after discontinuation of the neuroleptic drug.

Of note, Austedo, under NDA 208082, was recently approved by DNP (April 3, 2017) for the treatment of chorea associated with Huntington’s Disease (HD).

For this submission the Sponsor cross-references multiple sections, including pre-clinical and clinical studies, from NDA 208082.

To date the Sponsor has performed three Phase 3 clinical studies in patients with TD:

- Study SD-809-C-18 was a randomized, double-blind, placebo-controlled, flexible-dose, parallel-group study to evaluate the efficacy, safety, and tolerability of Austedo in patients with TD aged 18-75 years.
- Study SD-809-C-23 was a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study to evaluate the efficacy, safety, and tolerability of Austedo in patients with TD aged 18-80 years.
- Study SD-809-C-20 is an ongoing, open-label, single-arm study to evaluate the long-term safety and tolerability of Austedo for the treatment of patients with TD who have successfully completed Study C-18 or Study C-23.

Safety data in this NDA also included studies in patients with HD # SD-809-C-15 and # SD-809-C-16 and safety data from seven clinical studies in healthy volunteers which were performed under NDA 208082.

A total of 381 patients with TD were exposed to Austedo, and 108 were exposed for over 1 year. Over 500 patients received Austedo in the TD and HD clinical development programs, over 200 patients were exposed to Austedo, for either indication, for at least 12 months.

\(^1\) The vesicular monoamine transporter 2 (VMAT2) is an integral membrane protein that transports monoamines—particularly neurotransmitters such as dopamine, norepinephrine, serotonin, and histamine—from cellular cytosol into synaptic vesicles.
CSS requested in the 74-day letter that the Sponsor provide more data on dependence, withdrawal, and rebound as well as drug misuse, diversion, and overdose. The requested data was received on March 15, 2017.

II. CONCLUSIONS

1. The interpretation of potentially abuse-related adverse events (AEs) from Austedo in this study population is difficult because of the following:
   a. Some subjects had multiple psychiatric disorders such as schizophrenia, bipolar disorder, and depression; and
   b. Subjects were co-administered multiple psychoactive medication including (but not limited to) neuroleptics, benzodiazepines, anticonvulsants, opioids and mood stabilizers.

2. The current data on dependence, withdrawal, and rebound was provided for a small number of patients and collected over a short period of time, making it difficult to assess the presence or absence of withdrawal and/or rebound. Because Austedo, through inhibition of the VMAT2, affects a number of neurotransmitters including dopamine, serotonin and norepinephrine, the sudden reversal of long standing inhibition of Austedo, may cause a withdrawal syndrome with cardiovascular and neurological AEs. Additionally, rebound dyskinesias may also be disabling for patients with TD. Rebound dyskinesias were not evaluated in any clinical studies after drug discontinuation. For example, the AIMS, CGIC, PGIC, and CDQ were not administered. AIMS was administered to a fraction of patients in the on-going study # SD-809-C-20 but follow-up was not video recorded so, precise assessments of recurrent dyskinesias was not possible. However significant rebound was observed with another VMAT2 inhibitor, Valbenazine (NDA 209241), in Study # 1304 at one week for the dose of 80 mg. Therefore, the Sponsor should submit all the dependence, withdrawal, and rebound data collected from the on-going Study # SD-809-C-20 (see Recommendations).

III. RECOMMENDATIONS

1. Although no cases of abuse or misuse were reported in clinical trials, we recommend continuing the post marketing assessment of AEs suggestive of abuse-potential. These assessments should be included in the standard Periodic Adverse Drug Experience Reports (PADERS).

2. Sponsor should submit all the dependence and withdrawal and rebound data collected from the still on-going study # SD-809-C-20 as PMR including all AEs, vital signs, and available scores of efficacy and safety scales administered during the withdrawal period. Also, when assessing rebound it should be considered that during the first week of abrupt drug withdrawal the measures of disease symptom frequently return to baseline, and only in the next 2-3 weeks do these measures show rebound (Fountain and Chouinard, 1984).
Therefore, all scales should be used for at least 3 weeks (every week) during the discontinuation period.

**IV. DISCUSSION**

**CLINICAL STUDIES**

1. **Abuse Related Adverse Events in Phase 3 Studies**

Clinical studies for tardive dyskinesia included the following completed placebo-controlled studies:

- Study C-18: a randomized, double-blind, placebo-controlled, flexible-dose study of Austedo for the treatment of TD
- Study C-23: a randomized, double-blind, placebo-controlled, fixed-dose study of Austedo for the treatment of TD
- Study C-20 ongoing: an open-label, flexible-dose, long-term, safety study of SD-809 for the treatment of TD

The most frequent adverse events (AEs) (≥4% of total patients) were anxiety, somnolence, depression, headache, diarrhea, nasopharyngitis, fatigue, and urinary tract infection.

**Abuse potential-related adverse events**

The population treated with Austedo showed an increase of AEs such as somnolence, anxiety, insomnia, irritability, depression and fatigue and less frequent were AEs of paranoia, schizophrenia, acute psychosis, hallucinations, restlessness, and suicidal ideation.

**Study # SD-809-C-18: A Randomized, Double-Blind, Placebo-Controlled Study of SD-809 (deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia Aim to Reduce Movements in Tardive Dyskinesia (ARM-TD), Phase 2/3**

- The study was a randomized, double-blind, placebo-controlled, parallel-group study designed which evaluated the efficacy, safety, and tolerability of Austedo as the treatment of TD.
- The study included a screening period of up to 4 weeks, a 6-week titration period, a 6-week maintenance period, and a 1-week washout.
- After the completion of the study patients had the option to rollover into a long-term safety study (Study SD-809-C-20) or enter an additional 3-week safety follow-up period after treatment.

**Abuse potential-related adverse events during the study duration**

The most common abuse potential-related AEs included somnolence, insomnia, and suicidal ideation, see table 1.

**Table 1. Abuse potential-related adverse event the treatment period based on Table 14.3.1.2.4, study report, p 522.**
<table>
<thead>
<tr>
<th>Adverse Event PT</th>
<th>Austedo N=58 n (%)</th>
<th>Placebo N=59 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Qualifying AE</td>
<td>41 (70.7)</td>
<td>46 (61.0)</td>
</tr>
<tr>
<td><strong>Neurological Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>8 (13.8)</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Sedation</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (6.9)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Acute psychosis</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Affective disorder</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Confusional state</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Panic attack</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Mania</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Suicidal ideation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abuse-related adverse events that lead to drug discontinuation**

There was only one of serious AE leading to withdrawal from the study; confusional state.
Study SD-809-C-23: A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia, Phase 3

The study was a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study to evaluate the efficacy, safety, and tolerability of Austedo for the treatment of patients with TD.

- The study included a screening period (up to 4 weeks), dose-escalation period (4 weeks), and maintenance period (8 weeks); a 1-week washout period followed a maintenance period.
- Doses used: Austedo 12 mg/day, 24 mg/day, 36 mg/day and placebo
- Patients who completed the double-blind study were given the option of enrolling in a long-term safety study of Austedo (Study # SD-809-C-20)
- Patients who did not participate in the long-term safety (extension) study had a follow-up telephone contact 4 weeks after their last dose of study drug.
- Overall study participation was up to 20 weeks.

Abuse potential related adverse events

The most common abuse potential-related AEs included anxiety, depression, fatigue, insomnia, suicidal ideation, see table 2.

Table 2. Abuse potential-related Adverse Events in Patients with TD, based on Summary 15.28, page 481, study report.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo N=72 n (%)</th>
<th>Austedo All doses N=221 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE</td>
<td>34 (72.2)</td>
<td>106 (48)</td>
</tr>
<tr>
<td>Neurological Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnesia</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Psychomotor hyperactivity</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety/Anxiety dis.</td>
<td>2 (2.8)</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Hallucinations, visual</td>
<td>0</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>---</td>
<td>----</td>
</tr>
<tr>
<td><strong>Suicidal ideation</strong></td>
<td>0</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.4)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abuse Potential-Related Serious Adverse Events**
SAEs included: psychomotor activity, depression, psychotic disorder, and suicidal ideation.

**Abuse potential-related adverse events that led to drug discontinuation**
These AEs included: psychotic disorder, schizophrenia, suicidal ideation, psychomotor hyperactivity, and insomnia (the last AE of insomnia, resulted in such severe psychomotor hyperactivity and the patient was hospitalized.)

**Study # SD-809-C-20: On-going Open-Label, Long-Term Safety Study of SD-809 (Deutetrabenazine) for the Treatment of Moderate to Severe Tardive Dyskinesia** *(interim clinical study report at 54 week)*

- This study was an open-label, single-arm, long-term study which evaluated the safety and tolerability of long-term maintenance therapy (up to 106 weeks) with Austedo in patients with TD.
- Study population included patients with diverse background disorders such as schizophrenia, schizoaffective disorder, bipolar, and depression.
- A total of 304 patients had rolled over into this study (at the time of the data cutoff) after completion of a 1-week washout period and after the Week 13 evaluation of the parent studies (Studies SD-809-C-18 and SD-809-C-23). As of the date of the report (30 June 2016) 79 patients discontinued from the study.
- The study included a screening period, a titration period (up to 6 weeks), a long-term treatment period (up to 2 years), and a post-treatment safety follow-up period (4 weeks). The study participation is planned to be up to 110 weeks.
- All patients were treated with Austedo at a starting dose of 12 mg/day (6 mg twice daily) regardless of previous treatment in the parent studies. During the titration period the dose of Austedo was increased on a weekly basis in increments of 6 mg for a total daily dose up to 48 mg/day.
- There was a safety follow-up assessment 1 week following drug discontinuation (Week 107) for evaluation of safety, dyskinesias, and motor function.
- Patients had telephone follow-up contact 4 weeks after drug discontinuation at Week 110 to evaluate AEs.
- At the time of the NDA submission, 79 (~25%) patients discontinued from the study for various reasons including AEs (14) and deaths (3).

**Abuse-related adverse events at cut-off date June 30, 2016 (through 54 weeks of study duration).**

During the on-going study a number of neuro-psychiatric AEs possibly related to abuse potential included depressive disorders, somnolence, anxiety, fatigue and insomnia (Table 3).
Table 3. Treatment-emergent abuse-related adverse events in TD patients in the phase 3 study # SD-809-C-20 broken down by the prior treatment with Austedo vs placebo, based on Sponsor’s Table 15-15, p 460, study report.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Prior Placebo n (%), # of cases</th>
<th>Prior Austedo n (%), # of cases</th>
<th>Both groups-Total Doses up to 48 mg qd n (%), # of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 any TEAE</td>
<td>60 (58.8), 243</td>
<td>121 (59.9), 506</td>
<td>181 (59.5), 749</td>
</tr>
<tr>
<td><strong>Neurological Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>9 (8.8), 11</td>
<td>13 (6.4), 16</td>
<td>22 (7.2), 27</td>
</tr>
<tr>
<td>Sedation</td>
<td>1 (1.0), 1</td>
<td>2 (1.0), 2</td>
<td>3 (1.0), 3</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0</td>
<td>2 (1.0), 2</td>
<td>2 (0.7), 2</td>
</tr>
<tr>
<td>Altered state of consciousness</td>
<td>0</td>
<td>1 (0.5), 1</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective disorder</td>
<td>0</td>
<td>2 (1.0), 2</td>
<td>2 (0.7), 2</td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (1.0), 2</td>
<td>2 (1.0), 2</td>
<td>3 (1.0), 3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (8.8), 10</td>
<td>15 (7.4), 17</td>
<td>24 (7.9), 27</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (3.9), 4</td>
<td>5 (2.5), 7</td>
<td>9 (3.0), 11</td>
</tr>
<tr>
<td>Irritability</td>
<td>2 (2.0), 2</td>
<td>2 (1.0), 2</td>
<td>4 (1.3), 4</td>
</tr>
<tr>
<td>Depressive symptom</td>
<td>0</td>
<td>2 (1.0), 2</td>
<td>2 (0.7), 2</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1 (1.0), 1</td>
<td>5 (2.5), 6</td>
<td>6 (2.0), 7</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (6.9), 8</td>
<td>15 (7.4), 15</td>
<td>22 (7.2), 23</td>
</tr>
<tr>
<td>Hypomania</td>
<td>0</td>
<td>1 (0.5), 1</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>1 (1.0), 1</td>
<td>3 (1.5), 3</td>
<td>34 (1.3), 4</td>
</tr>
<tr>
<td>Hallucinations, auditory</td>
<td>1 (1.0), 2</td>
<td>1 (0.5), 1</td>
<td>2 (0.7), 2</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2 (2.0), 2</td>
<td>2 (1.0), 2</td>
<td>4 (1.3), 4</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>1 (1.0), 1</td>
<td>1 (0.5), 3</td>
<td>2 (0.7), 4</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>1 (1.0), 1</td>
<td>0</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td>Paranoia</td>
<td>1 (1.0), 1</td>
<td>0</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>4 (2.0), 4</td>
<td>4 (1.3), 4</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1 (1.0), 1</td>
<td>0</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td>Homicidal ideation</td>
<td>1 (1.0), 1</td>
<td>0</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (3.9), 4</td>
<td>10 (5.9), 11</td>
<td>14 (4.6), 15</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (1.0), 1</td>
<td>2 (1.0), 2</td>
<td>3 (1.0), 3</td>
</tr>
<tr>
<td>Drug withdrawal synd.**</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (0.3), 1</td>
</tr>
<tr>
<td><strong>Injury, Poisoning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intentional overdose*  & 1 (1.0), 1 & 0 & 1 (0.3), 1 \\
Accidental overdose & 0 & 1 (0.5), 1 & 1 (0.3), 1 \\

* - drugs included lorazepam and losartan
** - apparently opiate withdrawal

**Comment**

Patients who had a prior exposure to Austedo and underwent treatment in the parent studies SD-18 and -23 had a similar number of AEs as the patients who were first exposed to Austedo and in the parent study received placebo. However, there were some differences in cases of neuropsychiatric AEs. In the prior placebo group there was an increase in somnolence, anxiety, insomnia, irritability, suicide attempt and homicidality whereas depressive disorders, suicidal ideation and fatigue were higher in the group exposed prior to Austedo (highlight grey). Of great safety concern are AEs of suicidality and even homicidal ideation (one case) which occurred during the treatment with Austedo.

**Abuse-related adverse events leading to discontinuation**

During the study, 18 patients discontinued due to all AEs and 12 patients due to neuropsychiatric AEs, table 4.

**Table 4. Abuse-related adverse events that lead to discontinuation based on Summary table 15.19 study report, p 488.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total Austedo N=304 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE causing discontinuation</td>
<td>18 (5.9)</td>
</tr>
<tr>
<td><strong>Neurological Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td><strong>Suicide attempt</strong></td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Homicidal ideation</strong></td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning</strong></td>
<td></td>
</tr>
</tbody>
</table>
*Intentional overdose** 1 (0.3)
*drugs included lorazepam and losartan
**All 3 AEs occurred in the same patient # 141-0001

**Conclusions Regarding Adverse Events Profile in the Phase 2/3 Studies**

Austedo is a CNS active drug that causes a number of neuro-psychiatric abuse-potential related AEs which are of mixed sedative and stimulant types. These AEs are less frequent in this population than reported in the previous NDA 208082, which included AEs in phase 1 healthy volunteers of somnolence, restlessness, agitation, disturbance in attention, and depressed mood. In patients with Huntington’s disease they included somnolence, insomnia, agitation, restlessness, anxiety, suicidality, and paranoia. This decrease of AEs may be attributed to multiple allowed concomitant psychoactive medications which included neuroleptics, benzodiazepines, anticonvulsants, opioids and mood stabilizers. Thus the decrease does not necessarily reflect drug safety, as there were number of concerning AEs which led to drug discontinuation such as psychotic disorders, suicidality and homicidality.

Additionally, as the Sponsor states, a number of these listed AEs are consistent class (VMAT2)-related and disease-related AEs which were observed with TD and included depression, suicidality, anxiety, somnolence, akathisia, and parkinsonism.

**2. Evidence of Abuse, Misuse, Diversion and Overdose in Clinical Trials**

In response to CSS’ information request (March 15 2017, Seq 0007) the Sponsor states (p 6) that no cases of misuse, diversion, or overdose with Austedo occurred in Studies SD-809-C-18, SD-809-C-23, and SD-809-C-20.

Data on Drug Accountability was requested, but not received.
The Sponsor provided only his evaluation of drug accountability as measure of compliance however the number of tablets missing or otherwise not accounted for was not provided.

**3. Adverse events related to drug dependence and withdrawal**

Post-treatment AEs were monitored for all patients including those who terminated early. The post-treatment safety follow-up period was 1 week for all patients plus an additional 3 weeks for those patients who did not enter the open-label study.

The Sponsor states that in the Studies # SD-809-C-18 and # SD-809-C-23, patients, who rolled into Study # SD-809-C-20 had follow-up of one week, whereas the patients who did not start the Study # SD-809-C-20 had an additional 3 weeks of withdrawal evaluation.

In the Study # SD-809-C-18 very few AEs were reported during the discontinuation period in the Austedo group (N=58), including headache 1 (1.7%), hyperaesthesia 1 (1.7%) and anxiety 1 (1.7%), vs “0” in placebo group.
In the Study # SD-809-C-23 there were also very few AEs reported during the discontinuation period in the Austedo group (N=221): abdominal pain 1 (0.5%), dry mouth 1 (0.5%) and asthenia 1 (0.5%), vs “0” in placebo group.

In the open-label Study # SD-809-C-20, at the time of the NDA submission, only 34 patients completed the study. The follow-up visit was after one week and telephone contact after 4 weeks from drug discontinuation. During the follow-up period in this very small population there were total of 18 AEs, 4 SAEs (and one leading to death (brain stem infarction), all of which occurred in five patients. However, a causal relationship to drug withdrawal can be attributed mainly to the AEs presented in the table 5 below based on Mod 2.7.4.6.7, p 97 and IR March 15 2017 (Ad Hoc Summary 15.27, p 33/80).

**Table 5. Adverse events during drug discontinuation based on Summary table 15.27 IR response, p 33/80.**

<table>
<thead>
<tr>
<th>Adverse Event PT</th>
<th>Austedo (N=34) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal AE</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

**Conclusions regarding dependence and withdrawal**

The available data was acquired for too short a period of time (1 week) in the majority of patients (who rolled over into the on-going Study # SD-809-C-20). There are also too few patients assessed for dependence and withdrawal to draw conclusions on the presence or absence of withdrawal syndrome.

After completion of the Study # SD-809-C-20 all dependence and withdrawal data should be submitted as a PMR. Furthermore, in the post-marketing time, abuse, dependence and withdrawal should be monitored and results submitted in post-marketing periodic reports.

1. **Evaluation of rebound after abrupt drug discontinuation**
In response to CSS IR March 15 2017 the sponsor provided results from a number of safety and efficacy measures which were obtained during the first week of the abrupt drug withdrawal. Unfortunately, some key measurements, such as Abnormal Involuntary Movement Scale (AIMS), Clinical Global Impression of Change, Patient Global Impression of Change, Craniocervical Dystonia Questionnaire, and the Montreal Cognitive Assessment were not performed during the follow-up period.

The Sponsor only obtained one week of follow-up measures for the following scales:

- Hospital Anxiety and Depression Scale (HADS), depression and anxiety subscales
- Epworth Sleepiness Scale (ESS)
- Unified Parkinson’s Disease Rating Scale - UPDRS Motor Assessment Total Score
- Barnes Akathisia Rating Scale (BARS)
- Columbia Suicide Severity Rating Scale (C-SSRS)

On all the above scales, after one week of drug discontinuation, rebound was not observed, except for the C-SSRS. One patient in Study # SD-809-C-23 reported suicidal ideation during follow up, although the patient already had a history of suicidal ideation.

**Conclusions**
The available data on rebound was acquired for too short a period of time to make any conclusions on the presence or absence of rebound. The key efficacy measurements such as Abnormal Involuntary Movement Scale (AIMS), Clinical Global Impression of Change and Patient Global Impression of Change, and Craniocervical Dystonia Questionnaire were not acquired during the discontinuation period. Also, as it appears with the example of rebound anxiety for benzodiazepines, after the first week of abrupt drug withdrawal the measures of anxiety (Hamilton Rating Scale for Anxiety, HAM-A) return to baseline however only in the next 2-3 weeks anxiety measures show rebound (Fountain and Chouinard, 1984). Therefore all scales should be used in general for at least 3 weeks, 4 weeks preferably (every week) during the discontinuation period to evaluate rebound. It is recommended that the sponsor provides measurements for the possible rebound for the above listed scales or at least AIMS for 3 weeks after the drug discontinuation in the on-going study # SD-809-C-20.

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

/s/

ALICJA LERNER
08/28/2017

SILVIA N CALDERON
08/28/2017

MARTIN S RUSINOWITZ
08/28/2017

DOMINIC CHIAPPERINO
08/29/2017
Memorandum

Date: August 3, 2017
To: Sarah Seung, Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, Team Leader, OPDP

Subject: NDA 209885
OPDP labeling comments for AUSTEDO™ (deutetrabenazine) tablets, for oral use (Austedo)

In response to DPP’s consult request dated July 20, 2017, OPDP has reviewed the draft carton/container labeling for Austedo downloaded on August 1, 2017, from the EDR link provided by Sarah Seung, and has no comments at this time.

If you have any questions, please feel free to contact me by phone at 301-796-6796 or by email at Christine.Bradshaw@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials.

Thank you!

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

CHRISTINE J BRADSHAW
08/03/2017
I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

FDA inspected three clinical investigator (CI) sites (Drs. Steven Macina, Michael McManus, Lili Meisamy), the sponsor, Teva Pharmaceutical Industries Ltd. (Teva), and the CRO for NDA 209885. The field investigator detected a subject who was ineligible for the study but was enrolled, randomized and treated in Protocol SD-809 C-18 at the site of Dr. Lili Meisamy (Site #151). Since only 5 subjects were randomized at Site #151 and the data created from this site impacted overall efficacy result of the study, OSI recommended that DPP perform the efficacy analysis without this subject. According to the statistician of this application, the study remained positive after exclusion of this subject. Other regulatory deviations did not appear to have impact on the overall efficacy and safety outcomes of the study. The data submitted by the sponsor in support of the pending application appear to be acceptable. Observations noted are based on the Form FDA 483 and email communications with field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of EIRs.

II. BACKGROUND

The sponsor Teva submitted this 505(b)(2) NDA 209885 seeking approval for SD-809 (Austedo, deutetarbenaerazin) oral tablets for the treatment of tardive dyskinesia (TD). FDA granted the breakthrough therapy status for this indication. On 05/05/2015, Teva acquired Auspex Pharmaceuticals, Inc., who originally owned and developed this product to investigate chorea associated with Huntington’s disease (IND 112975) and TD (IND 120631). FDA

Reference ID: 4124140
approved Austedo tablets on 04/03/2017 for the treatment of chorea associated with Huntington’s disease (NDA 208082).

Teva submitted two 12 week randomized, double-blind, placebo-controlled studies: Protocol SD-809-C-18 and Protocol SD-809-C-23 to support the indication of TD. Following are brief descriptions of these two studies.

**Protocol SD-809-C-18**

Study subjects: 117 subjects were randomized  
Study sites: 41 centers total; 29 in U.S., 7 in Poland, 3 in Slovakia, and 2 in the Czech Republic  

Study Period:  
Study Initiation Date:  
Study Completion Date: (b) (6)

This was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety, and tolerability of SD-809 for the treatment of subjects aged 18 and 75 years with TD. The study included a screening period, a 6-week titration period, a 6-week maintenance period, and a 1-week washout. Subjects were equally randomized to receive either SD-809 or placebo. Subjects underwent dose adjustment over the initial 6 weeks of treatment to identify a dose of study drug that controlled dyskinesias and was well tolerated followed by 6 weeks of maintenance therapy at that dose. The investigator, in consultation with the subject and caregiver (if required), determined when an adequate level of dyskinesia control had been achieved. The dose of SD-809 was to be increased on a weekly basis until there was either adequate control of dyskinesias, the subject experienced a protocol-defined clinically significant adverse event (defined as related to study drug and either [a] moderate or severe in severity or [b] meets the criteria for a serious adverse event), or the maximal allowable dose was reached. The maximum total daily dose of SD-809 was 48 mg/day unless the subject was receiving a strong CYP2D6 inhibitor, in which case the maximum daily dose of SD-809 was limited to 36 mg.

The primary endpoint was the change in total Abnormal Involuntary Movement Scale (AIMS) score (Items 1 through 7) from baseline to Week 12 as assessed by blinded video rating. The key secondary efficacy endpoint was the proportion of subjects who were a treatment success at Week 12 based on the Clinical Global Impression of Change (CGI-C).

According to the sponsor, SD-809 demonstrated statistically significant treatment effects in this population with TD compared with placebo on both the primary efficacy endpoint and the key secondary efficacy endpoint.

**Protocol SD-809-C-23**

Study subjects: 298 subjects were randomized  
Study sites: 75 centers total: 38 in U.S., 19 in Poland, 7 in Hungary, 6 in the Czech Republic, 3 in Slovakia, and 2 in Germany
This was a randomized, double-blind, placebo-controlled, fixed-dose, parallel group study designed to evaluate the efficacy, safety, and tolerability of SD-809 for the treatment of subjects aged 18 to 80 years with TD. The study included a screening period, a 4-week dose-escalation period, an 8-week maintenance period, and a 1-week washout period. Subjects were randomized equally into 4 treatment groups: 12 mg/day, 24 mg/day, 36 mg/day, or placebo. In the 4-week dose-escalation period, subjects underwent forced titration at weekly interval of 6 mg/day increments starting at 12 mg/day to reach their randomized dose (12, 24, or 36 mg/day), then they remained at their doses for 8 weeks (8-week maintenance period). During the maintenance dose period, a one-time dose reduction of 6 mg/day was permitted for subjects who experienced a clinically significant adverse event.

The primary endpoint was the change in total Abnormal Involuntary Movement Scale (AIMS) score (Items 1 through 7) from baseline to Week 12 as assessed by blinded video rating. The key secondary efficacy endpoint was the proportion of subjects who were a treatment success at Week 12 based on the Clinical Global Impression of Change (CGI-C).

According to the sponsor, SD-809 demonstrated statistically significant treatment effects in this population with TD compared with placebo on both the primary efficacy endpoint and the key secondary efficacy endpoint.

**Rationale for CI Site Selection**

a. Dr. Steven Macina has 7 INDs, and no prior CDER inspections, and high enrollment (40 subjects total in both studies)

b. Dr. Michael McManus has 41 INDs and had the following CDER inspections:
   i. 06-NOV-2008: VAI
   ii. 08-SEP-2014: NAI

c. Dr. Lili Meisamy has no INDs and had no prior CDER inspections according to the OSI database. This site was selected mainly because the data generated from this site impacted the overall efficacy result of Study SD-809-C-18. The overall efficacy result would not be statistically significant if data from this site were not included in the sensitivity analysis.

**Rationale for Sponsor Inspection:**

OSI decided to inspect the sponsor at the completion of two CI inspections which were classified as VAI by the field investigators to ensure the data submitted were acceptable.

The sponsor was not consistent in the archiving of the primary endpoint data AIMS scores. The field investigators at the sites of Dr. Steven Macina (Site #108) and Dr. Michael McManus (Site #110) reported that the AIMS scores assessed by blinded video rating were not available.
for review. However, the field investigator at the site of Dr. Lili Meisamy (Site #151) reported that videos were available on disc, and the AIMS scores were available in paper for review.

The sponsor did not appear to have adequately monitored CI sites. The field investigator at the site of Dr. Lili Meisamy (Site #151) detected that an ineligible subject was enrolled, randomized, and treated in Protocol SD-809 C-18. This subject met exclusion criteria #17 (use of illicit drugs at Screening) and #18 (history of substance abuse in the previous 12 months) per Protocol C-18. This subject was one of the five subjects randomized at this site. According to the statistician, the study remained positive without this subject.

**Rationale for the CRO Inspection:**
OSI determined to inspect the CRO at the completion of the three CI inspections because verification of the efficacy data, the primary endpoint, was necessary for the application approval. As noted, the primary endpoint data AIMS scores rated by the blinded central readers were not available for review at two CI sites. Upon FDA’s request, the sponsor confirmed that the AIMS scores assessed by blinded video rating are located and archived with CRO.

**III. RESULTS (by site):**

<table>
<thead>
<tr>
<th>Name of CI, Address, Site #</th>
<th>Protocol # and Subject #</th>
<th>Inspection Date</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steven Macina, D.O.</td>
<td>SD-809-C-18 10 randomized SD-809-C-23 30 randomized</td>
<td>03/15/2017 to 03/31/2017</td>
<td>NAI Preliminary</td>
</tr>
<tr>
<td>1020 S. Anaheim Boulevard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suite 316, Anaheim, CA 92805</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site #108 for both studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michael McManus, M.D.</td>
<td>SD-809-C-18 7 randomized SD-809-C-23 1 randomized</td>
<td>03/22/2017 to 03/24/2017</td>
<td>VAI</td>
</tr>
<tr>
<td>1550 Hotel Circle North</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suite 450, San Diego, CA 92108</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site #110 for both studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lili Meisamy, D.O.</td>
<td>SD-809-C-18 5 randomized</td>
<td>03/06/2017 to 03/10/2017</td>
<td>VAI Preliminary</td>
</tr>
<tr>
<td>200 W. Magnolia Suite 102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fort Worth, TX 76104 Site #110</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teva Pharmaceutical Industries Ltd. (Teva)</td>
<td>SD-809-C-18 SD-809-C-23</td>
<td>03/08/2017 to 03/12/2017</td>
<td>NAI</td>
</tr>
<tr>
<td>3333 North Torrey Pines Court</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>La Jolla, CA 92037</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bracket</td>
<td>SD-809-C-18 SD-809-C-23</td>
<td>6/21, 6/22, 6/27 to 6/29, and 7/6/2017</td>
<td>NAI Preliminary</td>
</tr>
<tr>
<td>575 East Swedesford Road</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suite 200, Wayne, PA 19087</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviations from regulations.
OAI = Significant deviations from regulations. Data unreliable

Preliminary = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Steven Macina, D.O.
This site participated in both the SD-809-C-18 and SD-809-C-23 studies. In the SD-809-C-18 study, 16 subjects were screened and 10 were enrolled and randomized. Two discontinued and 8 finished the study. A complete review of all 16 screened subject records for this study was conducted. In the SD-809-C-23, 63 subjects were screened and 30 were enrolled into the study. Eight subjects discontinued, one was lost to follow-up and 21 subjects finished the study. A complete review of 12 out of 30 enrolled subject records and 100% informed consent forms (all 63) was conducted for this study.

No significant regulatory violations were noted. The primary endpoint data were verified. There was no evidence of under-reporting of AEs.

This clinical site appeared to be in compliance with Good Clinical Practices, and the data generated by this site appear acceptable in support of the respective indication.

2. Michael McManus, M.D.
This site participated in both the SD-809-C-18 and SD-809-C-23 studies. In the SD-809-C-18 study, 7 subjects were screened and all were enrolled and randomized into the double-blind, placebo-controlled phase of the study. One subject was lost to follow up and 6 finished the study. In the SD-809-C-23, 4 subjects were screened and one was enrolled into the study (three were screen failures) and this subject finished the study. A complete review of all subject records for both studies was conducted.

A regulatory violation was detected: An investigation was not conducted in accordance with the signed statement of investigator investigational plan. Specifically, the clinical investigator failed to ensure that the subject met the inclusion criteria before the subject was enrolled and randomized into the study. Subject # was enrolled and received the investigational drug on and completed the study on . The subject did not have a serum hepatitis B surface antigen (HBsAg) test performed before the enrollment as required by the protocol.

There was no evidence of under-reporting of AEs. Although a regulatory violation was noted, the data integrity is unlikely to be impacted. The written response from the investigator was adequate. The data generated by this site may be used in support of the respective indication.
3. **Lili Meisamy, D.O.**
This site participated in both the SD-809-C-18 and SD-809-C-23 studies. In the SD-809-C-18 study, 7 subjects were screened. Five were enrolled, randomized and completed the study. A complete review of all five enrolled subject records for this study was conducted. In the SD-809-C-23, 14 subjects were screened. Six were enrolled, randomized and completed the study. A complete review of 6 enrolled subject records was conducted for this study.

The field investigator detected a regulatory violation at this site for Protocol SD-809-C-18: An investigation was not conducted in accordance with the signed statement of investigator investigational plan. Specifically,

1. Subject [(b)(6)] was enrolled and treated in Protocol SD-809-C-18 despite ineligibility due to exclusion criteria. Subject [(b)(6)] acknowledged present use of illicit drugs at Screening with intermittent marijuana use and amphetamine abuse without a start/stop date. The subject met exclusion criteria #17 and #18 per Protocol SD-809-C-18.

2. Subject [(b)(6)] who was on a QT prolongation concomitant drug did not have ECG performed at Visit Week 4 as required by the protocol. ECGs performed at other visits were normal according to the email communications with the field investigator.

According to the statistician, the study remained positive without Subject [(b)(6)]. Otherwise, the data generated by this site appear acceptable in support of the respective indication.

4. **Teva Pharmaceutical Industries Ltd.**
FDA inspected the monitoring files of eight sites: 7 in USA (Sites #104, #107, #108, #110, #123, #151, and #153) and one in Poland (Site #512). It appeared that the sponsor maintained adequate oversight of the clinical trial. The monitoring of CI sites appeared to be adequate. There was no evidence of under-reporting of SAEs. No significant regulatory violations were noted.

5. **CRO**
The FDA field investigator reviewed the following documents: contract and amendments, scope of services, SOPs/Data Processing Guidelines specific to the AIMS data in rater station and AIMS data extract, subject screening score summary sheets, AIMS site rater administration guide, site rater training certificates, and site rate power point slides from the investigator meeting, and Central Rater Manuel. The line listings from the assignment were compared to the source documents. An error was identified: The site rater scores for 7 subjects at the Screening Visit were displayed as “-1” after data extraction where the actual number was “0”. [(b)(4)] conducted root cause analyses and identified the error as a non-internet browser compatibility issue. The issue was resolved in the Rater Station Web 4.2.1. Since the error only affected data extraction of the Screening visit scores at...
the CRO site not CI sites, it did not affect either the eligibility of subjects or the final results and analyses. The primary endpoint data were verifiable. The regulatory deviation noted did not appear to impact the data acceptability.

{See appended electronic signature page}

Jenn W. Sellers, M.D., PhD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan Thompson, M.D. on behalf of
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA #209885
DPP/Division Director/Mitchell Mathis
DPP/Project Manager/Sarah Seung
DPP/Medical Officer/Anandraj Mattai
DPP/Clinical Team Leader Medical Officer/Jasmine Gatti
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters
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/s/

JENN W SELLERS
07/13/2017

SUSAN D THOMPSON
07/13/2017
MEMORANDUM
REVIEW OF LABELS AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 30, 2017
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 209885
Product Name and Strength: Austedo (deutetrabenazine) tablets
6 mg, 9 mg, and 12 mg
Applicant/Sponsor Name: Teva Branded Pharmaceutical Products R&D, Inc.
Submission Date: December 30, 2016 and May 1, 2017
OSE RCM #: 2017-162
DMEPA Primary Reviewer: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO
This review evaluates the proposed container labels and prescribing information (PI) for Austedo, NDA 209885, for areas of vulnerability that could lead to medication errors. The Division of Psychiatry Products (DPP) requested this review as part of their evaluation of the Austedo (deutetrabenazine) 505(b)(2) submission for the treatment of tardive dyskinesia. The referenced drug, Xenazine (tetrabenazine) NDA 021894, was approved on August 15, 2008 for the treatment of chorea associated with Huntington’s disease.

2 BACKGROUND
Deutetrabenazine for the treatment of tardive dyskinesia (TD) was developed under IND 120631 and was granted breakthrough therapy designation on November 3, 2015. On December 30, 2016, Teva Branded Pharmaceutical Products R&D, Inc. submitted NDA 209885 Austedo (deutetrabenazine) as a 505(b)(2) application for the treatment of tardive dyskinesia. On April 3, 2017, NDA 208082 Austedo (deutetrabenazine) was approved for the treatment of chorea associated with Huntington’s disease.
3 ASSESSMENT
We reviewed the proposed labels and labeling for Austedo tablets. The proposed Prescribing Information (PI) includes revisions that provide for the inclusion of information related to the treatment of tardive dyskinesia. We note that no changes are proposed for the presentation of the product name, strengths or route of administration. However, in the PI, we identified the following areas of concern:

- The Dosage and Administration section of Highlights of Prescribing Information (HPI) has a dosing chart in which numerical doses do not have a unit of measure specified. Our concern is that this may lead to medication dosing errors.

- The Dosage and Administration section of the Full Prescribing Information (FPI) has dosing information for the tardive dyskinesia indication that may be confusing. Clarifying the dosing information may help to reduce the risk of medication dosing errors.

Additionally, as part of our evaluation, we considered whether updates to the container labels are needed to ensure consistency with the proposed indication and labeling in order to minimize risk of confusion. The container labels for Austedo were previously reviewed under NDA 208082 (Huntington’s indication). Our current review did not identify any additional areas of needed improvement to the approved container labels.

We provide recommendations in Section 5, below, to provide clarity and help minimize the potential for medication errors to occur with the use of this product.

4 CONCLUSION
We identified areas of the Dosage and Administration section of Highlights of Prescribing Information and Full Prescribing Information of the PI that need clarification in order to help ensure the safe use of the product. We provide recommendations in Section 5, below, to address our concerns. We advise these recommendations are implemented prior to approval of this application.

5 RECOMMENDATIONS FOR THE DIVISION OF PSYCHIATRY PRODUCTS
We recommend the following be implemented prior to approval of this NDA:

A. Dosage and Administration, Highlights of Prescribing Information

1. In the dosage table, under the column titled “Recommended Dose”, the first dose in the dosage range lacks the “mg” unit of measure. The lack of a unit of measure for each numerical dose may cause confusion and contribute to dosing errors.
Therefore, please revise as follows:

<table>
<thead>
<tr>
<th>Original</th>
<th>Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg-48 mg/day</td>
<td>6 mg-48 mg/day</td>
</tr>
<tr>
<td>12 mg-48 mg/day</td>
<td>12 mg-48 mg/day</td>
</tr>
</tbody>
</table>

Reference ID: 4118971
B. Dosage and Administration Section of the Full Prescribing Information

The starting dose information for the tardive dyskinesia indication may be confusing because it states:

Revise the following sentence (area of concern is highlighted):

To read:

“When first prescribed to patients who are not being switched from tetrabenazine (a related VMAT2 inhibitor), the recommended starting dose of AUSTEDO is 6 mg administered orally once daily for patients with Huntington’s disease and 12 mg per day (6 mg twice daily) for patients with tardive dyskinesia.”
APPENDIX A. LABELING SUBMITTED ON MAY 1, 2017

Prescribing Information

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/s/

LORETTA HOLMES
06/30/2017

LOLITA G WHITE
07/05/2017
Memorandum

Date: June 28, 2017

To: Sarah Seung, Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, Team Leader, OPDP

Subject: NDA 209885/O-1
OPDP labeling comments for AUSTEDO™ (deutetrabenazine)
tables, for oral use (Austedo)

In response to DPP’s consult request dated January 26, 2017, OPDP has reviewed the draft product labeling (PI), Medication Guide (MG) and carton/container labeling for Austedo.

OPDP has reviewed the draft carton/container labeling for Austedo provided by Sarah Seung via email on June 26, 2017 and has no comments at this time.

OPDP’s comments on the draft PI for Austedo are based on the version of the PI provided by Sarah Seung via email on June 13, 2017. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Medication Guide will be provided to DPP under separate cover.

If you have any questions, please feel free to contact me by phone at 301-796-6796 or by email at Christine.Bradshaw@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials.

Thank you!
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/s/

CHRISTINE J BRADSHAW
06/28/2017
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date: June 27, 2017

To: Mitchell Mathis, MD
   Director
   Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
   Team Leader, Patient Labeling
   Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD, RAC
   Team Leader
   Office of Prescription Drug Promotion (OPDP)

From: Shawna Hutchins, MPH, BSN, RN
   Senior Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Christine Bradshaw, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): AUSTEDO (deutetrabenazine)
Dosage Form and Route: Tablets, for oral use
Application Type/Number: NDA 209885
Applicant: Teva Pharmaceuticals
1 INTRODUCTION

On January 19, 2017, Teva Pharmaceuticals re-submitted for the Agency’s review an original New Drug Application (NDA 209885) for AUSTEDO (deutetrabenazine) Tablets, for oral use, a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington’s disease and tardive dyskinesia. This NDA was originally submitted on December 30, 2016, under NDA 208082, however, the Agency advised the applicant to resubmit the application under NDA 209885.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on January 26, 2017, for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) for AUSTEDO (deutetrabenazine) Tablets, for oral use.

2 MATERIAL REVIEWED

- Draft AUSTEDO (deutetrabenazine) Tablets, for oral use MG received on January 19, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 13, 2017.
- Draft AUSTEDO (deutetrabenazine) Tablets, for oral use Prescribing Information (PI) received on January 19, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 13, 2017.
- Approved AUSTEDO (deutetrabenazine) Tablets, for oral use (NDA 208082), labeling dated April 03, 2017.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
• ensured that the MG is consistent with the approved labeling where applicable

4 CONCLUSIONS
The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
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/s/

SHAWNA L HUTCHINS  
06/27/2017

CHRISTINE J BRADSHAW  
06/27/2017

BARBARA A FULLER  
06/27/2017
Division of Pediatric and Maternal Health Review

Date: 5/30/2017  Date consulted: 1/31/2017

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Jane Liedtka, M.D., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatric Products (DPP)

Drug: AUSTEDO (deutetrabenazine)

NDA: NDA 209885

Applicant: Teva Branded Pharmaceutical Products R&D., Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of tardive dyskinesia

Materials Reviewed:
- Applicant’s submitted background package and proposed labeling for NDA 209885
- DPMH review of INGREZZA (valbenazine), NDA 209241, Tamara Johnson, M.D., M.S., March 6, 2017.

Consult Question: “Review of the FPI for PLLR compliance.”
INTRODUCTION
The Division of Psychiatric Products (DPP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy and lactation section of AUSTEDO (deutetrabenazine) tablets.

REGULATORY HISTORY
On January 11, 2017, Teva Branded Pharmaceutical Products R&D submitted a 505(b) (2) new drug application for AUSTEDO (deutetrabenazine), NDA 209885. AUSTEDO is a deuterated form of tetrabenazine, a drug substance approved under the trade name, XENAZINE for the treatment of chorea associated with Huntington’s disease. XENAZINE (tetrabenazine) is a vesicular monoamine transporter 2 (VMAT) inhibitor.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 29, 2015</td>
<td>AUSTEDO (deutetrabenazine) submitted as NDA 208082 to the Division of Neurology Products (DNP) for the treatment of chorea associated with Huntington’s disease (HD).</td>
</tr>
<tr>
<td>May 27, 2016</td>
<td>NDA 208082 receives a Complete Response Letter.</td>
</tr>
<tr>
<td>October 3, 2016</td>
<td>The applicant resubmits NDA 208082 to DNP. The response is accepted as a Class 2 resubmission. The PDUFA goal date is April 3, 2017.</td>
</tr>
<tr>
<td>December 30, 2016</td>
<td>The applicant submits the tardive dyskinesia (TD) indication to the Division of Psychiatric Products (DPP) under the same NDA number (208082) as the HD indication.</td>
</tr>
<tr>
<td>January 4, 2017</td>
<td>The applicant is informed by FDA that the TD indication requires submission under a new application number. The PDUFA goal date is August 30, 2017.</td>
</tr>
<tr>
<td>January 11, 2017</td>
<td>Applicant resubmits TD application under NDA 209885.</td>
</tr>
<tr>
<td>April 3, 2017</td>
<td>AUSTEDO (NDA 208082) is approved for the indication treatment of chorea associated with Huntington’s disease.</td>
</tr>
</tbody>
</table>

The active ingredient of the applicant’s AUSTEDO (deutetrabenazine) is structurally related to the reference product, XENAZINE (tetrabenazine). Deutetrabenazine incorporates two trideuteromethoxy groups (-OCD$_3$) at the 9- and 10- positions, whereas the original tetrabenazine has two trihydromethoxy groups (-OCH$_3$) at the corresponding positions. The applicant’s product is supplied as 6 mg, 9 mg, or 12 mg tablets.
BACKGROUND

Drug Characteristics
Deutetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor and acts as a reversible depletor of monoamines, such as dopamine, serotonin, norepinephrine, and histamine, from nerve terminals. The precise mechanism by which deutetrabenazine reduces abnormal movements is unknown.

- Molecular weight – 323.46 Daltons
- Half-life of α-HTBZ and β-HTBZ (active metabolites of deutetrabenazine) is 9-10 hours
- % protein binding ranged from 82-85% (tetrabenazine); 60-68% (α-HTBZ) and 59-63% (β-HTBZ)
- Bioavailability – following oral administration absorption is > 80%, and is rapidly distributed in the brain, with highest binding in the striatum
- Serious adverse events from Phase 3 clinical trials include depression, suicidal ideation, Neuroleptic Malignant Syndrome (NMS), akathisia, and restlessness, sedation, somnolence, dysphagia and aspiration pneumonia.

Tardive Dyskinesia and Pregnancy
Tardive dyskinesia (TD) is a persistent, iatrogenic movement disorder associated with the chronic use of dopamine receptor-blocking agents. TD is most frequently characterized by oro-buccal-lingual stereotypy, but can progress to include chorea of the limbs and/or trunk. The incidence of TD varies among groups, with younger patients having an estimated one-year prevalence of 3-5%, and older patients (particularly postmenopausal women) reportedly having an incidence of as much as 30% after 1 year cumulative exposure to typical antipsychotics. 2 The pathophysiology of TD is poorly understood, but is thought to be the result of chronic blockade of D2 or possibly D3 receptors. Various treatments for TD have been proposed including ginkgo biloba, clonazepam, amantadine and dopamine-depleting drugs, such as tetrabenazine (used off-label). 3 Only one case was found in a literature search of pregnancy complicated by tardive dyskinesia. In this case a women with bipolar disorder developed tardive dyskinesia with exposure to risperidone. The TD was unresponsive to treatment with vitamin E, or clonazepam. The pregnancy resulted in the uncomplicated delivery of a healthy child. The TD improved after delivery (AIMS score decreased to 8 from 20), but had not completely resolved by six months postpartum. 4

Huntington’s disease and Pregnancy
Huntington’s disease is an inherited neurodegenerative disease characterized by progressive motor, cognitive, and psychiatric symptoms. It is associated with an unstable polymorphic

1 AUSTEDO proposed package insert
trinucleotide repeat (CAG) on the HD gene. The disease has a prevalence of 5-7/100,000 in the United States. The mean age of onset is 35-44 years, however 5-10% of cases are juvenile Huntington’s disease with an onset prior to age 21. Juvenile-onset HD has a more rapid disease progression compared to the adult-onset form. Because Huntington’s disease has a 50% risk of inheritance, many published studies focus on prenatal testing and decision-making. There are a few cases in the literature describing pregnancy and delivery in Huntington’s patients.

Table 1. Case Reports – Pregnancy in Huntington’s Disease Patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Parity</th>
<th>Huntington’s symptoms</th>
<th>Pregnancy Course</th>
<th>Medications</th>
<th>Delivery</th>
<th>Infant Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbot N and Soydemir F</td>
<td>Age 35</td>
<td>Chorea, personality change</td>
<td>Complicated by fall (related to chorea) and fractured humerus</td>
<td>venlafaxine</td>
<td>Spontaneous rupture of membranes (SRM), meconium, emergency Cesarean-section</td>
<td>&quot;normal Apgars&quot;</td>
</tr>
<tr>
<td>Hoskins KE, et al</td>
<td>Age 31/G2P1</td>
<td>Pregnancy #1- minimal HD symptoms</td>
<td>uncomplicated</td>
<td>not reported</td>
<td>Normal vaginal</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>Pregnancy #2 Wheel chair bound, impaired cognition, communication and swallowing</td>
<td>2nd pregnancy pregnancy - complicated by severe malnutrition, diabetes insipidus, pyelonephritis, and chorioamnionitis</td>
<td>paroxetine and clonazepam</td>
<td>Labor was induced at 33 weeks</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Draisci G, et al</td>
<td>Age 32/G2P1</td>
<td>Pregnancy #1- Minimal HD symptoms</td>
<td>First pregnancy - suspected placental abruption and preecampsia</td>
<td>not reported</td>
<td>Emergency Cesarean-section</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>Pregnancy #2 Chorea; mild dementia</td>
<td>2nd pregnancy uneventful</td>
<td>Planned Cesarean-section; unplanned high sensory (C6- C7) epidural block causing hypotension</td>
<td>not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Reviewer’s Table

Current State of the Labeling

AUSTEDO (deutetrabenazine) labeling was approved for the Huntington’s disease indication (NDA 208082) on April 3, 2017 and is in the PLLR format. The labeling contains a boxed warning for depression and suicidality.

- There is no boxed warning on embryofetotoxicity.
- There is a statement, “Based on animal data, may cause fetal harm.”
- Only non-clinical data are provided in the labeling.

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12 AUSTEDO labeling. Drugs@FDA.gov Accessed 4/4/2017
• There are no existing pregnancy testing/contraception recommendations, or drug-drug interactions with hormonal contraceptives.

Current labeling for Section 8.1 and 8.2 is as follows:

8.1 Pregnancy
Risk Summary
There are no adequate data on the developmental risk associated with the use of AUSTEDO in pregnant women. Administration of deutetrabenazine to rats during organogenesis produced no clear adverse effect on embryofetal development. However, administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

8.2 Lactation
Risk Summary
There are no data on the presence of deutetrabenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.
The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AUSTEDO and any potential adverse effects on the breastfed infant from AUSTEDO or from the underlying maternal condition.

Pregnancy and Lactation Labeling
On June 30, 2015, the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW
PREGNANCY
Nonclinical Experience
A dose-dependent increase in the incidence of seventh cervical rib occurred in fetuses of pregnant rats given oral doses of 5, 10, or 30 mg/kg/day BID deutetrabenazine or 30mg/kg/day

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14 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).
BID tetrabenazine throughout the period of organogenesis. The lowest dose of deutetrabenazine was similar to the maximum recommended human dose [MRHD] of 48 mg/day AUSTEDO on an mg/m² basis. Deutetrabenazine has not been assessed in embryo-fetal developmental studies in pregnant rabbits. Deutetrabenazine has not been assessed in a pre- and postnatal developmental study. When tetrabenazine was administered to pregnant rats from the beginning of organogenesis to lactation an increase in stillbirths and postnatal mortality was observed at 15 and 30 mg/kg/day, and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD for tetrabenazine on a mg/m² basis.

The reader is referred to the full Pharmacology/Toxicology review by Amy Avila, Ph.D.

**Applicant’s Review of Literature**
The applicant did not provide a review of the literature.

**DPMH’s Review of Literature**

Tetrabenazine is referenced in Reprotox which states, “Based on experimental animal data, therapy with tetrabenazine is not expected to increase the risk of congenital malformations, although offspring viability was decreased in rats. We did not locate human studies.”

TERIS states, “No epidemiological studies of congenital anomalies among infants born to women who were treated with tetrabenazine during pregnancy have been reported. A normal infant was born to a woman who was treated with tetrabenazine between 24 and 35 weeks of pregnancy.”

A search of PubMed and Embase revealed one case report in the literature of a pregnancy exposure to tetrabenazine. It is the same case mentioned in the report by TERIS. This case describes a woman with lupus who developed severe chorea gravidarum at 23 weeks gestation. The movements caused an inability to eat or sleep, and were not responsive to diazepam. Treatment was initiated with tetrabenazine 25mg three times a day at 24 weeks gestation. The patient was maintained on tetrabenazine for eight weeks. Prednisone was added at 27 weeks gestation following the development of polyarthritis. Fetal growth was normal. A female infant was delivered at 36 weeks following spontaneous rupture of membranes. The infant had a small ventricular septal defect.

**Summary**
There are insufficient data on tetrabenazine, and no studies on deutetrabenazine in pregnant women to inform drug-associated risks.

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**LACTATION**

*Nonclinical Experience*

There are no non-clinical data on tetrabenazine or deutetrabenazine and lactation.

*Applicant’s Review of Literature*

The applicant did not provide a literature review.

*DPMH Review of the Literature*

DPMH conducted a search of *Medications in Mother’s Milk*, the Drugs and Lactation Database (LactMed), Micromedex, and of the published literature in PubMed and Embase using the search terms “tetrabenazine,” or “deutetrabenazine,” and “lactation,” and “breastfeeding.”

Tetrabenazine and deutetrabenazine are not referenced in *Medications in Mother’s Milk*, LactMed, or in the published literature.

Micromedex states for tetrabenazine, “Infant risk cannot be ruled out.”

Briggs states, “No reports describing the use of tetrabenazine during lactation have been located. The molecular weight of the parent compound (about 317), and the plasma protein binding and half-lives of the two metabolites suggest that at least the metabolites will be excreted into breast milk. The effect of this exposure on a nursing infant is unknown. However, common adverse effects observed in adults, such as sedation, somnolence, insomnia, depression, akathisia, and other toxicities, are potential complications.”

*Summary*

There are no studies tetrabenazine or deutetrabenazine in lactation to inform drug-associated risks. However, based on the molecular weight of deutetrabenazine, exposure of the breastfed infant to deutetrabenazine and its metabolites is possible. Tetrabenazine is widely distributed in the brain, and numerous neurological and psychiatric side effects are noted in the labeling. Effects on the developing brain and nervous system are unknown. Given the potential risk to the breastfed infant, breastfeeding is not recommended during treatment with AUSTEDO and for 60 hours (6 half-lives) after the last dose.

**FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

*Nonclinical Experience*

In a study conducted with tetrabenazine, no effects on mating and fertility indices or sperm parameters (motility, count, density) were observed in rats. In female rats, disrupted estrous cyclicity was observed.

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18 http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Applicant’s Review of Literature
The applicant did not provide a review of the literature

DPMH review of literature
DPMH performed a literature review of Embase and PubMed using the search terms, “tetrabenazine and fertility,” “tetrabenazine and sperm,” “tetrabenazine and reproductive endocrinology,” “tetrabenazine and hormonal contraceptives,” and “tetrabenazine and ovulation.”

No studies on tetrabenazine and fertility or hormonal contraceptive agents were found in the searches of the published literature.

Summary
There are no clinical studies to inform a drug-associated risk for fertility. Section 8.3 will not be included in the labeling.

CONCLUSIONS
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of AUSTEDO labeling were structured to be consistent with the PLLR, as follows:

• Pregnancy, Section 8.1
  ➢ The “Pregnancy” section of labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” sections.
• Lactation, Section 8.2
  ➢ The “Lactation” section of labeling was formatted in the PLLR format to include: “Risk Summary.”

LABELING RECOMMENDATIONS
DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 5/16/2017. DPMH recommendations are below and reflect the discussions with DPP. DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant’s proposed pregnancy and lactation labeling)

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
-----------------------------------------USE IN SPECIFIC POPULATIONS-----------------------------------------
• Pregnancy: May cause fetal harm (8.1)

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Administration of deutetrabenazine to rats during organogenesis produced no clear adverse effect on embryofetal development. However, administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
Oral administration of deutetrabenazine (5, 10, or 30 mg/kg/day) or tetrabenazine (30 mg/kg/day) to pregnant rats during organogenesis had no clear effect on embryofetal development. The highest dose tested was 6 times the maximum recommended human dose of 48mg/day, on a body surface area (mg/m\(^2\)) basis.

The effects of deutetrabenazine when administered during organogenesis to rabbits or during pregnancy and lactation to rats have not been assessed.

Tetrabenazine had no effects on embryofetal development when administered to pregnant rabbits during the period or organogenesis at oral doses of up to 60 mg/kg/day. When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirth and offspring postnatal mortality was observed at 15 and 30 mg/kg/day, and delayed pup maturation was observed at all doses.

8.2 Lactation
Risk Summary
There are no data on the presence of deutetrabenazine or its metabolites in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.

APPENDIX A – Applicant’s Proposed Pregnancy and Lactation Labeling
HIGHLIGHTS OF PRESCRIBING INFORMATION
--------------------------USE IN SPECIFIC POPULATIONS--------------------------

- Pregnancy: Based on animal data, tetrabenazine may cause fetal harm. (8.1)

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Animal Data

8.2 Lactation

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

/s/

Catherine A Roca
05/30/2017

Jane E Liedtka
05/31/2017

Lynne P Yao
06/02/2017
This memo responds to your consult to us dated 5/2/2017 regarding sponsor’s cardiac safety assessment for Austedo. The QT-IRT received and reviewed the following materials:

- Your consult;
- Prior QT-IRT review for Austedo under NDA 208082 (DARRTs 12/8/2015);
- Prior QT-IRT review for Austedo under IND 120631 (DARRTs 12/12/2016);
- Study SD-809-C-18 study report (NDA 209885, Seq 0001, Link);
- Study SD-809-C-23 study report (NDA 209885, Seq 0001, Link);
- Clinical Pharmacology Review for NDA 208082 (DARRTs 4/13/2016);
- Response to FDA communicated dated December 28th 2016 (IND 120631, Seq 0049, Link);
- Revised label for NDA 209885 (Seq 0001, Link); and
- SD-809 Cardiac Safety Assessment (NDA 208082, Seq 0009, Link).
QT-IRT Comments for DPP

**Question from Division:** DPP requests QT-IRT to review the Cardiac Safety Data provided in NDA 209885, SDN 9 (dated 5/1/17) and comment on the Applicant’s assertion that SD-809 has no clinically significant cardiac liability. Additional data derived from modeling as well as a report by an external cardiovascular endpoint expert were provided in support of this.

**QT-IRT’s response:**
We disagree that SD-809 has no significant cardiac liability.

- In the thorough QT study only single doses of 12 and 24 mg were evaluated and the study did therefore not cover therapeutic (up to 24 mg BID) or supratherapeutic (CYP2D6 poor metabolizers or concomitant use with a CYP2D6 inhibitor) concentrations. Moreover, concentration-dependent QTc prolongation was observed in the study.
- The concentration-QTc model developed based on the thorough QT study data is based on the sum of \( \alpha \)-HTBZ and \( \beta \)-HTBZ. An important assumption of this model is that the inhibition of hERG by \( \alpha \)-HTBZ and \( \beta \)-HTBZ is similar and no data have been submitted to justify this assumption. The importance of this assumption is further strengthened by the observation that the ratio of \( \alpha \)-HTBZ and \( \beta \)-HTBZ is changed in the presence of a CYP2D6 inhibitor.
- SD-809 when administered alone may not pose a significant cardiac liability; however, the risk of excessive QTc prolongation could occur when it is administered with a concomitant QT prolonging medication, with a CYP2D6 inhibitor or to patients who are CYP2D6 poor metabolizers. Administration of multiple drugs that prolong the QT interval to patients with underlying risk factors for torsade is of a concern with the use of SD-809.
  - In studies C-23 and C-20, there were 3 patients with QTc >500 ms and 6 patients with QTc >480 ms. No patient taking placebo had excessive QTc prolongation in study C-23. Patients with QTc prolongation were taking concomitant medications that are known to prolong the QTc interval. Furthermore, 4 patients were also taking CYP2D6 inhibitors that increase exposure to (\( \alpha + \beta \))-HTBZ. The percentage of patients with categorical QTc outliers may be under-reported because the timing of the ECGs relative to dosing was not controlled in the phase 3 trials.
  - No patients experienced torsade de pointes, but there were 6 patients in TD trials who died of cardiac events (1 each of sudden death and ventricular tachycardia).
- In our opinion, the package insert for SD-809 should have similar warnings for QT prolongation as those described in the package insert for tetrabenazine.

**BACKGROUND**

AUSTEDO™ (deutetrabenazine; SD-809; d6-tetrabenazine) is approved as treatment for chorea associated with Huntington’s disease and is under FDA review as treatment for tardive dyskinesia. Deutetrabenazine is a vesicular monoamine transporter type 2 inhibitor (VMAT2) with the same mechanism of action as tetrabenazine (TBZ, Xenazine®) and valbenazine (Ingrezza™).

A thorough QT study has been conducted for deutetrabenazine, which did not show significant QTc prolongation following administration of a single dose of 12 and 24 mg (maximum therapeutic dose is 24 mg BID) deutetrabenazine (DARRTs 12/8/2015). As a result the TQT
study did not include sufficiently high concentrations to rule out QT prolongation at therapeutic or supratherapeutic (CYP2D6 poor metabolizers or co-administration with a CYP2D6 inhibitor) concentrations.

In December of 2016 another consult for deutetrabenazine was submitted to the QT-IRT requesting comments on how to proceed with co-administration for deutetrabenazine and antipsychotics (DARRTs 12/12/2016). Based on the significant dose-dependent QTc relationship observed in the thorough QT study for deutetrabenazine the QT-IRT proposed excluding patients with increased risk at baseline (e.g., QTcF > 450 ms, history of torsade de pointes, congenital long-QT), not allowing concomitant use of CYP2D6 inhibitors or drugs with QTc prolongation potential. Moreover, as the studies permit co-administration of antipsychotics the QT-IRT proposed incorporating more intensive ECG monitoring and dose reduction or discontinuation strategies for patients with marked increases in QTc (>500 ms or change from baseline > 60 ms) as well as monitoring serum electrolytes.

These recommendations were sent to the sponsor on December 28th 2016, and the sponsor provided a response (February 9th 2017). In the response the sponsor stated that they did not consider there to be a causal relationship between QTc prolongation and deutetrabenazine, when used alone or concomitantly with an anti-psychotic. However, they agreed to incorporating additional ECG monitoring in patients who required an increase of their antipsychotic medication in an open-label study (SD-809-C-20) as well as being open to discuss the need for ECG monitoring in future studies. Similarly, the sponsor agreed to the other comments.

Now the sponsor is submitting a cardiac safety assessment, which includes a report by an external cardiovascular endpoint expert, which they note is in response to communication at the midcycle meeting. In addition, they are proposing labeling changes based on the cardiac safety assessment. This review will focus on the submitted cardiac safety assessment first, as well as provide comments on the QT related labeling edits.

**Cardiac Safety Assessment**
The Cardiac Safety Assessment concludes that deutetrabenazine causes a small increase in the QTc interval at the maximum recommended labeled dose that is not clinically significant, which they believe is supported by sparse ECG data from patient studies and review of the cardiovascular adverse events from patient studies for tardive dyskinesia (TD). The reviewer will address these three points separately below.

**Modeling and simulation based on thorough QT study**
As described in the summary, the sponsor conducted a thorough QTc study including 12 and 24 mg of deutetrabenazine, 50 mg tetrabenazine and 400 mg moxifloxacin. This study was reviewed by the QT-IRT, and the reviewer concluded that it was not possible to rule out QTc prolongation as the highest dose studied did not cover therapeutic concentrations and the data collected showed a concentration-dependent QTc prolongation. Based on this data the sponsor developed a concentration-QTc model to predict the QTc prolongation with the maximum recommended dosing:

The risk of QT prolongation with maximum recommended dosing was determined from the patient studies. Individual maximal exposures (ie, Cmax) to the active circulating metabolites (total [α+β]-HTBZ) for pivotal study subjects with HD or TD were determined at steady state, normalized to the maximum recommended dose based on their CYP2D6 status, and then entered
 Plasma concentrations of total (α+β)-HTBZ obtained from the Phase 3 studies in subjects with TD and HD were incorporated into population pharmacokinetic models to generate predicted Cmax values. Sufficient PK sampling to characterize Cmax was obtained in the TD titration study (Study SD-809-C-18 [C-18]) and the HD studies (Studies SD-809-C-15 [C-15] and SD-809-C-16 [C-16] [Switch]). Maximal plasma concentrations from the TD fixed-dose study (SD-809-C-23 [C-23]) were not used as there was insufficient pharmacokinetic sampling to reliably estimate individual Cmax values.

In Studies C-15, C-16, and C-18, patients were titrated to an optimal dose, with a maximum dose of 48 mg/day. In all studies, plasma concentrations were obtained at steady state. TD subjects (n=46) had 2 plasma samples obtained in the absorption phase of total (α+β)-HTBZ and 2 plasma samples obtained predose representing trough concentrations. In Study C-15, HD subjects had 2 plasma samples obtained in the absorption phase of total (α+β)-HTBZ and one pre-dose or trough sample. In Study C-16, HD ARC-Switch subjects participating in the pharmacokinetic sub-study had 5 samples collected over 6 hours after dosing. Bayesian posteriori derived maximal plasma concentrations were obtained for each patient from a population pharmacokinetic model in subjects with TD (CP-16-11 in TD and SD-809-CLN-078 in HD). Each patient’s Cmax was then normalized to the maximal target dose based on CYP2D6 genotype and use of strong CYP2D6 inhibitors: 36 mg/day in CYP2D6 impaired patients and 48 mg/day in CYP2D6 unimpaired patients. Subsequently, peak concentration data from all patients in HD and TD studies were pooled and incorporated into the regression model characterizing the concentration-QTc relationship established in the TQT study (C-21) to derive the predicted placebo-adjusted change from baseline in QTcF and corresponding 90% 2-sided CIs. Results of the analysis are depicted in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>TD/HD patients (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximal recommended dose (mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Cmax at steady state (µg/mL)</td>
<td>103.9</td>
</tr>
<tr>
<td>Predicted placebo-adjusted change from baseline in QTcF (msec)</td>
<td>2.4</td>
</tr>
<tr>
<td>90% 2-sided CI</td>
<td>2.2, 9.5</td>
</tr>
</tbody>
</table>

* Includes poor metabolizers or patients receiving a strong CYP2D6 inhibitor
† Individual ΔQTcF predictions were calculated using the point estimate parameters of the regression model describing the relationship between Cmax and ΔQTcF developed using data from Study C-21.
‡ The 90th percentile of the individually-predicted ΔQTcF were used to estimate the 90th prediction interval.
§ Bilateral daily; CI=confidence interval; Cmax=maximum observed plasma concentration; HD=Huntington’s disease; QTcF=QT interval corrected for heart rate using Fridericia’s correction; TD=tau-dyskiniasia.

The sponsor is making a crucial assumption in their analysis, which is that α-HTBZ and β-HTBZ contribute equally to the QTc prolongation observed. The only in vitro information provided about α-HTBZ and β-HTBZ with regards to their activity on the hERG potassium channel is from an in vitro binding assay, which is not useful to support this assumption. The importance of the assumption of equal contribution is further emphasized by the observation that the ratio of α-HTBZ and β-HTBZ is not constant, which is exemplified by the greater increase in β-HTBZ compared to α-HTBZ in the presence of paroxetine (CYP2D6 inhibitor).
Central tendency and categorical outlier analysis

The sponsor included categorical outlier and central tendency analyses of QTc interval data from healthy volunteer studies without placebo and patient studies (TD and HD). The timing of ECG collection across the studies included are described in Table 1 (healthy volunteer studies) and Table 2 (patient studies). The lack of significant outliers in patient studies is not particularly informative because the timing of ECG collection relative to dose was not controlled.

A request for more intensive ECG collection, given the potential for co-administration with antipsychotics (DARRTs 12/16/2016) was communicated to the sponsor on December 28th 2016. However, at that point in time it could only be implemented in an open-label extension study (SD-809-C-20) and the sponsor proposed only to include it following dose increases of the antipsychotic medication (IND 120631, Seq 0049).

Overall, the outlier analysis in patients offers no information about the QTc magnitude and only few outliers were observed in the patient studies. In the placebo-controlled study C-23, 1 patient had QTc >500 ms and 3 patients had QTc >480 ms. In the open label extension study, 3 total patients (2%) had QTcF >480 ms at any postbaseline visit, and 2 total patients (1%) had QTcF >500 ms at any postbaseline visit.

The sponsor provided a narrative for each patient with QTc prolongation. These patients were treated with SD-890 and had concomitant QT prolonging and/or CYP2D6 medications. One patient in the open-label extension study died from a serious adverse event of ventricular tachycardia, but no other patients experienced a cardiac adverse event associated with QTc prolongation.

Patient 512-3026 (SD-809 12 mg/day) was a 66-year-old female who had ECG findings including prolonged QTcF. The patient’s QTcF was 494 ms at screening and 514 ms at baseline. At week 2, the patient’s QTcF was 506 ms. Subsequent QTcF values were all <500 ms. All of the patient’s ECG recordings had abnormal results and were clinically significant (prolonged QTcF interval). Relevant medical history included hypertension, cardiac failure, and cardiac pacemaker insertion. Relevant concomitant medications included ramipril and acetylsalicylic acid. No corresponding cardiac adverse event was reported. No action was taken with study drug as a result of the abnormal ECG findings, and the patient remained on 12 mg/day throughout the study.

Reviewer’s comment: According to Listing 16.2.8.15, concomitant medications also include haloperidol 2mg tid, a known QTc prolongation mediation and CYP2D6 inhibitor. A relationship between study drug and QTc prolongation cannot be excluded.

Patient 118-3007 (SD-809 12 mg/day) was a 51-year-old female who had ECG findings including prolonged QTcF. The patient’s QTcF was 486 ms at screening and 473 at baseline. No clinically significant ECG abnormalities were noted at weeks 2 and 4; the patient’s QTcF was 466 ms at week 2 and 457 ms at week 4. At weeks 8 and 12, ECG findings showed prolonged QTcF at 477 and 480 ms, respectively. Relevant medical history included hypertension. Relevant concomitant medication included losartan. The patient remained on 12 mg/day throughout the study.
event. No corresponding cardiac adverse event was reported. No action was taken with study drug as a result of the prolonged QTcF.

Reviewer’s comment: According to Listing 16.2.8.15, concomitant QT prolonging medications also include risperidone 3 mg bid and citalopram 20 mg qd, both drugs prolong the QTc interval and citalopram is an inhibitor of CYP2D6. A relationship between study drug and QTc prolongation cannot be excluded.

Patient 527-3001 (SD-809 36 mg/day) was a 61-year-old male who had ECG findings including prolonged QTcF. The patient’s QTcF from screening through week 2 could not be determined. At week 4, the patient’s ECG showed a nonspecific T-wave abnormality (potentially clinically significant), and QTcF was 424 ms. No QTcF was reported at week 8. At week 12, the patient’s ECG was a technically poor tracing that showed a QTcF interval of 487 ms (clinically insignificant). Relevant medical history included hypertension. Relevant concomitant medications included captopril. The patient was receiving 36 mg/day at week 4 and remained on 36 mg/day through week 12. No action was taken with study drug as a result of the abnormal ECG findings.

Reviewer’s comment: According to Listing 16.2.8.15, relevant concomitant medicaiton also include Fluansol depot 40 mg once monthly. Fluansol depot is an antipsychotic that is marketed outside of the U.S. Fluansol is known to prolong the QTc interval. A relationship between study drug and QTc prolongation cannot be excluded.

Patient 670 (SD-809 12 mg/day) was a 64-year-old female who had ECG findings including prolonged QTcF. The patient’s QTcF was 438 ms at screening and 459 ms at baseline. At week 4, the patient’s QTcF was 450 ms, and at week 12, the patient’s QTcF was 485 ms. No QTcF was reported for weeks 2 and 8. All of the patient’s ECGs were technically poor and had normal results, except for the result at week 12 (prolonged QTcF interval and left-axis deviation). Relevant medical history included hypertension, atrial fibrillation, and arrhythmia. Relevant concomitant medications included spironolactone, metoprolol, and amiodarone. No corresponding cardiac adverse event was reported. No action was taken with study drug as a result of the abnormal ECG findings, and the patient remained on 12 mg/day throughout the study.

Reviewer’s comment: According to Listing 16.2.8.15, concomitant medication also include tiapridal 100 mg bid and sertraline 100mg qd. Triapridal is an antipsychotic that is marketed outside of the US. Triapridal is known to prolong the QTc interval according to the German Summary of product characteristics, labelling and package leaflet. In addition to prolonging the QTc interval, amiodarone is a CYP2D6 inhibitor. Sertraline is also a CYP2D6 inhibitor. A relationship between study drug and QTc prolongation cannot be excluded.

Patient 250 (SD-809) is a 71-year-old female who received SD-809 in the SD-809-C-18 parent study and had ECG findings including prolonged corrected QT interval using Friederica’s formula (QTcF). Relevant medical history included hypercholesterolemia. Relevant concomitant medication included simvastatin. The patient’s QTcF was 417 ms at baseline and 433 ms at week 2. An ECG at week 4 visit showed clinically significant abnormal results and a QTcF of 482 ms.

1 http://db.cbg-mecb.nl/mri/spc/nlh-0752-001.pdf
The prolonged QT was considered a nonserious adverse event on the same day. The patient was on 36 mg/day at the time of the event. At week 6, the patient’s QTcF was 430 ms, and the dose of study drug was 24 mg/day. On the same day, the adverse event of prolonged QT was considered resolved. The patient’s QTcF in the subsequent visits was 418 ms at week 28, 431 ms at week 41, and 434 ms at week 55. Beyond week 6, ECGs were assessed as normal except on week 41 (not clinically significant). No action was taken as a result of this event.

Reviewer’s comment: According to Listing 16.2.8.13, relevant concomitant medication also include sertraline 100 mg qd (CYP2D6 inhibitor) and aripiprazole 50 mg qd (QT prolongation). A relationship between study drug and QTc prolongation cannot be excluded.

Patient is a 55-year-old female who received SD-809 in the SD-809-C-18 parent study who had a history of chronic obstructive pulmonary disease, hypertensive heart disease, and abnormal ECG. In the parent study, the baseline ECG revealed left axis deviation (LAD), left bundle branch block (LBBB), and a QTcF of 473 ms. In the present study, the baseline ECG also revealed LAD, LBBB, and a QTcF of 457 ms. Relevant concomitant medications included aripiprazole, lisinopril, and atorvastatin. ECGs through week 6 had QTcF values ranging from 452 to 495 ms. At week 41, the QTcF was 524 ms while the patient was receiving 24 mg/day; there were no meaningful changes on the ECG. Serum potassium values at the time of this ECG were not available. Upon review of the patient’s ECG tracings, it was noted that the ECG at week 41 (and at week 28 and 8 days after week 41) was scanned and read manually (using 3 raw beats from lead II) in contrast to electronically transmitted ECGs, which use a median value from all 12 leads. The QTcF was 492 ms at ET, at which time the patient had been off study drug for 30 days. No action was taken with study drug as a result of the prolonged QTcF.

Reviewer’s comment: According to Listing 16.2.8.13, relevant concomitant medication also include duloxetine 60 mg qd (CYP2D6 inhibitor) in addition to aripiprazole 50 mg qd (QT prolongation). A relationship between study drug and QTc prolongation cannot be excluded.

Review of cardiovascular safety events

There does not appear to be an increased risk of non-serious CV events with SD-809 treatment in the Phase 3 TD studies (Table 6, Table 7). There were 6 patients who experienced CV-related deaths (Table 8). Although some of the patients who died were taking concomitant drugs that prolong the QT interval, none of the scheduled ECGs obtained prior to the adverse event showed QTc prolongation >480 ms, expect for Patient who was treated with sotalol and died from ventricular tachycardia.

Patient (SD-809 24 mg/day) was a 77 year old male with a history of schizophrenia, hypertension, chronic kidney disease and hypercholesterolemia who died suddenly at a nursing home on day 6 of study. At baseline, relevant concomitant medications included haloperidol, olanzapine, valsartan, amlodipine, HCTZ, and atorvastatin. ECGs at screening and baseline were normal with no conduction abnormalities. At baseline, QTcF was 427 msec and serum potassium and magnesium were normal. No autopsy was performed.

Reviewer’s comment: Patient was taking antipsychotic drugs that are known to cause QTc prolongation: haloperidol is a QT prolonging drug known to cause TdP and olanzapine has a
conditional risk for TdP. Haloperidol is also a CYP2D6 inhibitor. Therefore, a relationship between study drug and death cannot be excluded.

Patient (SD-809 36 mg/day) was a 67 year old female with history of bipolar disorder, hypertension, diabetes mellitus, hypercholesterolemia, family history of heart disease, and morbid obesity. At baseline, relevant concomitant medications included aripiprazole, atorvastatin, acetylsalicylic acid, metoprolol, insulin aspart, insulin lispro. The patient had been doing well at the Day 29 phone contact and the patient was found deceased on Study Day 38. The patient was taking SD-809 24 mg/day. ECGs at baseline, Weeks 2 and 4 were normal with QTcF values in the low 400s; at Week 4, the QTcF was 427 msec. Serum potassium and magnesium were normal at baseline. No autopsy was performed.

Reviewer’s comment: There is no evidence in the narrative that the patient experienced excessive QTc prolongation. Aripiprazole is a QT prolonging drug but does not have a risk of TdP when taken as recommended.

In the long-term safety study of C-20, there were 4 CV deaths. Patient (SD-809 30 mg/day) was a 73 year old male with tardive dyskinesia and a history of hypertension, coronary revascularization (LAD PCI and stent in type 2 diabetes, and dyslipidemia. Relevant concomitant medications at baseline were ticagrelor, acetylsalicylic acid, lovastatin, nicotinic acid, metformin, glipizide, insulin glargine, insulin lispro, fish oil, and apixaban. The patient was taking SD-809 30 mg/day at the time of the atrial fibrillation/flutter. Patient was treated with sotalol on Day 272 through Day 297, which may have led to a prolonged QTc. Per direction from the sponsor, the study drug was discontinued on day 293 due to unexplained QT prolongation. On Day 297, patient had symptomatic hypoglycemia (40 mg/dl) – he ate, felt better, went to bed and died in his sleep. ECGs in showed atrial fibrillation with a controlled ventricular responses; in , the ECG showed atrial flutter with slow ventricular response that led to pacemaker implant. Subsequent ECGs show paced rhythms.

Reviewer’s comment: SD-809 was discontinued 5 days prior to death. QTc prolongation could have been caused by the antiarrhythmic drug sotalol.

Patient (SD-809 12 mg/day) was a 71 year old woman with a history of schizoaffective disorder, remote history of TIA or stroke, hypothyroidism and morbid obesity with previous gastric bypass surgery. Concomitant medications of relevance included: fludrocortisone, vilazodone, thioridazine, citalopram and donepezil. The patient was found deceased at home, sitting on toilet on Day 243. The patient was taking SD-809 12 mg/day at the time of onset of the event. There is no other clinical information. Between study days 13 and 132, the QTcF ranged between 436-470 msec with sinus bradycardia and heart rates < 50 beats/minute. At Day 196, QTcF was 454 msec and serum potassium and magnesium were normal. Other ECGS in have rates in the low 60s. BP and pulse were normal during study, except for an episode of hypotension on day 109 (BP 84/60 mmHg) for which the patient was started on Florinef on Day 224 by the patient’s primary care physician. The conduction intervals are generally normal.

Reviewer’s comment: Both citalopram and thioridazine are QT prolonging drugs known to cause TdP. The patient experienced QTc prolongation >450 ms.

2 http://medicine.iupui.edu/clinpharm/ddis/main-table
Patient was a 75 year old female with schizoaffective disorder, hypertension, diet controlled type 2 DM, hyperlipidemia and prior stroke from uncontrolled hypertension. Relevant concomitant medications include losartan, haloperidol, risperidone and alprazolam. The patient was hospitalized on day 47 for generalized weakness and found to be dyspneic and hypertensive (180/100 mmHg). The patient was taking SD-809 48 mg/day at the time of the events. Following treatment for hypertension and heart failure, the patient was discharged on day 55. Subsequently, the patient worsened again (fatigue, weakness) and eventually was found deceased on day 85. No autopsy was performed. In the parent study C-23, the patient received 18 mg BID with no cardiovascular adverse events. At Baseline in C-23, QTcF was 395 and during treatment QTcF ranged from 399 to 417.

Reviewer’s comment: There is no evidence in the narrative that the patient experienced excessive QTc prolongation even though the patient was taking 3 QT prolonging medications: haloperidol, risperidone and alprazolam.

Patient was a 70-year-old female with a history of hypertension, type 2 DM and depression. Relevant concomitant medications at study entry included bisoprolol, furosemide, glimepiride, simvastatin and sertraline. QTcF values ranged between 422 and 450. Subsequent ECGs were normal and no adverse events were recorded at the time. The patient was admitted with hypoglycaemia (unknown value) and advanced heart failure was reported at that time as well. During the hospitalization, there was a sudden deterioration in the patient’s general condition with respiratory distress. Two days later the patient expired. The fatal adverse event was initially called pulmonary embolism but later changed to heart failure, without explanation by the site investigator. No autopsy was performed. Detailed information, including hospital records, is pending.

Reviewer’s comment: There is no evidence in the narrative that the patient experienced excessive QTc prolongation. Sertraline is a CYP2D6 inhibitor.

Proposed labeling changes
In addition, the sponsor also includes proposed labeling changes for deutetrabenazine based on the cardiac safety assessment. The proposed changes (red) have been included below followed by comments from the reviewer.

Section 5.7 QTc Prolongation
Tetrabenazine, a closely related VMAT2 inhibitor, causes an increase (about 8 msec) in the corrected QT (QTc) interval.

A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor [see Clinical Pharmacology (12.2, 12.3)].
Reviewer’s Comment: The removal of the “A clinically relevant QT prolongation...” paragraph is not supported by the provided safety assessment as there are cases of QTc prolongation exceeding 480 ms. In addition, we do not agree with the removal with the last paragraph and propose that the label include...

Section 7.6 Drugs that Cause QTc Prolongation

Tetrabenazine, a closely related VMAT2 inhibitor, causes a small increase in the corrected QT (QTc) interval. Clinically relevant QT prolongation may also occur with AUSTEDO [see Warnings and Precautions (b)(4), Clinical Pharmacology (12.2)].

...drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thiopental, ziprasidone), antibiotics (e.g., moxifloxacin), Class IA (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications...

Reviewer’s Comment: We do not agree with the removal of this paragraph.

Section 12.2 Pharmacodynamics Cardiac Electrophysiology

The effect of a single 12-mg or 24-mg dose of AUSTEDO on the QT interval was studied in a randomized, double-blind, placebo-controlled crossover study in healthy male and female subjects with moxifloxacin as a positive control. At 24 mg, AUSTEDO caused an approximately 4.5 msec mean increase in QTc (90% CI: 2.4, 6.5 msec). Effects at higher exposures to AUSTEDO or its metabolites have not been evaluated.

Reviewer’s Comment: As noted previously in the review, the predictions based on the provided exposure-response analysis are not appropriate and the reviewer proposes to reject the proposed change.
Thank you for requesting our input into the development of this product under NDA 209885. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov
Table 1: ECG monitoring in phase 1 studies without placebo. [Source: Cardiac Safety Assessment, Table 5, Page 14]

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design (exposure)</th>
<th>Population, N</th>
<th>Treatment</th>
<th>ECG time points after dosing (hours)</th>
<th>No. ECGs at time point</th>
<th>ECG data presented in this report</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS-SD-009-CTP-00</td>
<td>Open-label, crossover (single dose)</td>
<td>Healthy subjects N=21</td>
<td>SD-809 25 mg (powder in capsule) TBZ 25 mg (capsule)</td>
<td>BL, 1, 2, 24</td>
<td>Single</td>
<td>X</td>
</tr>
<tr>
<td>AUS-SD-009-CTP-07 Part 1</td>
<td>Open-label, formulation selection (single dose)</td>
<td>Healthy subjects N=25</td>
<td>SD-809 15 mg (fed/fasted) TBZ 25 mg (fasted)</td>
<td>BL, 2, 4, 6</td>
<td>Single</td>
<td>X</td>
</tr>
<tr>
<td>AUS-SD-009-CTP-07 Part 2</td>
<td>Open-label, single dose</td>
<td>Healthy subjects N=24</td>
<td>SD-809 7.5, 12, 22.5 mg TBZ 25 mg</td>
<td>SD-809: BL, 2, 4, 6, 7, 10 TBZ: BL, 1, 2, 3, 4, 5</td>
<td>Triple</td>
<td>X</td>
</tr>
<tr>
<td>SD-809-C-08</td>
<td>Open-label, drug interaction (single dose)</td>
<td>Healthy subjects N=24</td>
<td>SD-809 22.5 mg (days 1 and 11) Paroxetine 20 mg/day (days 4-12)</td>
<td>BL, 2, 3, 4, 5, 6, 7, 8, 10</td>
<td>Triple</td>
<td>X</td>
</tr>
</tbody>
</table>
| SD-809-C-11     | Open-label, 5-way crossover, relative bioavailability (single dose) | Healthy subjects N=32 | SD-809 6, 12, 18, 24 mg/day | BL, Day 4                    | Single                | --                               | -- 

Source: Study CTP-09 CSR Table 1; Study CTP-07 CSR Table 1, Table 2, Table 3; Study C-08 CSR Table 1; Study C-11 CSR Table 1; Study C-21 CSR Table 4

8 Outlier includes QTcF >450, ≥480 or ≤500 (ECGs); change from BL in QTcF ≥30, ≤60 (patients).

9 Titrated to target dose over 3-4 days; BID=twice daily; BL=baseline; ECG=electrocardiogram; ET=early termination; HD=Huntington’s disease; PK=pharmacokinetic; N=number of subjects; QTc=corrected QT interval; QTcF=Fridensia’s correction formula; TBZ=tetrazenazine; TD=taurolidine dyskinesia; TQF=thoroug QT

Table 2: ECG monitoring in patient studies with TD or HD. [Source: Cardiac Safety Assessment, Table 10, Page 20]

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design (exposure)</th>
<th>Population, N</th>
<th>Treatment</th>
<th>ECG time points at time point</th>
<th>No. ECGs at time point</th>
<th>ECG data presented in this report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled, double-blind</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SD-809-C-18 TD</td>
<td>Double-blind, flexible-dose, placebo-controlled, efficacy study (12 weeks)</td>
<td>N=147</td>
<td>SD-809: 38 Placebo: 59</td>
<td>BL, Weeks 2 and 12/ET; BL, Weeks 4, 6, and 9 for patients on drugs that prolong the QT interval</td>
<td>Single</td>
<td>X</td>
</tr>
<tr>
<td>SD-809-C-23 TD</td>
<td>Double-blind, placebo-controlled, fixed-dose, efficacy study (12 weeks)</td>
<td>N=221</td>
<td>SD-809: 211 Placebo: 72</td>
<td>BL, Weeks 2, 4, 8, and 12/ET</td>
<td>Single</td>
<td>X</td>
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<tr>
<td>SD-809-C-15 HD</td>
<td>Double-blind, placebo-controlled, efficacy study (12 weeks)</td>
<td>N=80</td>
<td>SD-809: 45 Placebo: 45</td>
<td>Weeks 2 for patients on CelaLexarpro Weeks 4, 6, and 9 (if dose of study drug increased since the last ECG)</td>
<td>Single</td>
<td>X</td>
</tr>
<tr>
<td>Open-label</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD-809-C-20 TD</td>
<td>Open-label, long-term, safety study ≥106 weeks (ongoing)</td>
<td>N=343</td>
<td>SD-809 at 12 to 48 mg/day</td>
<td>BL, Weeks 2, 4, 6, 28, 41, 34, and 106/ET</td>
<td>Single</td>
<td>X</td>
</tr>
<tr>
<td>SD-809-C-16 HD</td>
<td>Open-label, long-term, safety study ≥142 weeks (ongoing)</td>
<td>N=121</td>
<td>ARC-Rollover: SD-809 at 6 to 72 mg/day ARC-Switch: SD-809 at 6 to 72 mg/day</td>
<td>BL, Weeks 8 and at ET For patients on CelaLexarpro Required at Week 2 Performed on Week 4 if dose of study drug increased since the last ECG</td>
<td>Single</td>
<td>X</td>
</tr>
</tbody>
</table>

Source: Study C-15 CSR Table 2; Study C-16 CSR Table 2; Study C-18 CSR Table 1, Study C-20 CSR Table 1; Study C-23 CSR Table 2

8 Outlier includes QTcF >450, ≥480 or ≤500 (ECGs); change from BL in QTcF ≥30, ≤60 (patients).

9 Titrated to target dose over 3-4 days; BID=twice daily; BL=baseline; ECG=electrocardiogram; ET=early termination; HD=Huntington’s disease; PK=pharmacokinetic; N=number of subjects; QTc=corrected QT interval; QTcF=Fridensia’s correction formula; TBZ=tetrazenazine; TD=taurolidine dyskinesia; TQF=thoroug QT

Reference ID: 4101420
Table 6: Patients with Cardiovascular-Related Adverse Events Reported in Phase 3 Studies During the Treatment Period (Safety Population) [Source: Cardiac Safety Assessment, Table 12, Page 22]

<table>
<thead>
<tr>
<th>Percent</th>
<th>C-18 (R, DB)</th>
<th>C-23 (R, DB)</th>
<th>C-20 (OL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=59)</td>
<td>SD-809 12-48 mg (N=58)</td>
<td>Placebo (N=72)</td>
</tr>
<tr>
<td>Patients with CV AEs (all)</td>
<td>5 (8.5)</td>
<td>2 (3.4)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Patients with CV AEs having a fatal outcome</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with CV SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with only nonserious CV AEs</td>
<td>5 (8.5)</td>
<td>2 (3.4)</td>
<td>2 (2.8)</td>
</tr>
</tbody>
</table>

Source: C-18 : C-18 Ad Hoc Summary 2, C-18 Ad Hoc Summary 1; C-18 Ad Hoc Summary 8; C-23 Ad Hoc Summary 1; C-23 Ad Hoc Summary 3; C-23 Ad Hoc Summary 2; C-23 Ad Hoc Summary 9; C-20 Ad Hoc Summary 3; C-20 Ad Hoc Summary 5; C-20 Ad Hoc Summary 7; C-20 Ad Hoc Summary 10

* One additional patient died during the follow-up period.
AE=adverse event; CV=cardiovascular; OL=open-label; R, DB=randomized, double-blind; SAE=serious adverse event

Table 7: Patients with Nonserious Cardiovascular-Related Adverse Events Reported in Phase 3 Studies During the Overall Treatment Period (Safety Population). [Source: Cardiac Safety Assessment, Table 14, Page 26]

<table>
<thead>
<tr>
<th>SOC Preferred term, n (%)</th>
<th>C-18 (R, DB)</th>
<th>C-23 (R, DB)</th>
<th>C-20 (OL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=59)</td>
<td>SD-809 12-48 mg (N=58)</td>
<td>Placebo (N=72)</td>
</tr>
<tr>
<td>Patients with a nonserious CV AE</td>
<td>5 (8.5)</td>
<td>2 (3.4)</td>
<td>2 (2.8)</td>
</tr>
</tbody>
</table>

Cardiac Disorders
- Atrial fibrillation
- Cardiac failure congestive
- Palpitations
- Right ventricular failure
- Sinus tachycardia
- Tachycardia

Investigations
- ECG QT prolonged

Nervous system disorders
- Dizziness
- Presyncope
- Syncope

Source: Study C-18 Ad Hoc Summary 9, Study C-20 Ad Hoc Summary 7, Study C-23 Ad Hoc Summary 10
AE=adverse event; ECG=electrocardiogram; N=number of patients in the group; n=number of patients; SOC=System Organ Class; R, DB=randomized, double-blind
Table 8: Patients with CV Deaths in the Tardive Dyskinesia Program [Source: Cardiac Safety Assessment, Table 13, Page 22]

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Study</th>
<th>Adverse Event Reporter Term</th>
<th>Study Day</th>
<th>SD-809 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>169-3010</td>
<td>C-23 (R, DB)</td>
<td>Cardiopulmonary arrest</td>
<td>38</td>
<td>18 mg BID</td>
</tr>
<tr>
<td>554-3006</td>
<td>C-23 (R, DB)</td>
<td>Sudden cardiac death</td>
<td>6</td>
<td>6 mg BID</td>
</tr>
<tr>
<td>169-3001</td>
<td>C-20 (OL)</td>
<td>Ventricular tachycardia</td>
<td>298</td>
<td>Off drug</td>
</tr>
<tr>
<td>169-3008</td>
<td>C-20 (OL)</td>
<td>Cardiac arrest</td>
<td>242</td>
<td>6 mg BID</td>
</tr>
<tr>
<td>546-3007</td>
<td>C-20 (OL)</td>
<td>CV and respiratory insufficiency</td>
<td>85</td>
<td>24 mg BID</td>
</tr>
<tr>
<td>509-3002</td>
<td>C-20 (OL)</td>
<td>Heart Failure</td>
<td>549</td>
<td>21 mg BID</td>
</tr>
</tbody>
</table>

Source: Study C-20 Ad Hoc Listing 1; C-23 Ad Hoc Listing 1  
DB=double-blind; OL=open-label; PT=preferred term; R=randomized
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARS JOHANNESEN
05/22/2017

CHRISTINE E GARNETT
05/22/2017
**RPM FILING REVIEW**  
( Including Memo of Filing Meeting)  
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<thead>
<tr>
<th>Application Information</th>
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<tbody>
<tr>
<td>NDA # 209885</td>
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<tr>
<td>BLA#</td>
</tr>
<tr>
<td>NDA Supplement #: S-</td>
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<tr>
<td>BLA Supplement #: S-</td>
</tr>
<tr>
<td>Efficacy Supplement Category:</td>
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<tr>
<td>New Indication (SE1)</td>
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<tr>
<td>New Dosing Regimen (SE2)</td>
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<tr>
<td>New Route Of Administration (SE3)</td>
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<td>Comparative Efficacy Claim (SE4)</td>
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<tr>
<td>New Patient Population (SE5)</td>
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<tr>
<td>Rx To OTC Switch (SE6)</td>
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<tr>
<td>Accelerated Approval Confirmatory Study (SE7)</td>
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<tr>
<td>Labeling Change With Clinical Data (SE8)</td>
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<tr>
<td>Manufacturing Change With Clinical Data (SE9)</td>
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<tr>
<td>Animal Rule Confirmatory Study (SE10)</td>
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<tr>
<td>Proprietary Name: Austedo (proprietary name found acceptable under pending NDA 208082)</td>
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<tr>
<td>Established/Proper Name: Deutetrabenazine</td>
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<tr>
<td>Dosage Form: Tablets</td>
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<tr>
<td>Strengths: 6 mg, 9 mg, 12 mg</td>
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<tr>
<td>Route(s) of Administration: Oral</td>
</tr>
<tr>
<td>Applicant: Teva Branded Pharmaceutical Products R&amp;D, Inc.</td>
</tr>
<tr>
<td>Agent for Applicant (if applicable):</td>
</tr>
<tr>
<td>Date of Application: 12/30/16</td>
</tr>
<tr>
<td>Date of Receipt: 12/30/16</td>
</tr>
<tr>
<td>Date clock started after Unacceptable for Filing (UN):</td>
</tr>
<tr>
<td>PDUFA/BsUFA Goal Date: 8/30/17</td>
</tr>
<tr>
<td>Action Goal Date (if different):</td>
</tr>
<tr>
<td>Filing Date: 2/28/17</td>
</tr>
<tr>
<td>Date of Filing Meeting: 2/8/17</td>
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<tr>
<td>Chemical Classification (original NDAs only):</td>
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<tr>
<td>☒ Type 1- New Molecular Entity (NME); NME and New Combination</td>
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<tr>
<td>☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination</td>
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<tr>
<td>☐ Type 3- New Dosage Form; New Dosage Form and New Combination</td>
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<tr>
<td>☐ Type 4- New Combination</td>
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<tr>
<td>☐ Type 5- New Formulation or New Manufacturer</td>
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<td>☐ Type 7- Drug Already Marketed without Approved NDA</td>
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<td>☐ Type 8- Partial Rx to OTC Switch</td>
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<td>☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)</td>
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<tr>
<td>☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)</td>
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<tr>
<td>Proposed indication(s)/Proposed change(s): Treatment of tardive dyskinesia</td>
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Type of Original NDA:  
AND (if applicable)  
☐ 505(b)(1)  
☒ 505(b)(2)  
Type of NDA Supplement:  
☐ 505(b)(1)  
☐ 505(b)(2)  


Type of BLA:  
☐ 351(a)  
☐ 351(k)  

*If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team*
**Review Classification:**

*The application will be a priority review if:*

- A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)
- The product is a Qualified Infectious Disease Product (QIDP)
- A Tropical Disease Priority Review Voucher was submitted
- A Pediatric Rare Disease Priority Review Voucher was submitted

<table>
<thead>
<tr>
<th>Standard</th>
<th>Priority</th>
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<tr>
<td>Pediatric WR</td>
<td>QIDP</td>
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<tr>
<td>Tropical Disease Priority Review Voucher</td>
<td>Pediatric Rare Disease Priority Review Voucher</td>
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</table>

**Resubmission after withdrawal?** ☐ **Resubmission after refuse to file?** ☐

**Part 3 Combination Product?** ☐

*If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults*

<table>
<thead>
<tr>
<th>Convenience kit/Co-package</th>
<th>Pre-filled drug delivery device/system (syringe, patch, etc.)</th>
<th>Pre-filled biologic delivery device/system (syringe, patch, etc.)</th>
<th>Device coated/impregnated/combined with drug</th>
<th>Device coated/impregnated/combined with biologic</th>
<th>Separate products requiring cross-labeling</th>
<th>Drug/Biologic</th>
<th>Possible combination based on cross-labeling of separate products</th>
<th>Other (drug/device/biological product)</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>☐ Fast Track Designation</th>
<th>☒ Breakthrough Therapy Designation (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</th>
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<tr>
<td>☐ Rolling Review</td>
<td>☐ Orphan Designation</td>
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<tr>
<td>☐ Rx-to-OTC switch, Full</td>
<td>☐ Rx-to-OTC switch, Partial</td>
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<td>☐ Direct-to-OTC</td>
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**Other:**

**Collaborative Review Division (if OTC product):**

List referenced IND Number(s): IND 112975, IND 120631

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<th>Goal Dates/Product Names/Classification Properties</th>
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<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>PDUFA/BsUFA and Action Goal dates correct in the electronic archive?</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the established/proper and applicant names correct in electronic archive?</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PMC response**

| ☐ FDAAA [505(o)] | ☐ PREA deferred pediatric studies (FDCA Section 505B) | ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) | ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |

**PMR response:**

Reference ID: 4061285
<table>
<thead>
<tr>
<th><strong>Application Integrity Policy</strong></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)? <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">Check the AIP list at:</a></td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If yes, explain in comment column.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If affected by AIP, has OC been notified of the submission?</strong></td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>User Fees</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td>Fee paid 12/12/16</td>
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<tr>
<td><strong>User Fee Status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</td>
<td></td>
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</tr>
<tr>
<td>Payment for this application (check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☒ Paid</td>
<td>☐ Exempt (orphan, government)</td>
<td>☐ Waived (e.g., small business, public health)</td>
<td>☐ Not required</td>
<td></td>
</tr>
<tr>
<td><strong>User Fee Bundling Policy</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the user fee bundling policy been appropriately applied? If no, or you are not sure, consult the User Fee Staff:</td>
<td>☒ Yes</td>
<td>☐ No</td>
<td></td>
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</tr>
<tr>
<td><strong>505(b)(2) (NDAs/NDA Efficacy Supplements only)</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].

• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?

If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.

• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• IF FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

NDA 021894 Xenazine Patent
No unexpired patents
Submitted P1 certification
Exclusivity
ODE (expired 8/15/15)
| Exclusivity                                                                 | YES | NO | NA | Comment                                                                 |
|----------------------------------------------------------------------------|-----|----|----|------------------------------------------------|---|
| Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm | ☐   | ☑  | NA | Other products: Tetrabenazine & (R)-N-[2-(6-Chloro-methoxy-1H-indol-3yl)propyl]acetamide |
| If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? | ☐   | ☐  | ☑  |                                                                                   |
| If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy | ☐   | ☐  | ☑  |                                                                                   |
| NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? | ☑   | ☑  | ☑  |                                                                                   |
| If yes, # years requested: 5-years | ☑   | ☑  | ☑  |                                                                                   |
| Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. | ☑   | ☑  | ☑  |                                                                                   |
| NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? | ☐   | ☑  | ☑  |                                                                                   |
| If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? | ☐   | ☑  | ☑  |                                                                                   |
| If yes, contact the Orange Book Staff (CDER-Orange Book Staff). | ☑   | ☑  | ☑  |                                                                                   |
| BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? | ☑   | ☑  | ☑  |                                                                                   |
| If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager | ☑   | ☑  | ☑  |                                                                                   |
| Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. | ☑   | ☑  | ☑  |                                                                                   |
### Format and Content

**Do not check mixed submission if the only electronic component is the content of labeling (COL).**

- All paper (except for COL)
- All electronic
- Mixed (paper/electronic)
- CTD
- Non-CTD
- Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
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<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>If not, explain (e.g., waiver granted).</td>
<td>☐</td>
<td>☒</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>Index:</strong> Does the submission contain an accurate comprehensive index?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:

- legible
- English (or translated into English)
- pagination
- navigable hyperlinks (electronic submissions only)

If no, explain.

<table>
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<tr>
<th>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</th>
<th>YES</th>
<th>NO</th>
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<th>Comment</th>
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<td>☐</td>
<td>☐</td>
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### Forms and Certifications

*Electronic* forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, *paper* forms and certifications with hand-written signatures must be included.

**Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

<table>
<thead>
<tr>
<th>Application Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Patent Information (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td>☑️</td>
<td>☐</td>
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<table>
<thead>
<tr>
<th>Financial Disclosure</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
<td>☑️</td>
<td>☐</td>
<td></td>
<td>FDA 3454 and 3455 submitted</td>
</tr>
</tbody>
</table>

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*  
*Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

<table>
<thead>
<tr>
<th>Clinical Trials Database</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td>☑️</td>
<td>☐</td>
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</tr>
</tbody>
</table>

*If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”*  
*If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant*

<table>
<thead>
<tr>
<th>Debarment Certification</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
<td>☑️</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Certification is not required for supplements if submitted in the original application. If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*  
*Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”*

<table>
<thead>
<tr>
<th>Field Copy Certification (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
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<th>Comment</th>
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<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td>☐</td>
<td>☑️</td>
<td></td>
<td>Both electronic submission and no CMC technical section</td>
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</tbody>
</table>

*Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*  
*If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.*
<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td>CSS consult sent on 1/20/17.</td>
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</table>

*If yes, date consult sent to the Controlled Substance Staff:*

<table>
<thead>
<tr>
<th>Pediatrics</th>
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<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>PREA</td>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

*For non-NMEs: Date of consult sent to Controlled Substance Staff:*

| iPSP Written Response provided to sponsor on 2/9/17. |

*If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?*

| iPSP Written Response provided to sponsor on 2/9/17. |

*If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?*

| Full Waiver |

*If no, may be an RTF issue - contact DPMH for advice.*

| Full Waiver |

<table>
<thead>
<tr>
<th>BPCA:</th>
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<tbody>
<tr>
<td>Is this submission a complete response to a pediatric Written Request?</td>
</tr>
</tbody>
</table>

*If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)*

2 [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm)

3 [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm)

Reference ID: 4061285
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<tr>
<th>Proprietary Name</th>
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<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tr>
<td>Is a proposed proprietary name submitted?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</td>
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<tr>
<td>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</td>
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<table>
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<td>Check all types of labeling submitted.</td>
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<td>☐</td>
<td>☐</td>
<td>Package Insert (Prescribing Information)(PI)</td>
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<td>Patient Package Insert (PPI)</td>
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<td>Instructions for Use (IFU)</td>
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<td></td>
<td>Medication Guide (MedGuide)</td>
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<td>Carton labeling</td>
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<td>Immediate container labels</td>
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<td>Diluent labeling</td>
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<td>Other (specify)</td>
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<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Electronic Content of Labeling (COL) submitted in SPL format?</td>
<td>☑️</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If no, request applicant to submit SPL before the filing date.</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
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<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the PI submitted in Physician Labeling Rule (PLR) format?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</td>
<td>☑️</td>
<td>☐</td>
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<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLFR) format?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
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<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>For applications submitted on or after June 30, 2015: If PI not submitted in PLLFR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</td>
<td>☑️</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLLFR format before the filing date.</td>
<td>☑️</td>
<td>☐</td>
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</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Sent on 1/26/17</td>
</tr>
<tr>
<td>Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? <em>(send WORD version if available)</em></td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Sent to PLT on 1/26/17</td>
</tr>
<tr>
<td>Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Sent to DMEPA on 1/26/17 CMC assigned on 1/19/17</td>
</tr>
</tbody>
</table>

**OTC Labeling**

Check all types of labeling submitted.

- Outer carton label
- Immediate container label
- Blister card
- Blister backing label
- Consumer Information Leaflet (CIL)
- Physician sample
- Consumer sample
- Other (specify)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Is electronic content of labeling (COL) submitted?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><em>If no, request in 74-day letter.</em></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>Are annotated specifications submitted for all stock keeping units (SKUs)?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td><em>If no, request in 74-day letter.</em></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>If representative labeling is submitted, are all represented SKUs defined?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td><em>If no, request in 74-day letter.</em></td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>All labeling/packaging sent to OSE/DMEPA?</td>
<td>☐</td>
<td>☐</td>
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</tr>
</tbody>
</table>

**Other Consults**

Are additional consults needed? *(e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)*

*If yes, specify consult(s) and date(s) sent: DPMH 1/31/17*

**Meeting Minutes/SPAs**

End-of Phase 2 meeting(s)?

Date(s):

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?

Date(s): 11/3/16

Any Special Protocol Assessments (SPAs)?

Date(s):
DATE: 2/8/17

BACKGROUND: Deutetrabenazine is a new molecular entity (in the Program). Deutetrabenazine is a deuterium-substituted form of tetrabenazine. Tetrabenazine is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor. Deutetrabenazine is also submitted under NDA 208082 for Huntington's disease. NDA 209885 is a 505(b)(2) application seeking approval for the treatment of tardive dyskinesia (TD). Deutetrabenazine for TD was developed under IND 120631. Deutetrabenazine was granted breakthrough therapy designation (November 2015).

Upon advice given to the Sponsor during the Pre-NDA meeting, the Sponsor submitted deutetrabenazine for TD to NDA 208082 as an Original-2 on 12/30/16. However, the Sponsor had to resubmit as a separate NDA under 209885. The Sponsor can retain the original submission date.

- Stamp Date: 12/30/16
- Filing Date: 2/28/17
- Day 74 Letter Date: 3/14/17
- PDUFA Goal Date: 8/30/17

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Sarah Seung</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Steve Hardeman and Paul David</td>
<td>N</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Jasmine Gatti</td>
<td>N</td>
</tr>
<tr>
<td>Division Director/Deputy</td>
<td>Mitchell Mathis/Tiffany Farchione</td>
<td>Y/Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>Ellis Unger/Robert Temple</td>
<td>N/Y</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Anandraj Mattai</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Jasmine Gatti</td>
<td>N</td>
</tr>
<tr>
<td>Social Scientist Review (for OTC products)</td>
<td>Reviewer: NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL: NA</td>
<td></td>
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<tr>
<td>OTC Labeling Review (for OTC products)</td>
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<td>TL: NA</td>
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<td>Clinical Microbiology (for antimicrobial products)</td>
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<td>Section</td>
<td>TL:</td>
<td>Reviewer</td>
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<tr>
<td>Clinical Pharmacology</td>
<td>NA</td>
<td>Kofi Kumi</td>
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<td>Y</td>
<td>Hao Zhu</td>
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<td>Genomics</td>
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<td>Pharmacometrics</td>
<td>Y</td>
<td>Kevin Krudys/Gopichand Gottipati</td>
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<tr>
<td>Biostatistics</td>
<td>Y</td>
<td>Semhar Ogbagaber</td>
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<td></td>
<td>Y</td>
<td>Peiling Yang</td>
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<tr>
<td>Nonclinical Pharmacology/Toxicology</td>
<td>Y</td>
<td>Amy Avila</td>
</tr>
<tr>
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<td>Aisar Atrakchi</td>
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<td>Statistics (carcinogenicity)</td>
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<td>Product Quality (CMC) Review Team:</td>
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<td>ATL: David Claffey</td>
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<tr>
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<td>RBPM: Teshara Bouie</td>
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<td>Labeling (BLAs only)</td>
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<tr>
<td>Other (e.g., Branch Chiefs, EA</td>
<td>N</td>
<td>Wendy Wilson-Lee</td>
</tr>
<tr>
<td>Reviewer)</td>
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<tr>
<td>OMP/OMPI/DMPP (MedGuide, PPI, IFU)</td>
<td>Y</td>
<td>Shawna Hutchins</td>
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<tr>
<td>PLT</td>
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<td>Barbara Fuller</td>
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<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU,</td>
<td>Y</td>
<td>Christine Bradshaw</td>
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<tr>
<td>carton and immediate container</td>
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<td>Susannah O'Donnell</td>
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<td>labeling)</td>
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<td>OSE/DMEPA (proprietary name, carton</td>
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<td>Lolita White</td>
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<td>and/or container labeling)</td>
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<td>Loretta Holmes</td>
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<td>OSE/DRISK (REMS)</td>
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**OC/OSI/DSC/PMSB (REMS)**

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<tr>
<th>Reviewer</th>
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<tbody>
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<td>TL:</td>
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**Bioresearch Monitoring (OSI)**

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<tr>
<th>Reviewer</th>
<th>Jenn Sellers</th>
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<tr>
<td>TL:</td>
<td>Susan Thompson</td>
<td>N</td>
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**Controlled Substance Staff (CSS)**

<table>
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<tr>
<th>Reviewer</th>
<th>Alicja Lerner</th>
<th>Y</th>
</tr>
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<tbody>
<tr>
<td>TL:</td>
<td>Corinne Moody</td>
<td>Y</td>
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**Other reviewers/disciplines**

- **DPMH**
  | Reviewer   | Catherine Roca | Y |
  | TL:        | Miriam Dinatale | Miriam Dinatale |
  |            | Jane Liedtka    | Y |

**Other attendees**

| Kim Updegraff | Y |

*For additional lines, highlight this group of cells, copy, then paste: select “insert as new rows”

**FILING MEETING DISCUSSION:**

**GENERAL**

- **505(b)(2) filing issues:**
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?

Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):

Applicant provided a scientific bridge under pending NDA 208082. See 505(b)(2) assessment to be completed.

- Per reviewers, are all parts in English or English translation?
  - If **no**, explain:

- **Electronic Submission comments**
  - List comments: Not Applicable

Version: 12/05/2016
<table>
<thead>
<tr>
<th><strong>CLINICAL</strong></th>
<th></th>
</tr>
</thead>
</table>
| **Comments**: Need to send IR for dataset correction. | ☑ Not Applicable  
☒ FILE  
☐ REFUSE TO FILE |
| • Clinical study site(s) inspections(s) needed? | ☑ YES  
☐ NO |
| If no, explain: |  |
| • Advisory Committee Meeting needed? | ☑ YES  
☐ NO  
☐ To be determined |
| **Comments**: |  |

*If no, for an NME NDA or original BLA, include the reason. For example:*

- this drug/biologic is not the first in its class
- the clinical study design was acceptable
- the application did not raise significant safety or efficacy issues
- the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease

<table>
<thead>
<tr>
<th><strong>CONTROLLED SUBSTANCE STAFF</strong></th>
<th></th>
</tr>
</thead>
</table>
| • Abuse Liability/Potential | ☑ Not Applicable  
☒ FILE  
☐ REFUSE TO FILE |
| **Comments**: |  |
|  |  |

<table>
<thead>
<tr>
<th><strong>CLINICAL MICROBIOLOGY</strong></th>
<th></th>
</tr>
</thead>
</table>
| **Comments**: | ☑ Not Applicable  
☒ FILE  
☐ REFUSE TO FILE |
|  |  |

Review issues for 74-day letter
<table>
<thead>
<tr>
<th>Section</th>
<th>Comments</th>
<th>File/Refuse To File</th>
<th>Review Issues for 74-day Letter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL PHARMACOLOGY</strong></td>
<td></td>
<td>☑ Not Applicable</td>
<td>☑ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td>☑ FILE</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology study site(s) inspections(s) needed?</td>
<td>☑ YES</td>
<td>☑ NO</td>
<td></td>
</tr>
<tr>
<td><strong>BIOSTATISTICS</strong></td>
<td></td>
<td>☑ Not Applicable</td>
<td>☑ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td>☑ FILE</td>
<td></td>
</tr>
<tr>
<td><strong>NONCLINICAL</strong> (PHARMACOLOGY/TOXICOLOGY)</td>
<td></td>
<td>☑ Not Applicable</td>
<td>☑ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td>☑ FILE</td>
<td></td>
</tr>
<tr>
<td><strong>PRODUCT QUALITY (CMC)</strong></td>
<td></td>
<td>☑ Not Applicable</td>
<td>☑ Review issues for 74-day letter</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td>☑ FILE</td>
<td></td>
</tr>
<tr>
<td><strong>New Molecular Entity (NDAs only)</strong></td>
<td></td>
<td>☑ Not Applicable</td>
<td></td>
</tr>
<tr>
<td>• Is the product an NME?</td>
<td>☑ YES</td>
<td>☑ NO</td>
<td></td>
</tr>
<tr>
<td><strong>Environmental Assessment</strong></td>
<td></td>
<td>☑ Not Applicable</td>
<td></td>
</tr>
<tr>
<td>• Categorical exclusion for environmental assessment EA) requested?</td>
<td>☑ YES</td>
<td>☑ NO</td>
<td></td>
</tr>
<tr>
<td>If no, was a complete EA submitted?</td>
<td>☑ YES</td>
<td>☑ NO</td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facility Inspection</strong></td>
<td></td>
<td>☑ Not Applicable</td>
<td></td>
</tr>
<tr>
<td>• Establishment(s) ready for inspection?</td>
<td>☑ YES</td>
<td>☑ NO</td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility/Microbiology Review (BLAs only)</td>
<td>Comments:</td>
<td></td>
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<td>----------------------------------------</td>
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<tr>
<td>☒ Not Applicable</td>
<td>□ FILE</td>
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<tr>
<td>□ REFUSE TO FILE</td>
<td>□ Review issues for 74-day letter</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CMC Labeling Review (BLAs only)</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Review issues for 74-day letter</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</th>
<th>☐ N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</td>
<td>☐ YES</td>
</tr>
<tr>
<td>☒ NO</td>
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<tr>
<td>If so, were the late submission components all submitted within 30 days?</td>
<td>☐ YES</td>
</tr>
<tr>
<td>☒ NO</td>
<td></td>
</tr>
<tr>
<td>What late submission components, if any, arrived after 30 days?</td>
<td>none</td>
</tr>
<tr>
<td>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</td>
<td>☒ YES</td>
</tr>
<tr>
<td>☒ NO</td>
<td></td>
</tr>
<tr>
<td>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</td>
<td>☒ YES</td>
</tr>
<tr>
<td>☒ NO</td>
<td></td>
</tr>
<tr>
<td>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</td>
<td>☒ YES</td>
</tr>
<tr>
<td>☒ NO</td>
<td></td>
</tr>
</tbody>
</table>
REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis Unger, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 4/4/17

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

<table>
<thead>
<tr>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upcoming Meetings</td>
</tr>
<tr>
<td>Mid-Cycle Meeting</td>
</tr>
<tr>
<td>Internal pre-Meeting for Mid-Cycle Communication</td>
</tr>
<tr>
<td>Label Planning</td>
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<tr>
<td>Mid-Cycle Communication T-con with Applicant</td>
</tr>
<tr>
<td>Labeling Meetings</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Pre-Meeting for Late-Cycle Meeting</td>
</tr>
<tr>
<td>Late-Cycle Meeting with Applicant</td>
</tr>
<tr>
<td>Wrap-up Meeting</td>
</tr>
</tbody>
</table>

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☒ No review issues have been identified for the 74-day letter.
☐ Review issues have been identified for the 74-day letter.

Review Classification:

☐ Standard Review
☒ Priority Review

ACTION ITEMS

☐ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).

☐ If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐ If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<table>
<thead>
<tr>
<th></th>
<th>If priority review, notify applicant in writing by day 60 (see CST for choices)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Send review issues/no review issues by day 74</td>
</tr>
<tr>
<td></td>
<td>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</td>
</tr>
<tr>
<td></td>
<td>Update the PDUFA V DARRTS page (for applications in the Program)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

Annual review of template by OND ADRAs completed: April 2016
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
02/24/2017