CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208082Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208082

COMPLETE RESPONSE

Teva Pharmaceuticals, Inc.
Attention: Christine Schulteis, PhD
Global Regulatory Affairs
3333 North Torrey Pines Court
Suite 400
La Jolla, CA 92037

Dear Dr. Schulteis:

Please refer to your New Drug Application (NDA) dated May 29, 2015, received May 29, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Austedo (deutetrabenazine) Oral Tablets 6 mg, 9 mg, and 12 mg.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

Your clinical pharmacology studies were not adequate to determine whether all major human metabolites of deutetrabenazine have been identified. This information is needed to assess whether the bridge to the listed drug on which you are relying (Xenazine) is scientifically justified to address the toxicity of all major metabolites of deutetrabenazine.

Please note that the method you proposed in your April 8, 2016, amendment to this NDA to assess potential major metabolites is acceptable, on face, and pending demonstration of suitable stability.

NONCLINICAL

The toxicokinetic analyses of metabolites in the pivotal nonclinical studies of deutetrabenazine are limited to quantitation of the primary metabolites of deutetrabenazine (i.e., alpha and beta-DHTBZ). If the results of the pending clinical pharmacology analyses identify additional major circulating human metabolites, you will need to demonstrate that each has been adequately assessed in the appropriate nonclinical studies or that plasma exposure to each does not exceed that in humans with Xenazine.

PRODUCT QUALITY

1. The drug substance specification does not include a test for [redacted] (b) (4). We acknowledge your commitment dated February 22, 2016, to add a test and acceptance criterion of not more than [redacted] (b) (4) as part of the drug substance specification and to amend the NDA with this test, acceptance criterion, and method validation report on or before March 22, 2016. However, the test method was not submitted until April 14, 2016, and validation data were not provided until May 9, 2016. These amendments to the NDA will be reviewed in the next cycle.

2. In your post-approval stability protocol, you indicate that at least one production batch of the product in the commercial packaging will be placed on long term stability annually. Because the registration stability batches were not manufactured at full commercial scale, we request that you update your post-approval stability commitment to include placing the first three commercial batches of each strength of the drug product on long-term stability through the proposed shelf life, and on accelerated stability for 6 months as per ICH Q1A(R2). The data should be tabulated and submitted in the annual report with a commitment to withdrawing or discussing any out of specification results in the distributed drug product to the Agency.

3. Per 21 CFR 25.15(d), revise your claim for categorical exclusion to include a statement that, to the applicant's knowledge, no extraordinary circumstances exist.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, July 2, 2015, which addresses the proposed proprietary name, Austedo. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. When submitting the safety update, include narratives for patients who dropped out of Study C-16 for any reason and provide ADaM datasets in the same format as submitted with the 120-Day Safety Update.

2. Review all Psychiatry system-organ-class (SOC) adverse events in Study C-15 and Study C-16 for accuracy of the Preferred Term coding of the verbatim report of the adverse event. Provide a separate analysis for each study of all Psychiatry SOC events that led to an adverse event, a dose reduction or a dose interruption regardless of whether the event was considered related to drug or not.

3. The data provided in the application suggest a possible rebound effect following withdrawal of deutetrabenazine. You need to conduct a systematic evaluation of clinical dependence. We recommend that you evaluate clinical dependence in patients as they complete Study ARC-HD (SD-809-C-16). We suggest you evaluate patients for signs and symptoms of clinical dependence for two weeks after discontinuing deutetrabenazine. In patients who chose to discontinue treatment with deutetrabenazine early, you should extend the follow up period after discontinuing deutetrabenazine to 3 weeks.

You should administer the following scales to evaluate patients for signs of rebound:

- Hospital Anxiety and Depression Scale (HADS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Epworth Sleepiness Scale (ESS)
- Montreal Cognitive Assessment (MoCA)
- Total Maximal Chorea Score (TMC)
- Unified Huntington Disease Rating Scale, including behavioral and cognitive scores
- Unified Parkinson's Disease Rating Scale Speech/Dysarthria
- Barnes Akathisia Rating Scale (BARS)
- Berg Balance Test Score (BBT)

We recommend you submit for FDA review your planned analyses for abuse potential and rebound.

CONTAINER LABELS

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

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Stacy Metz, PharmD, Senior Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

ELLIS F UNGER
05/27/2016