NDA 208082

WRITTEN REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Xuan-Tien Huynh, PharmD
Manager, Global Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380

Dear Ms. Huynh:

Reference is made to your September 10, 2019, Proposed Pediatric Study Request for deutetrabenazine (TEV-50717).

These proposed studies will investigate the potential use of deutetrabenazine in the treatment of tics associated with Tourette syndrome in children and adolescents ages 6 to 16 years.

Tourette syndrome (TS) is characterized by multiple motor tics and one or more vocal tics, although the motor and vocal tics need not occur concurrently. The Diagnostic and Statistical Manual of Mental Disorders (DSM 5) criteria specify that tics must have persisted for at least 1 year since first tic onset and that onset occurs prior to age 18 years.[1] The typical age of onset is between 5 and 8 years and the average age of diagnosis is 8 years (Bitsko et al. 2014).[2] Tic severity usually intensifies in mid-childhood and declines during adolescence and adulthood. The prevalence of TS in children and adolescents is estimated to be 0.5% to 1%. TS is frequently comorbid with other psychiatric conditions including attention deficit-hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, and anxiety. TS has been associated with impaired social functioning, difficulties completing activities of daily living, physical pain, suicidal ideation, and significant caregiver burden (Robertson et al. 2017).[3]

Deutetrabenazine is approved for the treatment of Huntington's chorea and tardive dyskinesia in adult patients and is associated with risks of QTc prolongation, neuroleptic malignant syndrome, akathisia, and sedation in these populations. Deutetrabenazine carries a boxed warning for suicidal ideation and behaviors in adult patients with Huntington's disease. Extrapolation of efficacy from the approved populations to the

[1] American Psychiatric Association, 2013, Diagnostic and Statistical Manual of Mental Disorders (5th Ed.).
[2] Bitsko RH, JR Holbrook, SN Visser, JW Mink, SH Zinner, RM Ghandour, SJ Blumberg, 2014, A National Profile of Tourette Syndrome, 2011–2012, J Dev Behav Pediatr, 35(5): 317–322.
[3] Robertson MM, V Eapen, HS Singer, D Martino, JM Scharf, P Paschou, V Roessner, DW Woods, M Haritz, CA Mathews, R Crnec, JF Leckman, 2017, Gilles de la Tourette Syndrome, Nat Rev, 3: 1–20.

pediatric population with TS is not supported by adequate data; consequently, safety and efficacy studies in children and adolescents are necessary to understand the benefit-risk profile in the pediatric population with TS. The doses to be evaluated in the safety and efficacy studies were selected based on data from an open-label pilot study that evaluated the safety, tolerability, preliminary efficacy, and pharmacokinetics of deutetrabenazine in pediatric patients ages 12 to 18 years with TS.

TS is a disorder that primarily begins in childhood; therefore, the efficacy of proposed treatments must be established in the pediatric population. Studies in patients younger than 6 years of age are infeasible because of the very low incidence of TS diagnosed prior to age 6, including in neonates.

The proposed studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on deutetrabenazine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Nonclinical study(ies):

Based on review of the available nonclinical toxicology data, no additional nonclinical studies are required at this time to support the clinical studies described in this Written Request.

Clinical studies:

Studies 1 and 2: Two adequate and well-controlled pharmacokinetic (PK), efficacy, and safety studies in pediatric patients ages 6 to 16 years with TS. Study 2 must be a fixed-dose study. These studies must evaluate multiple doses. The doses will be based on weight and CYP2D6 impairment status.

Study 3: Long-term safety study in children and adolescents ages 6 to 16 years with TS. The duration of this study should be at least 12 months. Long-term safety may be evaluated with an open-label extension to the short-term efficacy studies (Studies 1 and 2).

For each study, you must submit a protocol for review and agreement by the Agency.

Objective of each study:

Studies 1 and 2: To evaluate the PK, efficacy, and safety of deutetrabenazine in the treatment of tics associated with TS in pediatric patients ages 6 to 16 years.

Study 3: To evaluate the long-term safety of deutetrabenazine in pediatric patients with TS ages 6 to 16 years.

Patients to be Studied:

- *Age groups in which studies will be performed:*

  Studies 1, 2, and 3: Patients with tics associated with TS ages 6 to 16 years.

- *Number of patients to be studied:*

  - *Study 1:* You must randomize at least a total of 116 patients for a two-arm study. This is sufficient to provide at least 90% power for an assumed treatment effect of 6 units in magnitude with an assumed standard deviation of 9.5 units.

  - *Study 2:* You must randomize at least a total of 150 patients for a three-arm study. This is sufficient to provide at least 90% power for an assumed treatment effect of 6.5 units in magnitude with an assumed standard deviation of 9.5 units.

  - *Study 3:* This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial or, if the trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A combined total of at least 100 patients with TS who are exposed to deutetrabenazine for at least 6 months is the minimum requirement for long-term safety. A sufficient number of patients should continue to be exposed for at least 12 months to adequately characterize safety.

Study endpoints:

- *Pharmacokinetic Endpoints:* You must obtain PK data from adolescents (ages 12 to 16 years) and younger pediatric patients (ages 6 to less than 12 years) to adequately characterize the PK of the parent compound and its major

active metabolites. The PK endpoints must include AUC, half-life, Cmax, Tmax, apparent volume of distribution, and oral clearance.

- *Efficacy Endpoints:* The change in the total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS) must serve as the primary efficacy endpoint. This endpoint is specific to TS and is known to be sensitive to the effects of drug treatment of tics associated with TS in the target population.

- *Safety Endpoints:* Safety outcomes must include routine safety assessments collected at baseline and appropriate follow-up times, including vital signs (heart rate and blood pressure), weight, height (as measured by stadiometer), clinical laboratory measures (routine blood chemistry, including liver function tests and bilirubin; hematology; and urinalysis), electrocardiograms, and monitoring for adverse events as agreed upon in the protocol. Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children, you must provide an assessment of psychiatric adverse events (i.e., depressed mood, anxiety, suicidal and homicidal ideation and behaviors, and psychosis). You must collect blood samples for CYP2D6 genotyping.

  The following adverse events must be actively monitored:

  You must prospectively assess safety concerns including depression, QT prolongation, akathisia, agitation, restlessness, and sedation/somnolence. You should obtain serum prolactin levels in a subset of patients sufficient to characterize safety. Assessment methods and frequency of evaluation of these adverse events must be agreed upon with the Agency in the protocols. All clinical protocols must include a prospective assessment for suicidal ideation and behavior. These assessments must be agreed upon with the Agency in the protocol.

  A Data Monitoring Committee (DMC) must be included.

- *Statistical information, including power of study(ies) and statistical assessments:*

  - Sample Size Requirements: The efficacy studies must be designed with at least 90% statistical power to detect a clinically meaningful treatment effect. You must reach an agreement with the Agency on the treatment effect (postulated magnitude of treatment effect along with its standard deviation) used for sample size calculation.

    Analysis considerations: The efficacy studies must have detailed statistical analysis plans (SAPs), and you must obtain agreement with the Agency on the final plans.

With respect to the primary efficacy endpoint as well as any secondary endpoints intended for inclusion in labeling, the protocol should clearly describe the primary estimand for each endpoint and provide a rationale to support the proposed estimands. You must also plan to pre-specify in detail sensitivity analyses to assess the impact of the violation of the missing data assumptions required for the primary analysis.

- For each key safety endpoint, you must specify:
  - Definition of exposure time (time at risk)
  - Sample size requirements:
  - Analysis considerations

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - Dosage form: tablet
  - Route of administration: oral
  - Regimen: twice daily

  Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population studied (i.e., receives approval);
  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

(3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and, as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that deutetrabenazine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[4] You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[5] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before 7/31/2021. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[5] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

(1) the type of response to the Written Request (i.e., complete or partial response);
(2) the status of the application (i.e., withdrawn after the supplement has been filed or pending);
(3) the action taken (i.e., approval, complete response); or
(4) the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[6]

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial

[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

results. Additional information on submission of such information can be found on the Clinical Trials website.[7]

If you have any questions, call Hiren Patel, Regulatory Project Manager, at 301-796-2087.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

[7] www.ClinicalTrials.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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