

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208082Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208082	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Austedo Established/Proper Name: deutetrabenazine Dosage Form: Oral Tablets Strengths: 6 mg, 9 mg, and 12 mg		
Applicant: Teva Pharmaceuticals		
Date of Receipt: 10/3/16		
PDUFA Goal Date: 4/3/17		Action Goal Date (if different):
RPM: Stacy Metz, PharmD		
Proposed Indication(s): Treatment of chorea associated with Huntington's disease		

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.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 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.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Xenazine (tetrabenazine) tablets, 12.5 mg and 25 mg (NDA 21894)	Clinical studies information. Clinical Pharmacology information. Non-Clinical Toxicology information. Post-marketing data

- 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 literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The sponsor's reliance on FDA's finding of safety and effectiveness for Xenazine is for nonclinical chronic toxicity, carcinogenicity, and reproductive toxicology information, and some clinical pharmacology information referenced in the Xenazine label such as additional in vitro drug-drug interactions. The Sponsor was unable to obtain the listed drug, Xenazine, to complete BA/BE studies that directly compared SD-809 to Xenazine. The Sponsor's bridging strategy compared human PK data from patients enrolled in clinical study SD-809-C-16. Patients entered the study taking a stable dose of Xenazine. PK samples were drawn at baseline while they were on a stable dose of Xenazine on the day before switching to SD-809, and a second set of PK samples were drawn after switching patients to an equivalent, stable dose of SD-809 expected to be similar to their prior Xenazine dose. The C_{max} of the active α -HTBZ and β -HTBZ metabolites from SD-809 were below the C_{max} of the active metabolites from Xenazine. Additionally in this study, efficacy was evaluated using the Unified Huntington Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score. Patients who switched overnight from Xenazine to SD-809 experienced no loss in control of chorea compared to Xenazine, as assessed by the mean UHDRS TMC score, through Week 1.

The SD-809 NDA included additional clinical pharmacology information typically required for a 505(b)(1) NDA including a Mass Balance Recovery Study in healthy volunteers, in vitro and in vivo Drug-Drug interaction studies of SD-809 and several of its' metabolites.

RELIANCE ON PUBLISHED LITERATURE

¹For 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.

- 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 approval of the proposed drug product (i.e., 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 ☐

¹For 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.

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):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Xenazine (tetrabenazine) tablets, 12.5 mg and 25 mg	21894	Y

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 and potency.

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):

PATENT CERTIFICATION/STATEMENTS
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- 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 ☒ *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)

☒ 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)

Patent number(s):

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

Patent number(s):

Expiry date(s):

☐ 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)(ii): No relevant patents.
- ☐ 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 ☐

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/s/

STACY M METZ
03/31/2017

MEMORANDUM

REVIEW OF REVISED LABEL 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:	March 28, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208082
Product Name and Strength:	Austedo (deutetrabenazine) tablets 6 mg, 9 mg, 12 mg
Submission Date:	March 22, 2017
Applicant/Sponsor Name:	Teva Pharmaceuticals
OSE RCM #:	2016-2844-2
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Neurology Products requested that we review the container labels for Austedo (deutetrabenazine) tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The request is in response to the division's decision, since the completion of our previous label and labeling review^a, to require a Medication Guide (MG).

2 ASSESSMENT

On March 24, 2017, the division informed DMEPA that Austedo (deutetrabenazine) would be dispensed with a MG. We reviewed the container labels submitted on March 22, 2017 and note the container labels lack the medication guide statement required by 21 CFR 208.24(d).

3 CONCLUSION / RECOMMENDATIONS

The revised container labels are unacceptable from a medication error perspective. The product will be dispensed with a Medication Guide (MG); therefore, each container or package shall instruct the authorized dispenser to provide a MG to each patient and shall state how that MG is provided. We provide recommendations for Teva in Section 3.1.

^a Morris, C. Label and Labeling Review for Austedo (deutetrabenazine) (NDA 208082). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MARCH 16. 11 p. OSE RCM No.: 2016-2844

3.1 RECOMMENDATIONS FOR TEVA

We recommend the following be implemented prior to approval of this NDA 208082:

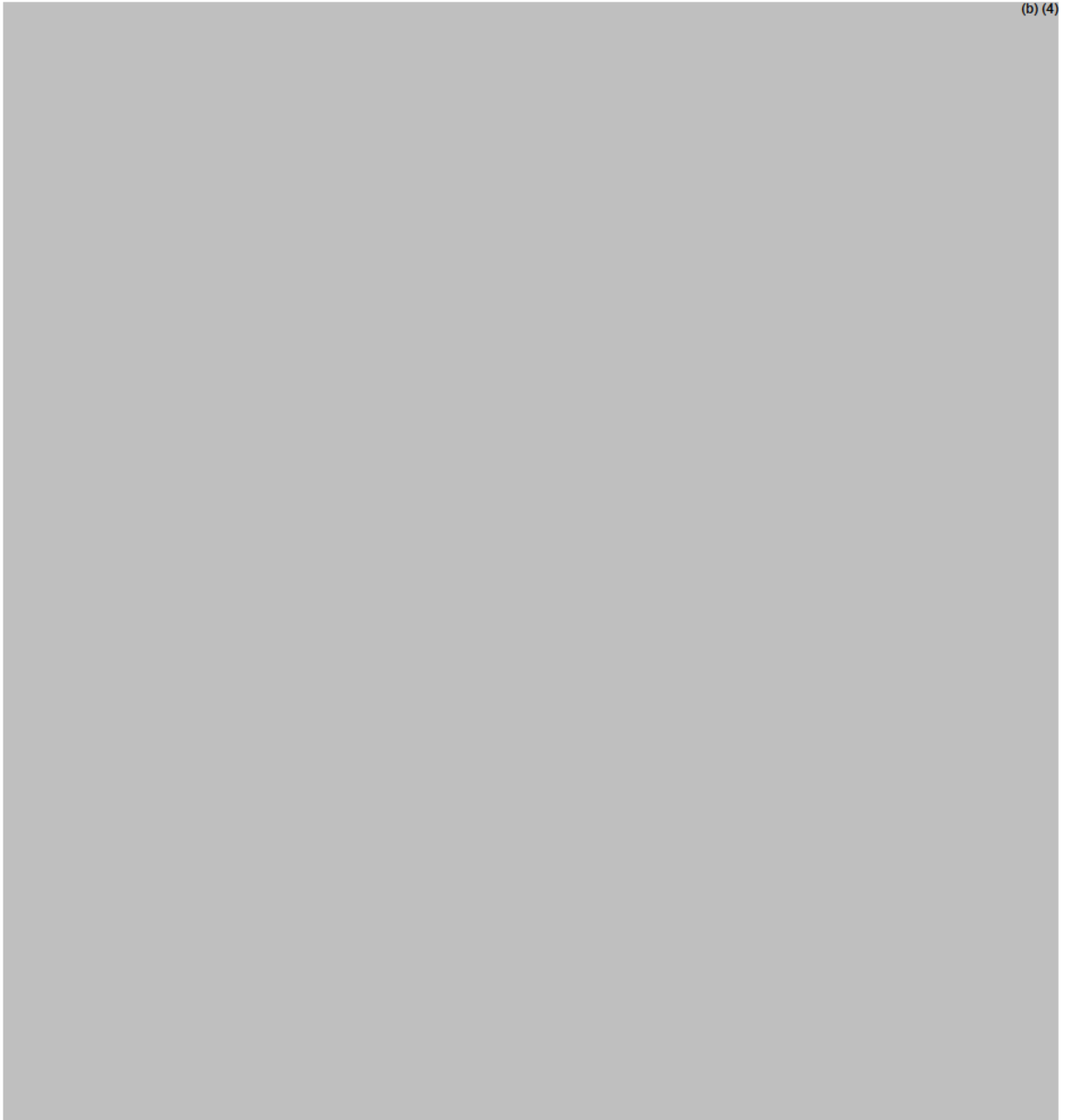
1. Your product will be dispensed with a Medication Guide (MG). Each container or package shall therefore instruct the authorized dispenser to provide a MG to each patient and shall state how that MG is provided. Add a statement similar to the statements copied below to the principle display panel of the carton labeling in accordance with 21 CFR 208.24(d).
 - a) “Attention Pharmacist: Dispense the enclosed Medication Guide to each patient.” or
 - b) “Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.”

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APPENDIX A.

CONTAINER LABELS SUBMITTED BY TEVA ON MARCH 22, 2017



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/s/

JOHN C MORRIS
03/28/2017

LOLITA G WHITE
03/28/2017



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 27, 2017

To: Billy Dunn, M.D., Director
Division of Neurology Products

From: Martin S. Rusinowitz, M.D., Senior Medical Officer
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: **NDA 208082**
Name: Austedo, (deutetrabenazine, SD-809, d6-tetrabenazine)
Indication: Chorea associated with Huntington's disease (HD)
Dosage: 6-mg, 9-mg, and 12-mg tablets
Proposed dosage range is 6 mg to 48 mg per day with a starting dose of 6 mg once daily and all doses above (b) (4) are administered in two divided doses
Sponsor: Auspex Pharmaceuticals (previous) / Teva Pharmaceuticals, Inc.(current)

Materials reviewed: NDA 20802 EDR May 29, 2014
CR letter May 27, 2016
CSS review by A. Lerner March 8, 2016 (in DARRTS)
Meeting Minutes Sep 20, 2016
Sponsor resubmission EDR Oct 3, 2016
Sponsor's request for clarification Dec 20, 2016

BACKGROUND

The Sponsor is developing Austedo (SD-809SD-809, deutetrabenazine; d6-tetrabenazine) as a treatment for chorea associated with HD, a neurodegenerative genetic autosomal dominant neuropsychiatric disorder characterized by progressive decline of motor and cognitive functions. Austedo is a vesicular monoamine transporter 2 (VMAT2) inhibitor which is structurally related to tetrabenazine.

This memorandum responds to a consult request from the Division of Neurology Products (DNP) to reply to the Sponsor's request for clarification (Dec 20, 2016, sequence 0030) of CSS's recommendations in DNP's CR letter (May 27, 2016) to evaluate dependence, withdrawal and rebound, after abrupt discontinuation of deutetrabenazine.

The Sponsor received a CR letter on May 27, 2016, after submission of a 505(b) (2) New Drug Application for Austedo (deutetrabenazine, SD-809), with Xenazine (NDA 021894, tetrabenazine) as the reference listed drug. In that letter CSS requested the Sponsor evaluate dependence, withdrawal and rebound at the conclusion of Study ARC-HD (SD-809-C-16). This request was a result of sparse clinical withdrawal data along with evidence of possible rebound in the first week follow-up after Study SD-809-C-15 First HD ended.

During a Type A meeting (Sep 20, 2016) the Sponsor had the following question for CSS:

Clarification Question for CSS:

Specifically, the team (at TEVA) would like further information on the statement highlighted in yellow below. We have investigated several of the scales listed in the CRL in First-HD and have not identified a rebound effect unique to SD-809. Any additional information that the review team could provide regarding the data assessed as suggesting a rebound effect would be of great assistance in assuring we can assess any effects correctly.

In the Meeting Minutes (dated October 18, 2016, Sequence 0029) CSS provided the following response:

The change in rating scales scores following withdrawal of study medication in study #SD-809-C-15 (First-HD) seems to indicate a possibility of the rebound, which was not captured in its entirety because the follow-up period after discontinuing study drug only lasted 1 week. It seems patients experienced rapid worsening of TMS, BARS, BBT and UPDRS dysarthria/speech question scores during the first week after drug discontinuation. This could indicate rebound and CSS recommended an extension of the follow-up period to clarify if the observed change in scores after discontinuation was indeed a rebound.

In response, the Sponsor provided their analyses of scales TMS, BARS, BBT and UPDRS dysarthria/speech demonstrating, in their opinion, there was no rebound during the one follow-up week. Additionally they proposed the following question to CSS:

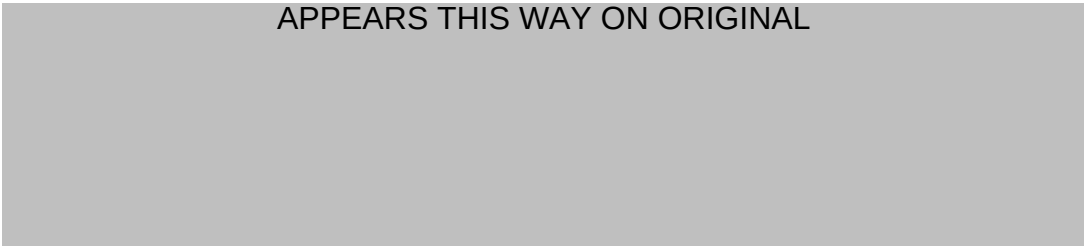
Question: Does FDA agree with Teva's definition of rebound and the resulting conclusions from the analysis from Study SD-809-C-15? If not, please provide further information on how FDA would define rebound in this data set.

Any further information FDA can provide regarding how to best define and therefore assess a possible rebound effect would be of great assistance. Teva would also be happy to schedule a brief teleconference to discuss this issue with FDA.

CSS RESPONSE

We understand and essentially agree with your definition of rebound and the resulting conclusions from the analysis from Study SD-809-C-15. Although there was re-emergence of many movements associated with HD, there were no other signs or symptoms reported which were associated with a withdrawal syndrome suggesting physical dependence. Thus, it appears deutetrabenazine does not produce physical dependence.

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/s/

MARTIN S RUSINOWITZ
03/27/2017

SILVIA N CALDERON
03/27/2017

MEMORANDUM

REVIEW OF REVISED LABEL 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:	March 23, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208082
Product Name and Strength:	Austedo (deutetrabenazine) tablets 6 mg, 9 mg, 12 mg
Submission Date:	March 22, 2017
Applicant/Sponsor Name:	Teva Pharmaceuticals
OSE RCM #:	2016-2844-1
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMO

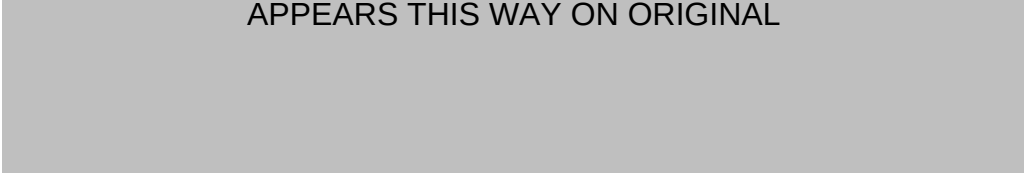
This memo presents our evaluation of the revised container labels for Austedo (deutetrabenazine) tablets (NDA 208082) to determine if the revised container labels are acceptable from a medication error perspective (See Appendix A for images of the revised container labels). The revisions are in response to recommendations made by the Office of Pharmaceutical Quality (OPQ) on February 28, 2017 and DMEPA during a previous label and labeling review^a OPQ requested Teva add the statement “protect from light and moisture” to the side panel of the container labels. DMEPA requested Teva to identify the format they intend to use to express the expiration date. To help minimize confusion, we recommended that Teva use a format similar to one of the following: MMMYYYY (for example, JAN2017) or MMMDDYYYY (for example, JAN012019). In an email dated March 20, 2017, Teva clarified their intention to use MM/YYYY as the expiration date format.

^a Morris, C. Label and Labeling Review for Austedo (deutetrabenazine) (NDA 208082). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MARCH 16. 11 p. OSE RCM No.: 2016-2844.

2 CONCLUSION

The revised container labels for Austedo (deutetrabenazine) are acceptable from a medication error perspective. We have no further recommendations at this time.

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APPENDIX A. REVISED CONTAINER LABELS FOR AUSTEDO SUBMITTED BY TEVA ON MARCH 22, 2017

Container labels

(b) (4)



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/s/

JOHN C MORRIS
03/23/2017

LOLITA G WHITE
03/23/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 23, 2017

To: Billy Dunn, MD, Director
Division of Neurology Products (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, DNP

Stacy Metz, PharmD, Senior Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: **NDA 208082**
OPDP labeling comments for AUSTEDO (deutetrabenazine) tablets, for oral use

In response to DNP's consult request dated October 31, 2016, OPDP has reviewed the proposed Package Insert (PI), Patient Package Insert (PPI), and carton and container labeling for Austedo.

PI: OPDP's comments are based on the substantially complete version of the draft PI received from DNP (Stacy Metz) on March 16, 2017, and are provided below.

PPI: The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the proposed PPI under a separate cover on March 23, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 22, 2017, and we do not have any comments.

If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments.

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

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/s/

ALINE M MOUKHTARA
03/23/2017

**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: March 23, 2017

To: William Dunn, MD
Director
Division of Neurology Products (DNP)

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

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

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Aline M. Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): AUSTEDO (deutetrabenazine)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 208082

Applicant: Teva Pharmaceuticals

1 INTRODUCTION

On May 29, 2015, Teva Pharmaceuticals submitted for the Agency's review a New Drug Application (NDA) for AUSTEO (deutetrabenazine) tablets, for oral use. On May 27, 2016, the Agency issued a Complete Response (CR) Letter. On October 3, 2016 the Applicant resubmitted the application which included data and documentation that responded to the deficiencies noted in the CR Letter. AUSTEDO (deutetrabenazine) tablets, for oral use are indicated for the treatment of chorea associated with Huntington's disease.

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 Neurology Products (DNP) on October 31, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for AUSTEDO (deutetrabenazine) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft AUSTEDO (deutetrabenazine) tablets, for oral use PPI received on October 3, 2016, and received by DMPP and OPDP on March 14, 2017.
- Draft AUSTEDO (deutetrabenazine) tablets, for oral use Prescribing Information (PI) received on October 3, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 14, 2017.
- Approved comparator labeling XENAZINE tablets, for oral use dated June 3, 2015.

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 APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labelings where applicable.

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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

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/s/

SHARON W WILLIAMS
03/23/2017

ALINE M MOUKHTARA
03/23/2017

MARCIA B WILLIAMS
03/23/2017

LASHAWN M GRIFFITHS
03/23/2017

LABEL AND LABELING REVIEW

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 16, 2017
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208082
Product Name and Strength:	Austedo (deutetrabenazine) tablets 6 mg, 9 mg, 12 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals
Submission Date:	October 3, 2016
OSE RCM #:	2016-2844
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

This review presents our evaluation of the proposed labels and labeling for Austedo (deutetrabenazine) tablets (NDA 208082) in response to a consult from DNP.

On October 3, 2016, Teva Pharmaceuticals submitted a Class 2 Resubmission of their 505(b)(2) NDA 208082 to the Agency for Austedo (deutetrabenazine) in support of the proposed indication of treatment of chorea associated with Huntington's disease. Teva previously received a Complete Response Letter on May 27, 2016 due to clinical pharmacology, toxicokinetic, and product quality issues.^a

1.1 PRODUCT INFORMATION

Austedo (deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. The proposed indication of Austedo is treatment of chorea associated with Huntington's disease. The marketing application is a 505(b)(2), referencing the Listed Drug Xenazine (NDA 021894) and Austedo is assigned Orphan Drug status.

The Sponsor proposes to supply Austedo as 6 mg, 9 mg, and 12 mg tablets for oral administration in bottles of sixty tablets. Austedo dosing should be individualized and titrated over several weeks to balance effectiveness of reducing chorea and tolerability. The starting and maximum recommended daily dose depends on previous Xenazine use status and metabolic pathway determinants, respectively (See Appendix A).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

^a Complete Response (CR) letter was issued on May 27, 2016.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container labels, Highlights of Prescribing Information (HPI), Full Prescribing Information (PI), and Patient Information for areas for improvement to decrease the risk for medication error. We identified the following five areas needing improvement:

1. The HPI and PI contain error prone abbreviations (b) (4) which may be misinterpreted and lead to medication error. In addition, these sections do not identify the route of administration.
2. Section 2 of the PI does not clearly communicate the maximum daily dose. We are concerned for wrong dose medication error, specifically overdose.
3. The PI is missing the degree symbol in section 16.2 which may lead to confusion and increase the risk of degraded drug medication errors.
4. The Patient Information contains storage information, which is inconsistent with the PI and container labels, which may increase the risk for degraded drug medication errors.
5. The sponsor did not define the format for the expiration date on the container label, which may increase the risk for degraded drug medication errors.

We provide our recommendations in Section 4.1 and 4.2 to minimize the risk for medication errors with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the container label, Highlights of Prescribing Information (HPI), Full Prescribing Information (PI), and Patient Information where improvements are needed to increase clarity, improve readability, and promote the safe use of Austedo. We provide our recommendations in Sections 4.1 and 4.2. We recommend Teva implement these improvements prior to approval of this application.

4.1 RECOMMENDATIONS FOR THE DIVISION

We recommend Teva implement the following prior to the approval of this NDA:

1. Highlights of Prescribing Information, Dosage and Administration Section
 - a. The starting dose statement is presented as (b) (4) Error
prone abbreviations can be misinterpreted and have been involved in harmful medication errors. Thus, we recommend you replace the error-prone abbreviation (b) (4) with (b) (4) "once daily. In addition, add the word "orally" to clarify the route of administration. Specifically, we recommend the statement is revised to read :
 - i. "6 mg per day, given as 6 mg orally once daily".
2. Full Prescribing Information, Section 2.2 (b) (4)
 - a. The starting dosing statement does not include the route of administration and may lead to medication error of wrong route. We recommend you add "administered orally" in the dosing statement so that it reads, "The starting dose should be 6 mg administered orally once

daily” to prevent this information from being overlooked and minimize the risk for wrong route errors.

- b. The table (See Appendix A, Table 2a.) in this section uses error-prone abbreviations (b) (4). Error prone abbreviations can be misinterpreted and have been involved in harmful medication errors. We recommend you replace the symbols (b) (4) in the Table with (b) (4) “once daily” and “twice daily” to prevent misinterpretation and confusion.
- c. As presented the maximum single dose is lacks clarity and may lead to medication error of overdose. Specifically, the statement (b) (4) (b) (4) (b) (4) should be revised to state “The dose should not exceed a recommended maximum daily dose of 48 mg (maximum single dose of 24 mg administered twice daily)”. We recommend the addition of the word “maximum” just prior to the word “single” to reinforce that this is the maximum single dose and to decrease risk of potential dosing errors.

3. Full Prescribing Information, Section 16.2 Storage

- a. The degree symbol (°) is missing following the 15 and 59 within the storage statement. The omission of this symbol may lead to confusion and medication error of degraded product. We recommend the degree symbol be added for clarity.

4. Patient Information, How Should I Store Austedo

- a. The storage statement, (b) (4), (b) (4) is not consistent with PI and container labels, which provides for Austedo to be stored at 25°C (77°F) with excursions permitted 15°C to 30°C (59°F to 86°F). The inconsistency in storage requirements poses risk for degraded drug medication errors. Additionally, there is a misplaced apostrophe in the temperature, which is currently presented as 77°F.
 - i. Ensure all storage statements are consistent across the container, PI, and Patient Information.
 - ii. Correct the misplaced apostrophe in 77°F.

4.2 RECOMMENDATIONS FOR TEVA PHARMACEUTICALS

We recommend Teva Pharmaceuticals implement the following recommendation prior to approval of this NDA:

1. Container Label

- a. The placeholder for the expiration date does not indicate the expiration date format that you intend to use, which poses a risk of degraded drug medication

error. Please identify the format you intend to use to express the expiration date. To help minimize confusion, we recommend that you use a format similar to one of the following: MMMYYYY (e.g. JAN2017) or MMMDDYYYY (for example, JAN012019).

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Austedo (deutetrabenazine) that Teva Pharmaceuticals submitted on October 3, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Austedo (deutetrabenazine) and the Listed Drug		
Product Name	Austedo (NDA 208082)	Xenazine (NDA 021894)
Initial Approval Date	N/A	08/15/2008
Active Ingredient	deutetrabenazine	tetrabenazine
Indication	Treatment of chorea associated with Huntington's disease	Treatment of chorea associated with Huntington's disease
Route of Administration	Oral	Oral
Dosage Form	Tablet	Tablet
Strength	6 mg, 9 mg, 12 mg	12.5 mg, 25 mg
Dose and Frequency	The starting dose should be 6 mg once daily and should be titrated up at weekly intervals by 6 mg per day, to allow the identification of a dose that reduces chorea and is tolerated. Daily doses of 12 mg and higher per day should be given in two divided doses. The dose should not exceed a recommended maximum daily dose of 48 mg (single dose of 24 mg administered twice daily). Patients who are switching from tetrabenazine should receive an initial dose as listed in Table 2a. <u>Dosing adjustments in Poor CYP2D6 Metabolizers and those taking CYP2D6 inhibitors</u> The maximum recommended dose should not exceed 36 mg per day	<u>Dosing Recommendations Up to 50 mg per day</u> The starting dose should be 12.5 mg per day given once in the morning and be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. If a dose of 37.5 to 50 mg per day is needed, it should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. <u>Dosing Recommendations Above 50 mg per day</u> The dose should be individualized accordingly to their status as PMs or EMs. <i>Extensive and Intermediate CYP2D6 Metabolizers</i> The dose should be titrated up slowly at weekly intervals

	(maximum single dose of 18 mg).	by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. <i>Poor CYP2D6 Metabolizers</i> The recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg. <u>Dosage Adjustments with CYP2D6 Inhibitors</u> <i>Strong CYP2D6 Inhibitors</i> The total dose should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg.
How Supplied	Bottles of 60 tablets 6 mg - NDC 68546-170-60 9 mg - NDC 68546-171-60 12 mg - NDC 68546-172-60	Bottles of 112 tablets 12.5 mg - NDC 67386-421-01 25 mg - NDC 67386-422-01
Storage	Store at 25° C (77° F); excursions permitted to 15-30°C (59-86° F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4) bottle (b) (4) (b) (4)	(b) (4) bottle (b) (4) (b) (4)

Table 2a presents the proposed dosing table from Section 2.2 Individualization of Dose in the Full Prescribing Information for Austedo (deutetrabenazine) that Teva Pharmaceuticals submitted on October 3, 2016

Table 2a.

Current tetrabenazine daily dose	Initial total daily dose of AUSTEDO	Initial regimen of AUSTEDO
12.5 mg	6 mg	6 mg (b) (4)
25 mg	12 mg	6 mg
37.5 mg	18 mg	9 mg
50 mg	24 mg	12 mg
62.5 mg	30 mg	15 mg
75 mg	36 mg	18 mg
87.5 mg	42 mg	21 mg
100 mg	48 mg	24 mg

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 27, 2017, we searched the L: drive and AIMS using the terms, Austedo and deutetrabenazine, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous label and labeling review^b. We provided recommendations to the Division for improvements to the PI and to the Sponsor for the container labels. We confirmed the Sponsor implemented our recommendations for the container labels provided in this resubmission.

APPEARS THIS WAY ON ORIGINAL

^b Myers, D. Label and Labeling Review for Austedo (deutetrabenazine) NDA 208082. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 10 30. RCM No.: 2015-1299.

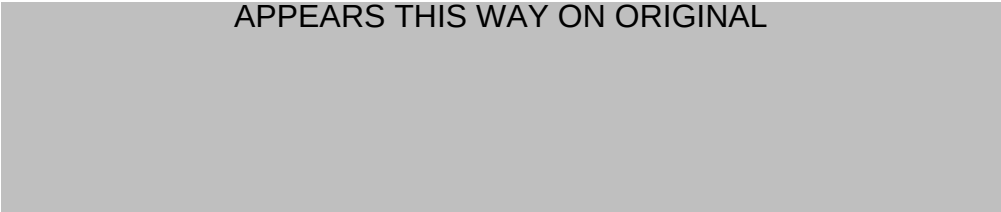
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Austedo (deutetrabenazine) labels and labeling submitted by Teva Pharmaceuticals on October 3, 2016.

- Container labels
- Prescribing Information (No image)
- Patient Information (No image)

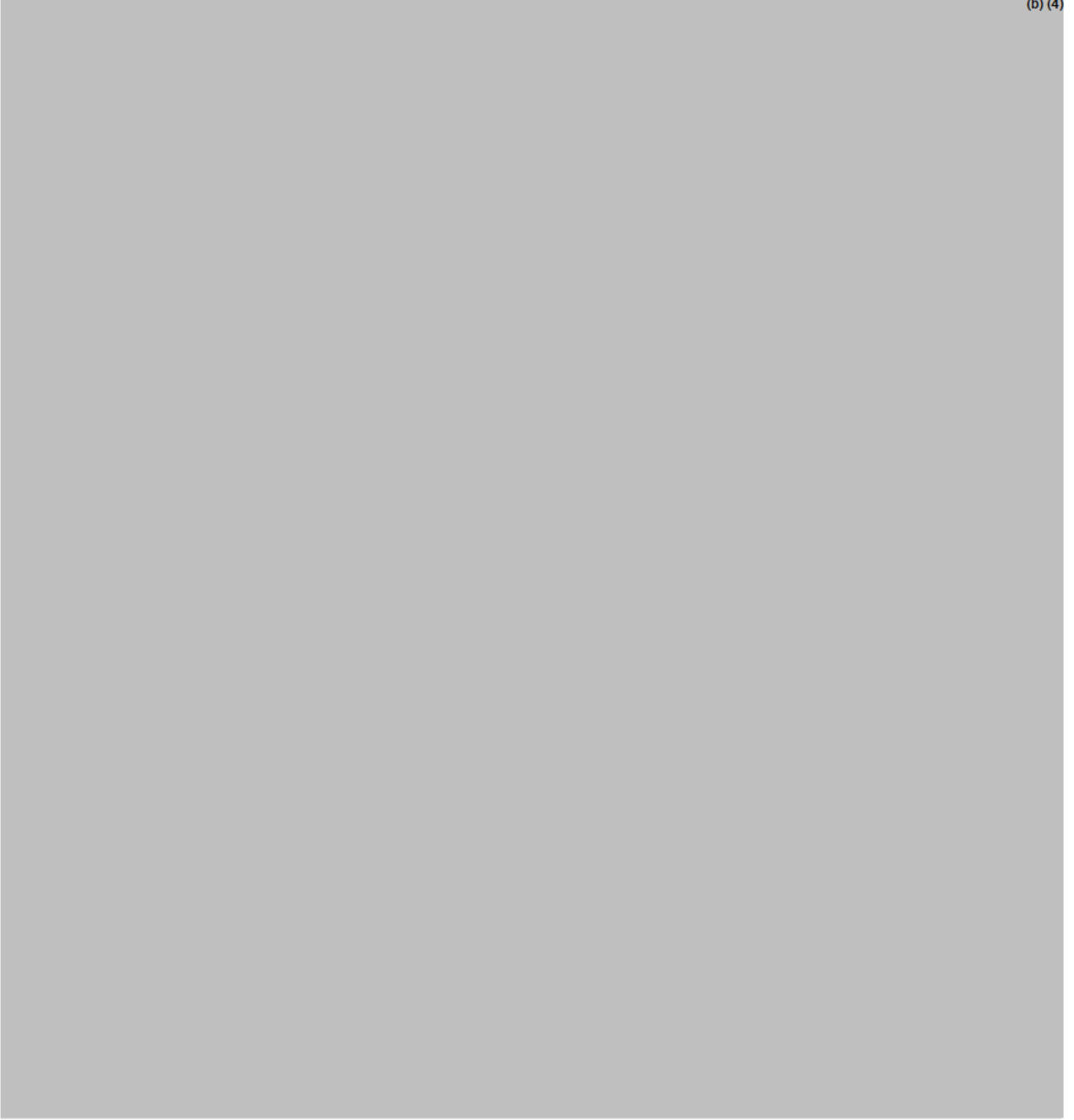
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^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

G.2 Label and Labeling Images

(b) (4)



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/s/

JOHN C MORRIS
03/16/2017

LOLITA G WHITE
03/16/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: July 12, 2016

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): AUSTEDO (deutetrabenazine)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 208082

Applicant: Teva Pharmaceuticals, Inc.

1 INTRODUCTION

On May 29, 2015 Teva Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) for AUSTEDO (deutetrabenazine) tablets, for oral use. The proposed indication is for the treatment of chorea associated with Huntington's disease.

On August 8, 2015 the Division of Neurology Products (DNP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for AUSTEDO (deutetrabenazine) tablets, for oral use.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for AUSTEDO (deutetrabenazine) tablets, for oral use.

2 CONCLUSIONS

Due to outstanding clinical pharmacology, nonclinical and product quality deficiencies, DNP has issued a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

NYEDRA W BOOKER
07/12/2016

MARCIA B WILLIAMS
07/12/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 6, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Stacy Metz, Regulatory Project Manager, DNP

Tracy Peters, Acting Associate Director for Labeling, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: Comments on draft labeling (PI), Patient Package Insert (PPI), and
Carton/Container Labeling for AUSTEDO (deutetrabenazine)
Tablets, for Oral Use

NDA: 208082

This memo is in response to the Division of Neurology Products (DNP) labeling consult request dated August 4, 2015. Reference is made to a Complete Response (CR) letter that was issued on May 27, 2016. Therefore, the Office of Prescription Drug Promotion (OPDP) defers comment on the Applicant's labeling at this time. Please send us a new consult request for review of the proposed labeling during subsequent review cycle when the application is otherwise adequate.

If you have any questions, please contact Aline Moukhtara (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
06/06/2016

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)]

Application Information		
NDA # 208082 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Austedo Established/Proper Name: Deutetrabenazine (SD-809) Dosage Form: Oral tablets Strengths: 6 mg, 9 mg, and 12 mg		
Applicant: Teva Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 5/29/15 Date of Receipt: 5/29/15 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 5/29/16		Action Goal Date (if different):
Filing Date: 7/28/16		Date of Filing Meeting: 7/17/16
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of chorea in patients with Huntington's disease.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: <i>The application will be a priority review if:</i> • 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	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR 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)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	☒	☐		

to the supporting IND(s) if not already entered into tracking system.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm If yes, explain in comment column.		☐	☒		
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☐ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>		☒	☐		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:																					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☒																		
• 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)]?		☐	☒																		
<i>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.</i>																					
• 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 border="1"> <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> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<i>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 will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																					
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	☐	☒																			
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)(13)]?	☐	☐	☒																		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☐	☐																		
If yes, # years requested:																					
Note: An applicant can receive exclusivity without requesting it;																					

<i>therefore, requesting exclusivity is not required.</i>				
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				
<i>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.</i>				

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?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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:	☒	☐		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	
If yes , BLA #				
Forms and Certifications				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>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].</i> <i>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...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☒	☐	☐	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	Consult to CSS 6/4/15
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☐	☒		

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☐	☐	☒	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☐	☐	☒	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
BPCA:				
Is this submission a complete response to a pediatric Written Request?	☐	☐		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i> ³				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	☒	☐		
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?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	☐	☐	☒	
Has a review of the available pregnancy and lactation data been included?	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☒	☐		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☒	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☒	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	QT-IRT 8/4/15
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☐		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/19/15	☒	☐		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	☐			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7/21/16

BACKGROUND:

NDA 208082
 Austedo™ (deutetrabenazine)
 Treatment of chorea associated with Huntington's disease
 Teva Pharmaceuticals
 Product developed under IND 112975
 Standard Review under the Program

Key PDUFA Goal Dates

Submission Receipt date: May 29, 2015
 Filing Meeting: July 17, 2015
 Day 60 letter: July 28, 2015
 Day 74: August 11, 2015
 Action Goal date: May 29, 2016

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacy Metz	y
	CPMS/TL:	Jackie Ware	n
Cross-Discipline Team Leader (CDTL)	Dave Podskalny		y
Division Director/Deputy	Billy Dunn/Eric Bastings		y
Office Director/Deputy	Ellis Unger		y
Clinical	Reviewer:	Ken Bergmann	y
	TL:	Dave Podskalny	y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	n/a	
	TL:	n/a	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	n/a	
	TL:	n/a	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	n/a	

	TL:	n/a	
Clinical Pharmacology	Reviewer:	Kristina Dimova	y
	TL:	Angela Men	y
• Genomics	Reviewer:	n/a	
• Pharmacometrics	Reviewer:	Xiaofeng Wang	
Biostatistics	Reviewer:	Xiangmin Zhang	y
	TL:	Kun Jin	y

APPEARS THIS WAY ON ORIGINAL

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Chris Toscano	y
	TL:	Lois Freed	y
Statistics (carcinogenicity)	Reviewer:	n/a	
	TL:	n/a	
Product Quality (CMC) Review Team:	ATL:	Martha Heimann	y
	RBPM:		
• Drug Substance	Reviewer:	Gene Holbert	
• Drug Product	Reviewer:	Sherita McLamore Hines	
• Process	Reviewer:	Masihuddin Jaigirdar Rakhi Shah	
• Microbiology	Reviewer:	Masihuddin Jaigirdar Rakhi Shah	
• Facility	Reviewer:	Donald Obenhuber	
• Biopharmaceutics	Reviewer:	Jing Li/Okpo Eradiri	y
• Immunogenicity	Reviewer:	n/a	
• Labeling (BLAs only)	Reviewer:	n/a	
• Other (e.g., Branch Chiefs, EA Reviewer)	Wendy Wilson-Lee		n
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Nyedra Booker	
	TL:	Melissa Hulett	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Aline Moukhtara	y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Deborah Myers	
	TL:	Danielle Harris	
OSE/DRISK (REMS)	Reviewer:	Jasmine Kumar	
	TL:	Jamie Wilkins Parker	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	
	TL:	n/a	

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	y
	TL:	Mike Klein	n
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

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):		☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO see 505(b)(2) assessment to be completed
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO	
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments	

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☐ YES ☒ NO ☒ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
<u>APPLICATIONS IN THE PROGRAM (PDUFA V)</u> <u>(NME NDAs/Original BLAs)</u> • 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? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	no late submission components
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ellis Unger Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 10/29/15 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ 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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

STACY M METZ
05/24/2016

M E M O R A N D U M

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

DATE: April 6, 2016

TO: Billy Dunn, M.D.
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspection of Quotient Clinical Limited, Nottingham,
UK, covering the following application:

NDA 208082 Deutetrabenazine, SD-809, sponsored by Teva
Pharmaceuticals, USA

Reviewer Recommendation:

This OSIS reviewer recommends that the results from clinical portion of Study (b)(4) 113049 (SD-809-C-12) should be accepted for further Agency review. Please note that the EIR review of the bioanalytical inspection at (b)(4) was finalized in DARRTS on 2/18/2016.

The inspection was conducted by ORA Investigator Lauren E. Swantko at Quotient Clinical Limited, from December 07 to December 11, 2015. The inspection was initiated in support of review of NDA 208082. The clinical portion of the following study was audited:

Study #: (b)(4) 113049 (SD-809-C-12)
Study Title: "An Open-Label, Two-Period Study Designed to Evaluate and Compare the Mass Balance Recovery, Metabolite Profile and Metabolite Identification of Oral Doses of Both [¹⁴C]-SD-809 and [¹⁴C]-

Tetrabenazine in Healthy Male Subjects"
Study Period: 7/17/2012-8/25/2012

The audit included a thorough review of study records, including study protocol compliance, informed consent, institutional review board approvals, case report forms, examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff.

Following the inspection, no objectionable conditions were found and no Form FDA-483 was issued.

Conclusions:

Following a review of the inspection report, this reviewer recommends that results from the clinical portion of the following study be accepted for further Agency review.

(b) (4) **113049 (SD-809-C-12)**

Final Classification:

NAI: Quotient Clinical Limited, Nottingham, UK
(**FEI: 3007590770**)

Email cc:

OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta
OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Li
CDER/OND/DNP/Dunn

ORA (b) (4)/Lauren E. Swantko

Draft: XFL 3/11/2016
Edits: MFS 3/11/2016; JC 04/062016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ Quotient Clinical Limited, Nottingham, United Kingdom

OSIS file #BE6950; NDA 208082

FACTS: (b) (4)

Xingfang Li -A

Digitally signed by Xingfang Li -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Xingfang Li -A,
0.9.2342.19200300.100.1.1=2000576511
Date: 2016.04.06 13:43:39 -04'00'

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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

/s/

XINGFANG LI

04/06/2016

SEONGEUN CHO

04/06/2016



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 8, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

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

Subject: **NDA 208082/IND 112975**
Name: Austedo™, (deutetrabenazine, SD-809, d6-tetrabenazine)
Indication: Chorea associated with Huntington's disease (HD)
Dosage: 6-mg, 9-mg, and 12-mg tablets
the proposed dosage range is 6 mg to 48 mg per day with a starting dose of 6 mg once daily and all doses above (b) (4) are administered in two divided doses
Sponsor: Auspex Pharmaceuticals (previous)// Teva Pharmaceuticals, Inc.(current)

Materials reviewed: NDA is in EDR May 29 2014
PDUFA 5/16/2016

Table of Contents

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III. RECOMMENDATIONS (TO BE CONVEYED TO THE SPONSOR)	3
APPENDIX 1, FOR DNP. ANALYSIS OF HUMAN DEPENDENCE DATA	4

I. BACKGROUND

This memorandum responds to a consult request from the Division of Neurological Products (DNP) to evaluate the abuse potential of Austedo (deutetrabenazine) NDA 208082.

The Sponsor submitted 505(b)(2) New Drug Application for Austedo (deutetrabenazine, SD-809), with Xenazine (NDA 021894, tetrabenazine) as the reference listed drug.

This review contains only the analysis of clinical dependence data of Austedo in a population of patients with Huntington's disease as no other abuse potential data was submitted with this NDA. Also, Austedo was submitted with data on the reference drug Xenazine. Xenazine is not a scheduled drug. Xenazine is a centrally-acting, oral inhibitor of vesicular monoamine transporter, type 2 (VMAT2), that was first approved in the United Kingdom ~35 years ago for treatment of chorea. In the United States the drug was approved as a treatment for chorea associated with Huntington's disease (HD) in 2008.

The Sponsor is developing SD-809SD-809 (deutetrabenazine; d6-tetrabenazine) as a treatment for chorea associated with HD which is a neurodegenerative genetic autosomal dominant neuropsychiatric disorder characterized by progressive decline of motor and cognitive functions. Chorea is the name of abnormal involuntary writhing movements which are the hallmark of the disorder.

Austedo (SD-809SD-809, deutetrabenazine) was developed to improve the pharmacokinetic profile of tetrabenazine which is characterized by the rapid metabolism of its circulating active metabolites resulting in large fluctuations in their plasma concentrations and the need for frequent dosing which is thought to contribute to poor drug tolerability.

SD-809SD-809 (deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2)¹ inhibitor which is structurally related to tetrabenazine. According to the Sponsor, placement of two trideuteromethoxy groups (-OCD3) at the 9- and 10-positions during the synthesis of SD-809 attenuates CYP2D6-mediated metabolism of Austedo relative to tetrabenazine, without changing the target pharmacology of the drug.

Regarding regulatory history of Austedo, the orphan-drug designation was granted for treatment of Huntington's disease Nov 5 2014. However, a designation of Breakthrough Therapy and Fast Track Designation were denied April 2 2015.

To date, the Sponsor performed six Phase 1 studies in healthy adult volunteers and two Phase 3 studies in subjects with chorea associated with HD; a total of 295 subjects received the drug, including 117 subjects with chorea associated with HD and 178 healthy adult volunteers.

II. CONCLUSIONS (to be conveyed to the Sponsor)

1. Austedo (SD-809, deutetrabenazine) has never been marketed in the U.S. As a New Molecular Entity (NME), its abuse potential is unknown.
2. There are no preclinical and clinical studies designed to evaluate abuse potential and dependence of Austedo.

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. In nigrostriatal pathway and mesolimbic pathway dopamine-releasing neurons, VMAT2 function is also necessary for the vesicular release of the neurotransmitter GABA.

3. The clinical data which compares adverse events including neuro-psychiatric adverse events following administration of Austedo and tetrabenazine is too small to make any judgments about similarity or lack of abuse potential of these two drugs, although these data seem to show more neuro-psychiatric adverse events for Austedo.
4. Very little data was provided to see a difference in abuse potential for Austedo and tetrabenazine.

III. RECOMMENDATIONS (to be conveyed to the Sponsor)

1. There is no systematic evaluation of clinical dependence, the data provided by the sponsor is too limited to allow any final conclusions, and therefore, additional evaluation of clinical dependence is needed. In particular, the data submitted so far raises the possibility of the rebound phenomena, which are concerning. Of note, one possibility is to evaluate dependence at the end of the trial ARC-HD (SD-809-C-16) which is still on-going.
2. A rebound is of particular concern in the study population as it may increase symptoms of Huntington's disease, including chorea, worsen balance problems and increase possibility of falls, injuries and fractures and also psychiatric disorders (depression, psychosis, suicidality).
3. Evaluation of clinical dependence either at the end of the trial lasting at least 4 weeks or an independent clinical dependence study will be necessary as PMR. Dependence evaluation may be performed at the end of the on-going study SD-809-C-16-ARC HD for the duration of 3-4 weeks and include a summary of all adverse events broken down by weeks (1, 2, 3, 4) and a comparison of the scores from the follow-up period. All scales should be administered biweekly with the baseline scores (which were acquired before the start of drug administration) for the following scales:
 1. Hospital Anxiety and Depression Scale (HADS),
 2. Columbia Suicide Severity Rating Scale (C-SSRS),
 3. Epworth Sleepiness Scale (ESS),
 4. Montreal Cognitive Assessment (MoCA).
 5. Total Maximal Chorea Score (TMC)
 6. Unified Huntington Disease Rating Scale, including behavioral and cognitive scores
 7. Unified Parkinson's Disease Rating Scale Speech/Dysarthria
 8. Barnes Akathisia Rating Scale (BARS)
 9. Berg Balance Test Score (BBT)
4. CSS invites the Sponsor to submit protocols prior to conducting the studies which we will review to provide advice to the Sponsor.

APPENDIX 1. For DNP. Analysis of Human Dependence Data

This assessment of human dependence is based on the withdrawal data mainly from the Study SD-809-C-15 (First-HD) and Study SD-809-C-16 (ARC HD) and includes following items:

- adverse events reported at the follow-up visit week 13 one week after drug discontinuation (from the study SD-809-C-15-First HD)
- comparison of vital signs from the follow-up period (1 week) with the baseline for the
- comparison of the scores from the follow-up period (1 week) with the baseline for the scales:
 - Hospital Anxiety and Depression Scale (HADS)
 - Columbia Suicide Severity Rating Scale (C-SSRS)
 - Epworth Sleepiness Scale (ESS)
 - Montreal Cognitive Assessment (MoCA)
 - Total Maximal Chorea (TMC)
 - Unified Huntington Disease Rating Scale Total Motor Score (UHDRS TMS)
 - Barnes Akathisia Rating Scale (BARS),

The data submitted by the sponsor is very limited and not complete as it includes only one follow-up visit at 1 week (week 13) after the drug discontinuation.

Adverse Events occurred during 1 Week of Discontinuation Period

STUDY SD-809-C-15 First HD

The sponsor submitted only adverse events which were reported at follow-up visit Week 13, one week after drug discontinuation for the Study SD-809-C-15 (First-HD), and additionally the data for 8 subjects follow-up telephone call at Week 16 (4 weeks after drug discontinuation) is included who did not continue to the next Study SD-809-C-16 (ARC HD).

According to the sponsor, only 9 patients reported adverse events, 4 patients (8.9%) who had received SD-809 and 5 patients (11.1%) who had received placebo.

Table 1. Withdrawal symptoms reported at follow-up visit week 13

Body System Or Organ Class	Austedo N (45) (AEs, %)	Placebo N (45) (AEs, %)
Psychiatric disorders		
Anxiety	1 (2.2)	0
Nervous system disorders		
Dizziness	1 (2.2)	0
Gastrointestinal disorders		
Abdominal pain	1 (2.2)	0

Nausea	1 (2.2)	0
Musculoskeletal disorders		
Back pain	1 (2.2)	0
General disorders		
Fatigue	1 (2.2)	0
Metabolism and nutrition disorders		
Decreased appetite	1 (2.2)	0

STUDY SD-809-C-16 ARC-HD**The study is still on-going.**

According to 120 Safety update there were 12 patients who withdrew from ARC-HD.

Nine ARC-Rollover subjects (from the study SD-809-C-16 First-HD) withdrew early, 6 subjects withdrew due to AEs: 1 major depression, 1 suicidal ideation, 1 worsening chorea, 1 anxiety, and 2 depression.

Three ARC-Switch subjects (patients who switched from Xenazine treatment) withdrew early, 1 subject due to an AE (failure to thrive: irritability, frustration, increased OCD, loss of appetite), and 1 subject due to lack of improved chorea control.

According to the 74-day letter response 11 subjects withdrew, four (three in the Rollover Cohort and one in the Switch Cohort) and had follow-up safety data within 4 weeks after discontinuing therapy (see modified table 4, page 9):

- one patient had suicidal ideation 1 week after last dose (answered Yes to question # 2 C-SSRS “Non-Specific Active Suicidal Thoughts”)
- one patient had suicidal ideation (answered Yes to question # 1 C-SSRS “Wish to be dead”) on day 1 after last dose
- one patient had worsening of chorea on 5th day of discontinuation

Table 4: Subjects from Study SD-809-C-16 with Follow-up Data within 4 Weeks of Discontinuing Therapy

	Reason for Study Withdrawal	First Dose Date/Last Dose Date	Duration (days)		HADS					
Subject				Visit (date)	Anx	Depr	C-SSRS	ESS	MoCA	TMC
Rollover Cohort										
220-3521	AE (Worsening Chorea)	01 Feb 2014/ 14 Dec 2014	317	Baseline (31 Jan 2014)	8	5	No	8	23	9
				5 days after last dose (19 Dec 2014)	5	3	No	6	-	11
007-3043	AE (Suicidal Ideation)	13 Dec 2013/ 08 Oct 2014	300	Baseline (12 Dec 2013)	3	2	No	8	25	15
				1 week after last dose (15 Oct 2014)	12	6	Yes to Q2 ^a	4	22	24
100-3422	Withdrawal of Consent (Moved)	10 Apr 2014/ 22 Jul 2014	104	Baseline ^b (10 Apr 2014)	0	9	No	0	18	12
				1 day after last dose (23 Jul 2014)	2	0	Yes to Q1	0	16	12
				9 days after last dose (31 Jul 2014)	0	0	No	0	-	-

CSS comment

There is a very **weak signal** for withdrawal for the Study SD-809-C-15 but number of subjects is really small and it is just one visit at 1 week.

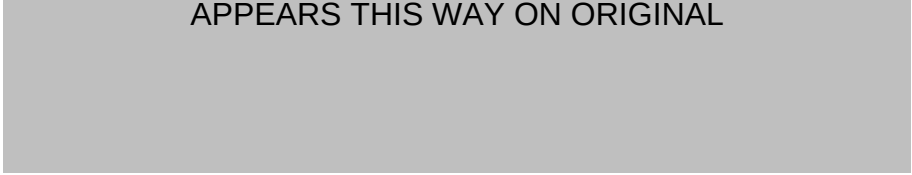
However, there is a possible signal for withdrawal/ rebound in these few subjects that the data is already available from the Study SD-809-C-16, and it is concerning.

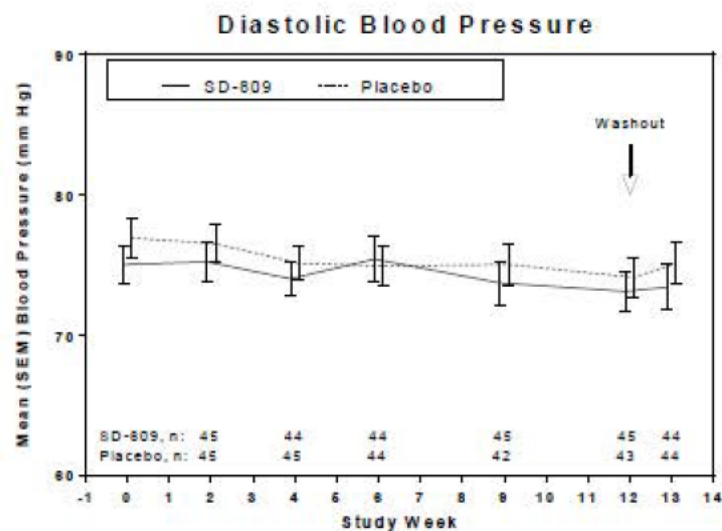
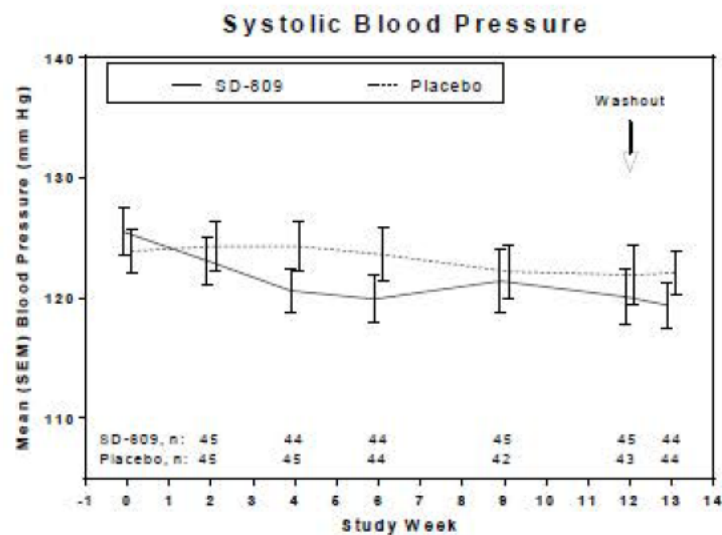
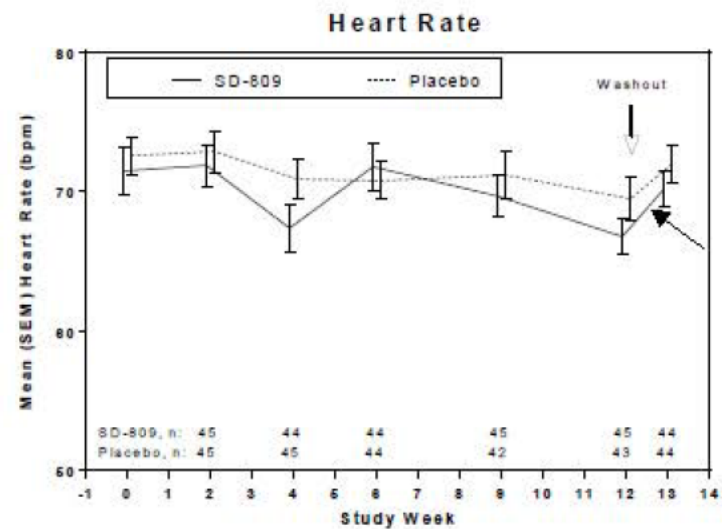
VITAL SIGNS

Vital signs evaluation was carried during the study and 1 week after drug discontinuation. As Fig 21, page 141, shows the changes to systolic and diastolic blood pressure during withdrawal week were minimal during however the heart rate seemed to be increasing after the drug discontinuation, however was not reaching baseline (arrow).

Figure 21. Heart Rate and Blood Pressure Over Time (Safety Population; N=90)

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COGNITIVE, BEHAVIORAL AND DISEASE-SPECIFIC NEUROLOGICAL SCALES

The scales which seem to show withdrawal/rebound are highlighted in blue.

Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS) includes 14-item (7 items for anxiety and 7 items for depression); higher scores reflect greater frequency or severity of the symptoms over the preceding week.

Table 2: Change from Baseline to Week 13 in Hospital Anxiety and Depression Scale (Study SD-809-C-15, Intent-to-Treat Population; N=90)

		SD-809 (N=45)		Placebo (N=45)	
Time Point	Statistic	Value	Change from Day 0	Value	Change from Day 0
Anxiety Subscore					
Day 0	n	45		45	
	Mean (SD)	3.6 (3.30)		3.9 (2.70)	
Week 13	n	44	44	44	44
	Mean (SD)	2.9 (3.39)	-0.5 (2.71)	2.6 (2.84)	-1.3 (2.00)
Depression Subscore					
Day 0	n	45		45	
	Mean (SD)	2.1 (2.63)		3.2 (2.57)	
Week 13	n	43	43	44	44
	Mean (SD)	2.2 (2.93)	0.0 (2.97)	2.4 (2.63)	-0.8 (1.59)

Source: Study SD-809-C-15, Table 14.3.13.1.

Abbreviation: SD = standard deviation.

From the Study SD-809-C-15 (First-HD), page 116, and 119.

Figure 9. Depression Subscale Score of the Hospital Anxiety and Depression Scale Over Time (Safety Population; N=90)

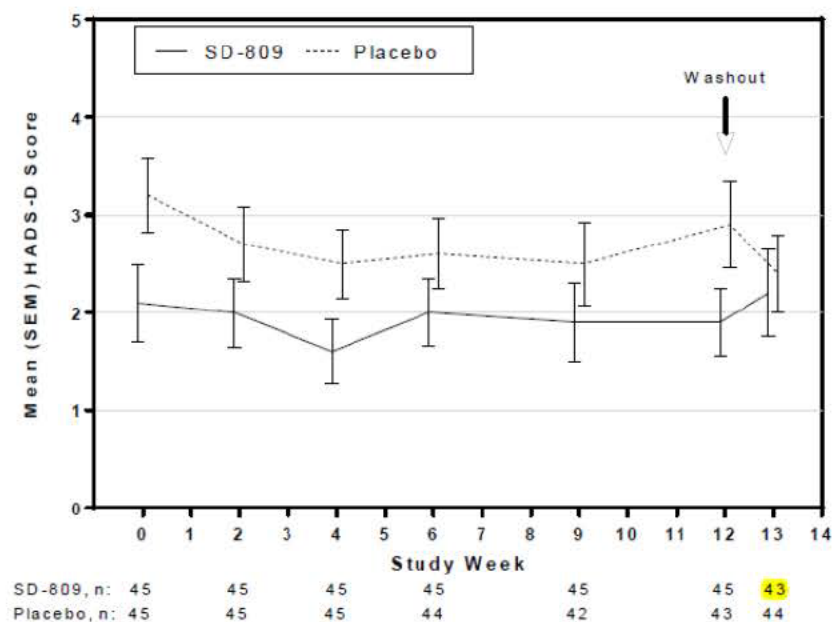
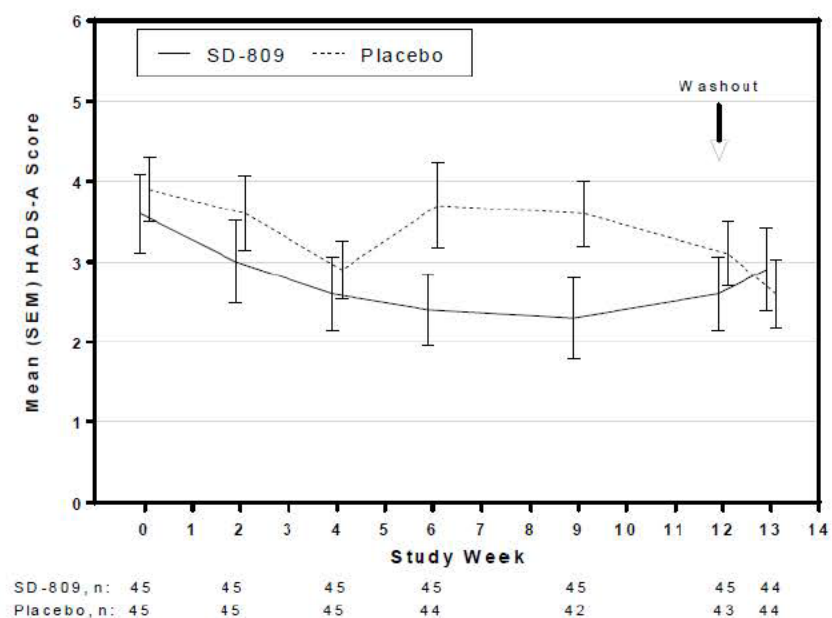


Figure 10. Anxiety Subscale Score of the Hospital Anxiety and Depression Scale Over Time (Safety Population; N=90)



CSS comment

There is a minimal increase of the HADS depression scores during washout period above baseline.

Epworth Sleepiness Scale (ESS)

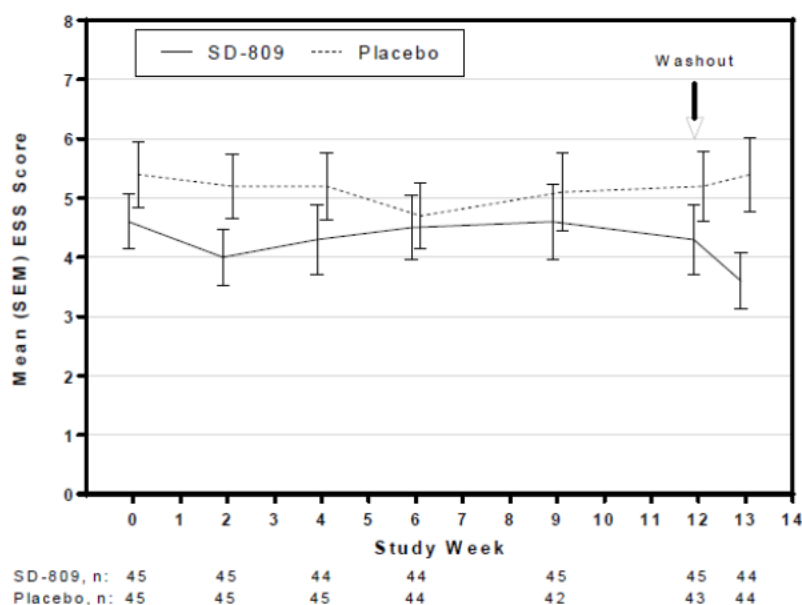
Epworth Sleepiness Scale (ESS) has 8-item scale, and provides an assessment of general level of daytime sleepiness.

Table 3: Change from Baseline to Week 13 in Epworth Sleepiness Scale (Study SD-809-C-15, Intent-to-Treat Population; N=90)

Time Point	Statistic	SD-809 (N=45)		Placebo (N=45)	
		Value	Change from Day 0	Value	Change from Day 0
Day 0	n	45		45	
	Mean (SD)	4.6 (3.09)		5.4 (3.77)	
Week 13	n	44	44	43	43
	Mean (SD)	3.6 (3.19)	-1.1 (2.90)	5.4 (4.06)	-0.1 (3.67)

Source: SD-809-C-15, Table 14.3.15.
Abbreviation: SD = standard deviation.

Figure 11. Epworth Sleepiness Scale Total Score Over Time (Safety Population; N=90)



CSS comment

Sleepiness scores at baseline and follow-up week 13 are different, and there is a clear decrease of the scores for Austedo vs placebo during the washout period (Study SD-809-C-15, Figure 11, page 122/811), which actually means that patients are less sleepy without the drug ...

Total Maximal Chorea (TMC) Score Over Time - Efficacy Measurement in the Study

TMC is a Primary Efficacy endpoint in this study. TMC is determined from the Item 12 of the Unified Huntington's Disease Rating Scale. Higher scores indicate more chorea. Of note, TMC score ≥ 8 was an inclusion criterion.

Figure 3 from study SD-809-C-15 (First HD), page 75 and Table 19, page 76.

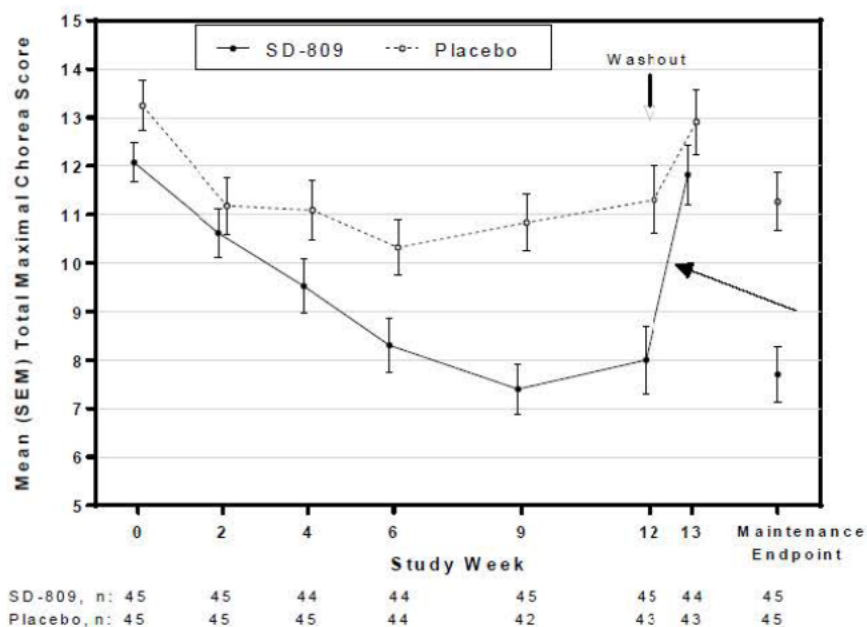
Table 19. Change in Total Maximal Chorea Over Time (Intent-to-Treat Population; N=90)

	SD-809 (N=45)			Placebo (N=45)		
	n	Mean (SD) TMC	Mean Change from Baseline ^a	n	Mean (SD) TMC	Mean Change from Baseline ^a
Screening	45	11.91 (2.695)	--	45	12.96 (3.655)	--
Day 0	45	12.22 (3.089)	--	45	13.53 (3.811)	--
Baseline ^a	45	12.07 (2.727)	--	45	13.24 (3.488)	--
Week 2	45	10.62 (3.359)	-1.44 (2.108)	45	11.18 (3.956)	-2.07 (2.807)
Week 4	44	9.52 (3.682)	-2.38 (2.820)	45	11.09 (4.188)	-2.16 (3.041)
Week 6	44	8.30 (3.664)	-3.67 (2.726)	44	10.32 (3.796)	-2.81 (2.800)
Week 9	45	7.40 (3.480)	-4.67 (2.757)	42	10.83 (3.774)	-2.21 (2.899)
Week 12	45	8.00 (4.748)	-4.07 (3.818)	43	11.30 (4.591)	-1.85 (3.188)
Maintenance Therapy ^a	45	7.70 (3.868)	-4.37 (2.953)	45	11.26 (4.075)	-1.99 (2.666)
Week 13	44	11.82 (4.065)	-0.26 (2.656)	43	12.91 (4.380)	-0.50 (2.708)

Source: Table 14.2.8.2 and Listing 16.2.6.1.1.

Abbreviations: CI, confidence interval; SD, standard deviation; TMC, Total Maximal Chorea.

Notes: TMC is determined from Item 12 of the Unified Huntington's Disease Rating Scale. TMC score ≥8 was an inclusion criterion.

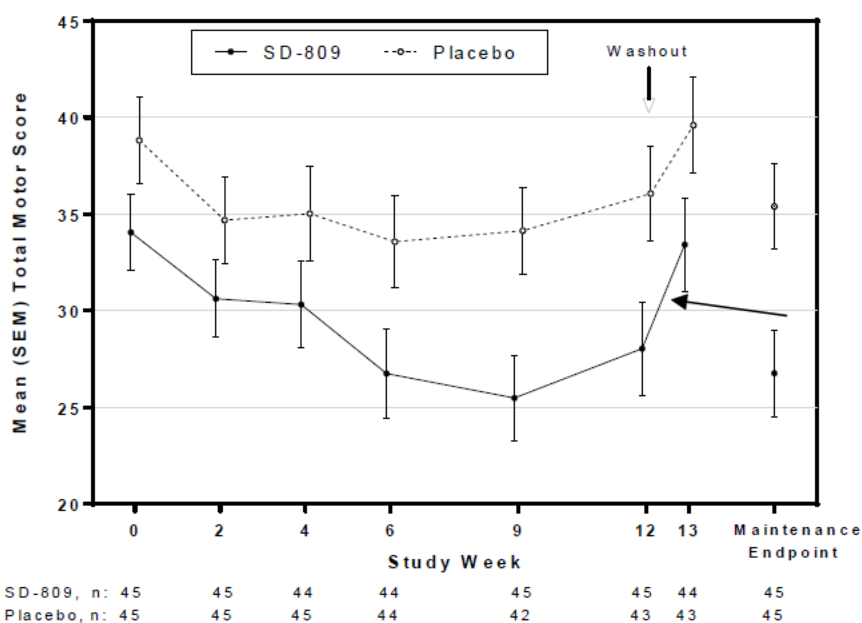
^a Baseline value is defined as the mean of the values from the Screening and Day 0 visits. Maintenance therapy value is defined as the mean of the values from the Week 9 and Week 12 visits.**Figure 3. Total Maximal Chorea Score Over Time (Intent-to-Treat Population; N=90)**CSS conclusion

After abrupt discontinuation of the drug chorea score very rapidly worsens within 1 week (arrow), which is also much higher than placebo, and reaches baseline state, however because there is no longer follow-up data it is unknown if it reaches state of rebound....

Unified Huntington Disease Rating Scale Total Motor Score (UHDRS TMS) Over Time (Intent-to-Treat Population; N=90)- Efficacy Measurement in the study

The UHDRS TMS is an Efficacy Measurement in the study. TMS assesses all of the motor features of HD and including chorea, dystonia, eye movements, dysarthria, finger and hand movements, rigidity, bradykinesia, and gait. Lower TMS scores indicate better motor function.

Figure 6. Change in Unified Huntington Disease Rating Scale Total Motor Score Over Time (Intent-to-Treat Population; N=90)



CSS comment

Again, like with Total Maximal Chorea Score (above), after abrupt discontinuation of the drug Huntington disease score rapidly worsens within 1 week (arrow), and reaches baseline state, however because there is no longer follow-up it is unknown if it reaches state of rebound....

Barnes Akathisia² Rating Scale (BARS), page 127

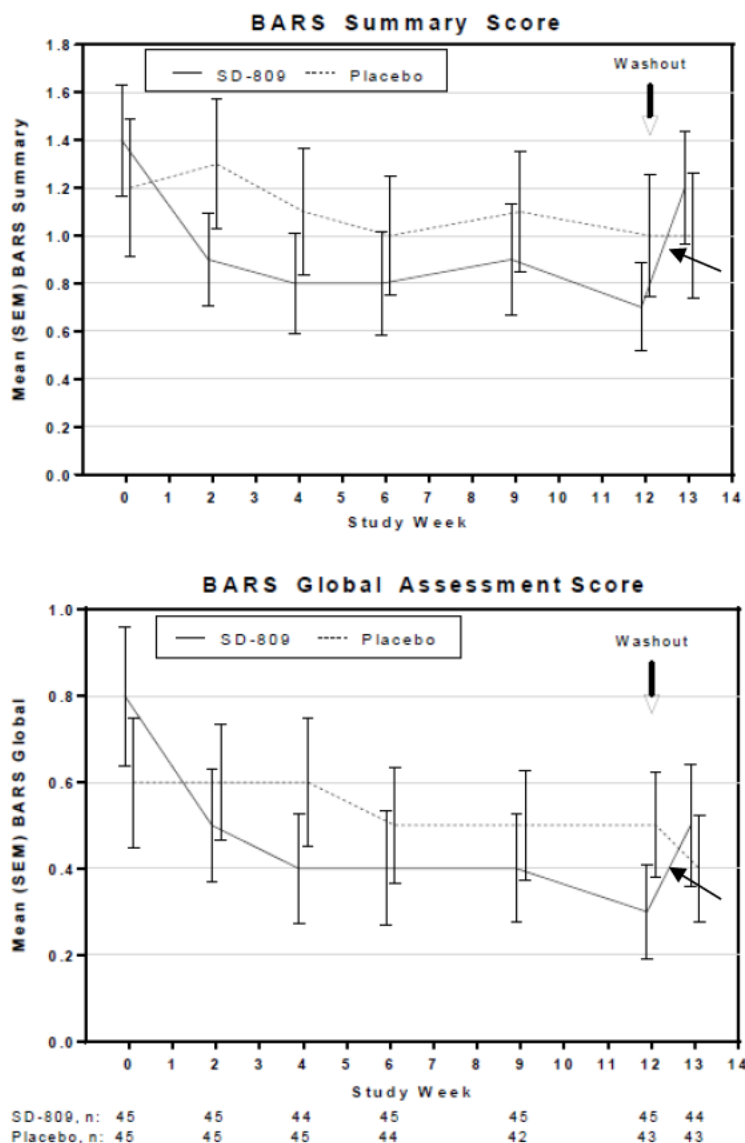
² Akathisia

Movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, akathisia may range in intensity from a sense of disquiet or anxiety, to excruciating discomfort, particularly in the knees. Akathisia is frequently associated with the use of dopamine receptor antagonist antipsychotic drugs and drugs which block dopaminergic transmission in the brain.

Another major cause of the akathisia is the withdrawal observed in dependent individuals after sudden cessation of opioids, barbiturates, cocaine, and benzodiazepine.

Barnes Akathisia Rating Scale evaluates drug-induced akathisia. The scale provides a summary score (objective assessment of akathisia and subjective measures, including self-awareness and distress) and a global clinical assessment. Higher scores indicate more akathisia and restlessness.

Figure 14. Barnes Akathisia Rating Scale Summary and Global Assessment Scores Over Time (Safety Population; N=90)



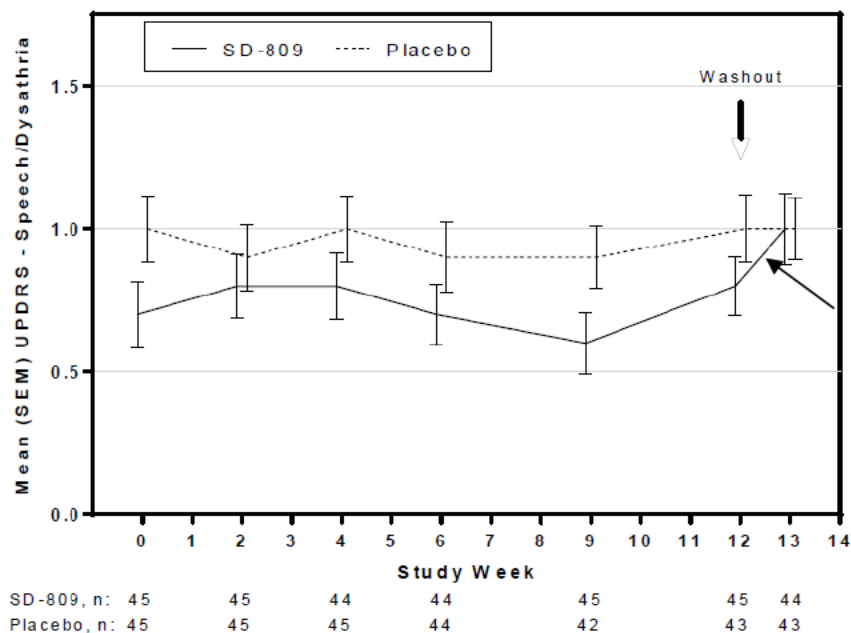
CSS comment

Again, like with other motor scales there is seen a very sharp rebound (arrow) in the first week after drug discontinuation, which could potentially suggest the rebound after the first week...

Unified Parkinson's Disease Rating Scale Speech/Dysarthria, page 124

UPDRS speech/dysarthria was evaluated as an aspect of Parkinsonism. Higher scores indicate more impaired speech.

Figure 13. Unified Parkinson's Disease Rating Scale Speech/Dysarthria Question over Time (Safety Population; N=90)



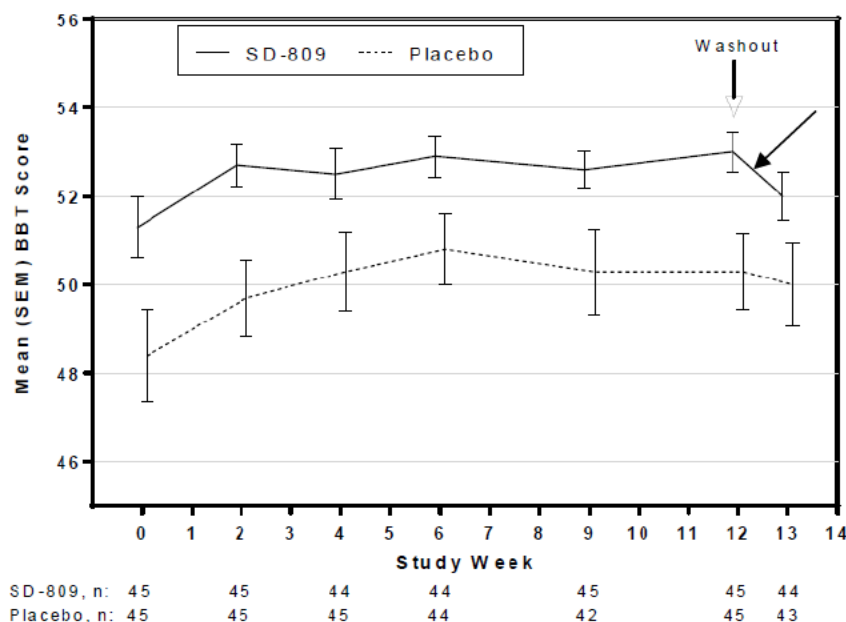
CSS comment:

UPDRS Speech/Dysarthria Scale seems to indicate an increase of symptoms after Austedo withdrawal with overshoot of the score (arrow) comparing to the baseline which might indicate rebound.

Berg Balance Test Score (BBT)

Berg Balance Test Score was a Key Secondary Efficacy endpoint. Higher scores indicate better balance.

Figure 16. Berg Balance Test Score Over Time (Safety Population; N=90)



CSS comment:

There seems to be a rapid worsening of the balance score during withdrawal period in Austedo group (arrow).

Montreal Cognitive Assessment (MoCA)

Montreal Cognitive Assessment is a validated rapid-screening Scale for assessing mild cognitive dysfunction. Higher scores indicate better cognitive function.

The MoCA was administered at baseline but was not administered during the follow-up week 13 visit for study First HD (SD-809-C-15). However, 80 subjects who rolled-over into study SD-809-C-16 (ARC HD) had MoCA assessment in most cases at ~1 week following study drug withdrawal in First-HD.

Study First-HD (SD-809-C-15) and ARC-HD SD-809-C-16

- **Baseline:** MoCA scores: SD-809 (N=45) were 23.7 (3.78) and placebo (N=45) 22.8 (4.00).
- **One week after discontinuation:** For 80 subjects who enrolled in Study SD-809-C-16, MoCA scores assessed at Baseline (at ~1 week following study drug withdrawal in First-HD, which would equal a follow-up visit), mean (SD) MoCA scores were 23.9 (4.35)

The data shows no changes in of the MoCA score at 1 week after discontinuing drug

Columbia Suicide Severity Rating Scale (C-SSRS)

As the sponsor states, only one subject # 333-3564 in the placebo group answered affirmatively to Question 1 (“wish to be dead”) of the C-SSRS at the Week 12 visit, that is during the study.

Apparently no subject answered positively any question in the C-SSRS at the Week 13 follow-up visit.

CSS conclusions

The provided withdrawal data is very limited and not complete, the major problem is that withdrawal was only examined during one week from discontinuation.

However, it seems that there is some withdrawal (AEs) and a possible rebound on a number of disease-related scales, such as Total Maximal Chorea Score, UHDRS Total Motor Score, Barnes Akathisia Rating Scale, and possibly Berg Balance Test, in fact Unified Parkinson's Disease Rating Scale Speech/Dysarthria seemed even to show rebound.

Therefore is suggested to evaluate withdrawal and rebound symptoms at the end of current on-going trial SD-809-C-15 ARC HD and for at least 3 weeks, biweekly.

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/s/

ALICJA LERNER
03/08/2016

MICHAEL KLEIN
03/08/2016

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 17, 2016

TO: Stacy Metz, Pharm.D., Regulatory Health Project Manager
Ken Bergmann, M. D., Medical Officer
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 208082

APPLICANT: Teva/Auspex Pharmaceuticals , Inc.

DRUG: Austedo (deutetrabenazine)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard
INDICATION: Treatment of chorea associated with Huntington's disease
CONSULTATION REQUEST DATE: August 2, 2015
DIVISION ACTION GOAL DATE: May 29, 2016
PDUFA DATE: May 29, 2016
INSPECTION SUMMARY: April 15, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two domestic clinical investigator sites were inspected in support of this application. The inspections of Drs. Mallonee and Claassen revealed minor deviations that would not adversely impact data acceptability. The pending classification for Drs. Mallonee and Claassen are Voluntary Action Indicated (VAI). A summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, while the inspectional findings represent observed deficiencies, these findings are unlikely to have a significant impact on overall results. The data submitted from the two sites are acceptable and may be used in support of the pending application.

II. BACKGROUND:

The Applicant has conducted this study in support of approval for the use of SD-809 (d6-Tetrabenazine) in the treatment of chorea associated with Huntington's disease (HD). The Applicant-sponsored one study: Study Protocol SD-809 in Chorea affected subjects was submitted in support of the application.

Huntington's Disease is characterized by progressive loss of medium spiny neurons in the striatum and to a lesser extent of pyramidal neurons in the cortex. The disease is due to a mutation in the polyglutamine repeat sequence in the Huntington's gene located on Chromosome 4. The most commonly recognized motor sign of HD is the voluntary movement chorea, which can affect all muscle groups. Chorea has the potential to interfere with daily functioning. In its early stages, chorea can contribute to impaired speaking, writing, and activities of daily living such as feeding, dressing, and bathing, and at later stages, chorea can cause gait, poor postural control, with an increased risk of falling. Clinical experience in patients with a genetic predisposition to HD implicates a relative excess of dopamine in the pathogenesis of these involuntary movements. These observations led to the development of tetrabenazine, which depletes presynaptic dopamine, as a treatment for chorea associated with Huntington disease. Tetrabenazine is approved in the United States and several European countries as a therapy for the treatment of chorea associated with Huntington disease. While generally effective in the treatment of chorea, tetrabenazine has limitations for use in Huntington's disease patients due to serious adverse events associated with peak concentration after dosing. To address the limitations, the applicant developed a deuterated form of tetrabenazine (referred to as SD-809) which is eliminated more slowly than tetrabenazine (b) (4) SD809 (b) (4) has been shown to reduce plasma fluctuation and dosing frequency and thus, has the potential to improve overall tolerability as compared to tetrabenazine which in turn reduce toxicity as well as a less frequent dosing schedule which is preferred as it may improve medication compliance.

The Applicant sponsored one clinical trial SD/809-C-15 in support of the application:

Protocol: SD 809-C-15 entitled: "A Randomized, Double-Blind, and Placebo-Controlled Study of Extended Release for the Treatment of Chorea Associated with Huntington's Disease"

A brief description of the key design features is presented below.

Protocol SD809-C-15

The objectives of this study were: 1) to evaluate the efficacy of SD-809 ER in reducing the chorea associated with HD, and 2) to evaluate the safety and tolerability of titration and maintenance therapy with SD-809 ER.

This protocol was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety, and tolerability of SD-809 ER for the treatment of chorea associated with HD. Approximately 90 subjects were randomized (1:1) into the study, with approximately 45 subjects receiving SD-809 ER and 45 subjects receiving placebo. The study was conducted at 30 centers in the U.S. The study was divided into a screening period, a titration period, and a maintenance period. The duration of the study was 16 weeks.

The Division of Neurology Products (DNP) requested inspection of two domestic clinical investigator sites due to high subject enrollment, and significant results pertinent to decision-making. Site selection was a team effort with statistical input. This would be the first approval of this new formulation.

III. RESULTS (by protocol/site):

Name of CI, Site #, and Location	Protocol and # of Subjects	Inspection Dates	Final Classification
William M. Mallonee, M.D. Wichita, KS 67226 Site#83	Protocol SD-809- C-15 13 subjects	9/21- 25/2015	Pending (preliminary classification VAI)
Daniel Claassen, M.D. Nashville, TN 37232-2551 Site# 31	Protocol SD-809- C-15 7 subjects	8/31- 9/17/2015	Pending (preliminary classification VAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data generated are unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

**1. William Mallonee, M.D.
Wichita, KS 67226**

For Protocol SD809-C-15, a total of 13 subjects were screened, three subjects were reported as screen failures, 10 subjects were enrolled, and 10 subjects completed the study.

A review of the medical records/source documents was conducted. The medical records for 13 subjects enrolled were reviewed, including drug accountability records, protocol deviations, vital signs, laboratory test results, IRB records; informed consent documents inclusion/exclusion criteria, and concomitant medications. Source documents were compared to data listings, including primary efficacy endpoints and adverse events.

At the conclusion of the inspection no Form FDA 483 was issued to Dr. Mallonee. Our investigation found inadequate documentation, lack of progress notes for certain visits, many write-overs, and pre-populating of forms to save time.

OSI Reviewer's Comment: The findings appear isolated in nature and unlikely to impact overall reliability of efficacy and safety data from this site.

In general, the records reviewed were adequate and the data verifiable except for the above noted findings. There were no known limitations to this inspection.

Although minor regulatory deviations were noted, these findings are unlikely to have a significant impact on overall results. The data generated by this site are considered reliable and appear acceptable in support of the pending application.

**2. Daniel Claassen, M.D.
Nashville, TN 37232-2551**

At this site, a total of seven subjects were screened, seven subjects were enrolled into the study, and seven subjects completed the study.

The medical records/source data for seven subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, patients' diaries for inclusion/exclusion criteria, concomitant medications, and source documents were compared to data listings and adverse events reporting.

At the conclusion of the inspection, a 2-item Form FDA 483 was issued to Dr. Claassen. The medical records reviewed disclosed minor protocol deviations and inadequate record keeping. The inspectional observations discussed with clinical investigator included, but were not limited to the following:

1. According to the protocol, blood draws were required at certain visits. For two subjects, blood draws were not completed due to inability to obtain blood samples.

As a result, these two subjects (3622 and 3625) were instructed to come back at a later date and attempt blood draws. In all instances, participant did complete their blood draws and safety was not compromised. These unscheduled visits were solely for drawing blood.

OSI Reviewer's Comment: The inability to draw blood is understandable, and the clinical investigator's instruction to the subjects to return to complete the blood draw is acceptable, even though it is a protocol deviation. The finding is isolated in nature with no impact on acceptability of the data.

2. Subject # 3622 recent medical history documented the patient was suffering complication due to excessive alcohol use and his decision to reduce his alcohol intake to 6 beers a week. This subject was also using "marijuana every Friday". The clinical investigator did not confirm/verify the exclusion criteria regarding alcohol intake and marijuana use items #17 and #18 prior to enrollment.
3. Subject #3626 had changes to the medical records after enrollment. For example, alcohol use was changed from "None to Yes" 2 months after screening, and alcohol frequency changed from "1 beer/week to "4 beers/week 3months after screening. No explanation/reason(s) was provided for the change

OSI Reviewer's Comment: The clinical investigator responded to the observations and promised to make appropriate changes to remedy the situation. The findings are isolated in nature and unlikely to impact reliability of the data.

The clinical investigator acknowledged the inspectional observations in a written response dated 10/2/2015 in which he agreed with the observations and stated that he will address the discussed findings in his future studies. OSI finds his written response acceptable.

The medical records reviewed disclosed no adverse findings that would impact the reliability of the data. In general, the records reviewed were found to be in order except for the above noted findings. There were no limitations to this inspection.

Although minor deviations were noted, the data from Dr. Claassen's site are considered reliable and appear acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
02/18/2016

SUSAN D THOMPSON
02/18/2016

KASSA AYALEW
02/22/2016

LABEL AND LABELING REVIEW

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 30, 2015
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208082
Product Name and Strength:	Austedo (deutetrabenazine) Tablets, 6 mg, 9 mg, and 12 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals
Submission Date:	May 29, 2015
OSE RCM #:	2015-1299
DMEPA Primary Reviewer:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review is written in response to a request from the Division of Neurology Products (DNP) to review the proposed labels and labeling for Austedo (deutetrabenazine) tablets [NDA 208082] for vulnerabilities to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling identified areas that can be improved to increase clarity, improve readability, and increase prominence of important information to minimize the risk of medication errors and promote the safe use of Austedo.

Section 2.1 (b) (4) *Dosing Information* states (b) (4)

The statement, “Swallow (b) (4) whole, do not chew, crush, or break” is also included on the container label. This is critical information necessary for the safe use of Austedo that should be prominently placed in the *Highlights of Prescribing Information* to minimize the potential for wrong technique medication errors. Additionally, the statement (b) (4) can be revised to improve readability.

In the Dosage and Administration Section of the *Highlights of Prescribing Information* the starting dose is presented using the error-prone abbreviation (b) (4). Error prone abbreviations

can be misinterpreted and have been involved in harmful medication errors¹. Thus, they should not be used to communicate dosing information. We also note that the intended route of administration is not included in this section, which could increase the potential for wrong route medication errors.

Additionally, in the table included in Section 2.2, (b) (4) we note the inclusion of (b) (4). The symbols (b) (4) in the Table should be revised to (b) (4) (b) (4) “once daily” and “twice daily” to prevent misinterpretation and wrong frequency errors.

We also noted that the route of administration is not included in Section 2.2 (b) (4). While the route of administration is stated in Section 2.1, (b) (4) *Dosing Information*, this information may be less likely to be overlooked if it is included in the dosing statement. Also in Section 2.2, addition of (b) (4) (b) (4) may (b) (4) (b) (4) mitigate the potential for dosing errors.

In Section 16.2 *Storage* the degree symbol (°) is missing following the 15 and 59 within the storage statement and should be revised for clarity.

Review of the container labels noted that the middle digits of the National Drug Code (NDC) numbers are in sequential order (e.g., 170, 171, and 172). Our post-marketing experience indicates that similarity of the NDC product code (middle 3 digits) has led to selecting and dispensing of the wrong strength and wrong drug. These middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Assignment of sequential numbers is not an effective differentiating feature (e.g., 170, 171, and 172). Therefore, we recommend changing these numbers or increasing the prominence of the middle digits by increasing the font size (e.g., XXXX-XXXX-XX).

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling that can be revised to increase clarity, improve readability, and add important critical information to mitigate the potential for medication errors and promote safe use of Austedo. We provide recommendations in Sections 4.1 and 4.2 below and advise they are implemented prior to the approval of this NDA.

¹ ISMPs List of Error-Prone Abbreviations, Symbols and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 OCT 29]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information, *Dosage and Administration Section*

1. Consider adding the statement, “Austedo should be swallowed whole. Do not chew, crush, or break tablets” to the *Dosage and Administration Section*. Inclusion in this section will increase the prominence of this information and help to minimize the potential for wrong technique medication errors.
2. Consider adding the statement “Austedo should be administered with food [see *Clinical Pharmacology* (12.3)]” to the *Dosage and Administration Section*. Inclusion in this section may help providers to more easily access this important information regarding appropriate dose administration.
3. To minimize the risk for misinterpretation and wrong frequency errors, please consider replacing the error-prone abbreviation (b) (4) with (b) (4) “once daily” in the starting dose statement. To provide clarity regarding the route of administration, also consider adding the word “orally” so that this statement reads “6 mg orally once daily”.

B. Full Prescribing Information, Section 2.1 (b) (4) *Dosing Information*

1. Consider revising the statement (b) (4) to read “Austedo should be swallowed whole. Do not chew, crush, or break tablets” to improve readability.

C. Full Prescribing Information, Section 2.2 (b) (4)

1. Consider adding “administered orally” in the dosing statement so that it reads, “The starting dose should be 6 mg administered orally once daily” to prevent this information from being overlooked and minimize the risk for wrong route errors.
2. Consider replacing the symbols (b) (4) in the Table with (b) (4) “once daily” and “twice daily” to prevent misinterpretation and confusion. Mistakes can result from the use of error-prone abbreviations and should be avoided when communicating dosing information.
3. Consider adding (b) (4) (b) (4) (b) (4).

D. Full Prescribing Information, Section 16.2 *Storage*

1. Consider adding the degree symbol (°) following the 15 and 59 within the storage statement for clarity.

4.2 RECOMMENDATIONS FOR AUSPEX PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA 208082:

A. Container Labels

1. Our post-marketing experience indicates that similarity of the product code numbers of the NDC (middle 3 digits) has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 170, 171, and 172). If these numbers cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits or putting them in bold type. As an example: XXXX-**XXXX**-XX.

See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013.

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Austedo that Teva Pharmaceuticals submitted on May 29, 2015.

Table 2. Relevant Product Information for Austedo	
Initial Approval Date	N/A
Active Ingredient	Deutetrabenazine
Indication	The treatment of chorea associated with Huntington's disease
Route of Administration	Oral
Dosage Form	Tablets
Strength	6 mg, 9 mg, and 12 mg
Dose and Frequency	Starting dose should be 6 mg once daily. Austedo should be titrated up at weekly intervals by 6 mg per day, to allow the identification of a dose that reduces chorea and is tolerated. Daily doses of 12 mg and higher per day should be given in two divided doses. The dose should not exceed a recommended maximum daily dose of 48 mg (single dose of 24 mg administered twice daily). If clinically significant adverse events such as somnolence or dizziness occur, titration should be stopped and the dose should be reduced.
How Supplied	Bottles of 60 tablets
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On September 29, 2015, we searched the L:drive and AIMS using the term, Austedo to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews^{2,3}, and we confirmed that there are no outstanding recommendations.

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

² Harris, J. Proprietary Name Review for Austedo IND11295. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015FEB24. RCM No.: 2014-43007.

³ Harris, J. Proprietary Name Memorandum for Austedo NDA 208082. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015JUN22. RCM No.: 2015-650424.

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/s/

DEBORAH E MYERS
10/30/2015

DANIELLE M HARRIS
10/30/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208082

Application Type: New NDA

Name of Drug/Dosage Form: Austedo (deutetrabenazine) Oral Tablets 6 mg, 9 mg, and 12 mg

Applicant: Teva Pharmaceuticals

Receipt Date: 5/29/15

Goal Date: 5/29/16

1. Regulatory History and Applicant's Main Proposals

Pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50, Teva Pharmaceuticals, Inc., has submitted an original new drug application, NDA 208082, AUSTEDOTM (deutetrabenazine) 6, 9, and 12 mg tablets. Xenazine®, NDA 21894, is the reference listed drug.

The targeted indication for AUSTEDO tablets in this NDA is for the treatment of chorea associated with Huntington's disease. Orphan designation was granted on November 5, 2014, under Designation Request # 12-3832.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by [September 4, 2015](#). The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:**
- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:** *A horizontal line must separate the TOC from the FPI.*
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:**
- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Selected Requirements of Prescribing Information

Comment: *There must be no white space between the product title and Initial U.S. Approval.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

Selected Requirements of Prescribing Information

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Selected Requirements of Prescribing Information

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

Selected Requirements of Prescribing Information

- “See 17 for PATIENT COUNSELING INFORMATION”

If a product **has** FDA-approved patient labeling:

- “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

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8.4 Pediatric Use

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9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

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10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

STACY M METZ
08/06/2015



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 30, 2015

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

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

Subject: **NDA 208, 082/IND 112975**
Name: Austedo™, deutetetrabenazine, SD-809 (d6-tetrabenazine)
Indication: Chorea associated with Huntington's disease
Dosage: ER tablets (6 mg, 9 mg and 12 mg), and the proposed dosage range for SD-809 is 6 mg to 48 mg per day
Sponsor: Auspex Pharmaceuticals (old)// Teva Pharmaceuticals, Inc.(new)

Materials reviewed: NDA is in EDR May 29 2014
Filing meeting is scheduled for 7/17/2015

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I. BACKGROUND

This memorandum responds to a consult request from the Division of Neurological Products (DNP) to evaluate the abuse potential of Austedo™ (deutetrabenazine) NDA 208082 for Filing Meeting on July 17 2015. The Sponsor is submitting 505(b)(2) New Drug Application for deutetrabenazine (SD-809), with tetrabenazine (NDA 021894) as the reference listed drug.

The Sponsor is developing SD-809SD-809 (deutetrabenazine; d6-tetrabenazine) as a treatment for chorea associated with Huntington's disease (HD) which is a neurodegenerative genetic

autosomal dominant neuro-psychiatric disorder characterized by progressive decline of motor and cognitive functions. Chorea is the name of abnormal involuntary writhing movements which are the hallmark of the disorder.

SD-809 (deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2)¹ inhibitor which is structurally related to tetrabenazine. Two trideuteromethoxy groups (-OCD₃) are inserted at the 9- and 10-positions during the synthesis of SD-809 to replace two trihydromethoxy groups (-OCH₃) at the corresponding positions in tetrabenazine. According to the Sponsor, Deuterium placement at these positions within SD-809 affects metabolism advantages relative to tetrabenazine by attenuating CYP2D6-mediated metabolism, without changing the target pharmacology of the drug.

Of note, Tetrabenazine (Xenazine®), is a centrally-acting, oral inhibitor of vesicular monoamine transporter, type 2 (VMAT2), that was first approved in the United Kingdom ~35 years ago for treatment of chorea; in the United States the drug was approved as a treatment for chorea associated with HD in 2008.

SD-809 (deutetrabenazine) was developed to improve pharmacokinetic profile of tetrabenazine which is characterized by the rapid metabolism of its circulating active metabolites resulting in large fluctuations in their plasma concentrations and the need for frequent dosing which is thought to contribute to poor drug tolerability.

Regarding regulatory history of Deuterotetrabenazine: the orphan-drug designation was granted for treatment of Huntington's disease Nov 5 2014; however a designation of Breakthrough Therapy and Fast Track Designation were denied April 2 2015.

Importantly, the Division did not contact CSS during IND stage to make recommendations on assessment of abuse potential. Since we have just been contacted at filing, our recommendations were not submitted to the company in a timely manner so that they could be considered.

To date, the Sponsor performed six Phase 1 studies in healthy adult volunteers and two Phase 3 studies in subjects with chorea associated with HD; a total of 295 subjects have received the drug, including 117 subjects with chorea associated with HD and 178 healthy adult volunteers.

II. CONCLUSIONS (to be conveyed to the Sponsor)

1. SD-809 (deutetrabenazine) has never been marketed in U.S. As a New Molecular Entity (NME), its abuse potential is unknown.
2. There are no preclinical and clinical studies designed to evaluate abuse potential.

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. In nigrostriatal pathway and mesolimbic pathway dopamine-releasing neurons, VMAT2 function is also necessary for the vesicular release of the neurotransmitter **GABA**.

3. The clinical data which compares adverse events including neuro-psychiatric adverse events following administration SD-809 and tetrabenazine is too small to make any judgments about similarity or lack of thereof between these two drugs.
4. CSS does not see abuse potential which would distinguish it from tetrabenazine but the sponsor provided very limited data.
5. Because pharmacokinetic profile of the drug is different than tetrabenazine evaluation of dependence is recommended, which can be accomplished performing animal dependence study.

III. SPECIFIC RECOMMENDATIONS (to be conveyed to the Sponsor)

1. To perform animal dependence study
2. The Sponsor should provide the data from the follow-up from the study SD-809-C-15-First HD to include adverse events occurring within the 4 weeks of follow-up period and also to include comparison of scores from the follow-up period with the baseline before the drug administration for following scales: Hospital Anxiety and Depression Scale (HADS), Columbia Suicide Severity Rating Scale (C-SSRS), Epworth Sleepiness Scale (ESS), Montreal Cognitive Assessment (MoCA). Additionally, adverse events from the follow-up data of 4 weeks from the study SD-809-C-C-16 ARC-HD maybe added. Also, evaluation of severity of disease symptoms after drug withdrawal and comparison with the baseline should be performed to assess rebound phenomena.

*The animal study should be performed during NDA clock to provide important data for labeling of the drug.

IV. GENERAL RECOMMENDATIONS

According to 21 CFR § 314.50 (5) (vii), the abuse potential section of an NDA includes a proposal for scheduling and all scientific data that form the basis of the proposal. The abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:

- Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)
- Pharmacokinetics and pharmacodynamics (including all data on receptor binding of the drug and its active metabolites)
- Primary data from abuse potential studies in animals including:
 - discrimination study
 - self-administration
 - dependency study
- Primary data from abuse potential studies in humans including:
 - human abuse potential study
 - dependence in humans must be assessed
- Adverse events related to abuse potential from clinical studies
- Information and data related to abuse potential in integrated summaries of safety and efficacy (ISS and ISE)
- Information related to overdose

- Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies
- Epidemiological data related to abuse.

In the NDA the Sponsor should provide the following information and data related to abuse potential from all clinical studies, including raw data and adverse events coded with the most recent MedDRA terminology, that includes:

- Descriptions and details of all reports in all clinical studies, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for, and related to drug withdrawal and withdrawal symptoms, and any other indication of dependence.
- Adverse events data related to abuse should be broken down by gender, age (non-elderly, elderly) and by population healthy volunteers, patients with other disorders treated with the drug and patients with chorea.
- Case narratives of patients in clinical trials who are discontinued from studies for lack of compliance to study medication or procedures, or who discontinue participation without returning the study medication.
- Tabulation of patients who were discontinued from the study, or dropped out for reasons related to potential abuse and diversion, including narratives describing reasons and follow-up information.
- All post-marketing safety reports of AEs related to potential abuse.
- The details of abuse potential evaluation are described in the FDA draft Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>
- CSS invites the Sponsor to submit protocols prior to conducting the studies which we will review and provide comments to the Sponsor.

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/s/

ALICJA LERNER
07/30/2015

MICHAEL KLEIN
07/30/2015