DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

WRITTEN REQUEST

Takeda Pharmaceuticals USA, Inc.
Attention: Joanna Sambor, M.S.
Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Sambor:

Reference is made to your May 28, 2015 Proposed Pediatric Study Request for Brintellix (vortioxetine) tablets.

To obtain needed pediatric information on vortioxetine, 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 (FDAAA) of 2007, that you submit information from the studies described below.

Background

General Advice for Developing a Drug for Pediatric Major Depressive Disorder

Pediatric major depressive disorder (MDD) is associated with significant social, academic and developmental impairment (Birmaher 2010), with prevalence rates of 1-2% in children (Zalsman 2006) and 11% in adolescents (Merikangas 2010). Along with the above morbidities, MDD is associated with an elevated risk of suicide, with suicide being reported as the third leading cause of death in 10-22 year-olds (Centers for Disease Control and Prevention 2013).

Under current regulations (21 CFR 201.57(f)(9)(iv) in the 2008 CFR), a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity, if it were believed that depression was essentially the same disease in adults and children.

Under FDAAA (2007), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (1998).

This approach also requires some belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies

pertinent to pediatric patients. At the present time, however, there are insufficient data to support reliance on studies in adults with MDD to support an indication in pediatrics. Our concern about the ability to extrapolate data from adults with MDD to pediatric patients with MDD is more than theoretical; although we acknowledge that fluoxetine and escitalopram have been demonstrated to be effective in treating MDD in pediatric patients, other antidepressant drugs have not been reliably demonstrated to be of benefit in pediatric MDD.

Previously studied antidepressants, with the exceptions of fluoxetine and escitalopram, have not shown efficacy for the treatment of pediatric MDD. Those negative findings have led to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Therefore, adequate evaluation of the effect of an antidepressant in pediatric MDD, even for an antidepressant already approved in adult major depressive disorder, will require two independent, adequate and well controlled clinical trials in pediatric patients, in addition to pharmacokinetic and safety information in the relevant pediatric age groups.

For pediatric MDD, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17). We are waiving the pediatric study requirement for ages 0 to 6 years, including neonates, in the treatment of MDD because necessary studies are impossible or highly impractical. This is because of the low prevalence of MDD in this age range.

The inclusion of a placebo control group is scientifically necessary; neither the safety nor the efficacy data would be interpretable without a placebo control group. If the studies could not provide meaningful safety and efficacy data, it is difficult to justify exposing pediatric patients to the study drug (Refer to ICH-E10 guidelines: Choice of Control Group and Related Issues in Clinical Trials). High-risk patients (e.g., at risk for suicide or with unstable illness) will be excluded from the studies. Patients in the placebo and active drug groups will be permitted to receive concomitant non-pharmacologic treatments during the course of the studies. In addition, patients in the placebo and active drug groups will be withdrawn from the study if they have an exacerbation of illness that requires definitive treatment. Therefore, the withholding of known effective treatment from pediatric patients who are included in a placebo group is ethically acceptable as presenting no more than a minor increase over minimal risk (21 CFR 50.53).

Specific Study Requirements for a Development Program in Pediatric Major Depressive Disorder

Objective/Rationale

The overall goal of the development program should be to establish the safety and efficacy of the study drug in the treatment of pediatric major depressive disorder, and to develop other information, e.g., pharmacokinetic data, pertinent to use of the drug in the pediatric population.

Required Studies

- Nonclinical Toxicology Study
- Pediatric Pharmacokinetic Study
- Children (ages 7-11), Efficacy and Safety Study
- Adolescents (ages 12-17), Efficacy and Safety Study

Study Design

- *Nonclinical studies*:

  Based on review of the nonclinical toxicology data that have already been submitted, no additional animal studies are required at this time to support the clinical studies described in this Written Request. In addition to standard nonclinical toxicology studies, you have submitted results from a study assessing general toxicity, neurobehavioral development, and reproductive development in juvenile rats administered vortioxetine orally from postnatal day (PND) 21 to PND 91. We consider this study adequate to support studies in pediatric patients (6 years of age and older).

- *Pharmacokinetic Study:*

  Study 1: Pediatric Pharmacokinetic Study

  You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population pharmacokinetic approaches. You must perform preliminary tolerability studies (in which pharmacokinetic data can be obtained) to explore the range of tolerated doses before conducting the definitive efficacy and safety studies. You must use the pharmacokinetic and tolerability information to establish doses for the clinical efficacy and safety trials in pediatric patients 7-11 years of age and 12-17 years of age. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, under Clinical/Pharmacological (Draft)].

  We acknowledge that you have submitted a pediatric tolerability and pharmacokinetic study report in patients 7-17 years of age. We consider this study is adequate to support studies in pediatric patients.

- *Clinical studies:*

  Study 2: Child Efficacy and Safety Study (Ages 7-11)

  You must conduct a randomized, double-blind, placebo- and active-controlled, parallel-group, short-term, fixed-dose efficacy and safety study of vortioxetine in the treatment of pediatric patients (ages 7 to 11 years) with a diagnosis of MDD. The trial should be designed in a way that fully evaluates the drug in children, therefore the study must assess at least 2 fixed doses, and must include an active control (fluoxetine) arm. The selected doses must be agreed upon by the Agency. The fixed-dose design is necessary for assessing potential dose-response relationships for efficacy and safety and to determine the lowest effective dose. The protocol and statistical analysis plan (SAP) must be submitted and agreed upon by the Agency before the study is initiated.

Study 3: Adolescent Efficacy and Safety Study (Ages 12-17)

You must conduct a randomized, double-blind, placebo- and active-controlled, parallel-group, short-term, fixed-dose efficacy and safety study of vortioxetine in the treatment of pediatric patients (ages 12 to 17 years) with a diagnosis of MDD. The trial should be designed in a way that fully evaluates the drug in children, therefore the study must assess at least 2 fixed doses, and must include an active control (fluoxetine) arm. The selected doses must be agreed upon by the Agency. The fixed-dose design is necessary for assessing potential dose-response relationships for efficacy and safety and to determine the lowest effective dose. The protocol and SAP must be submitted and agreed upon by the Agency before the study is initiated.

Study 4: Long-term Safety Study

You must collect longer-term safety data for a minimum duration of 6 months of exposure to vortioxetine in pediatric patients (ages 7 to 17 years) with a diagnosis of MDD. The longer-term safety data could be obtained from open-label studies, e.g., a longer-term open-label extension of the controlled efficacy studies, or from separate longer-term open-label safety studies. The long-term safety data must evaluate doses at or above the dose or doses identified as effective in an adequately designed efficacy trial, as described above. The protocol must be submitted and agreed upon by the Agency before the study is initiated.

Studies 2, 3, and 4 must allow for early discontinuation for patients whose symptoms worsen or are not adequately controlled on assigned treatment. At least 50% of patients assigned to active drug must complete to the nominal endpoint of these studies in order for the studies to be considered a completed trial and, therefore, responsive to this request. You must collect and provide complete information for the reasons patients discontinue from the studies.

Age Groups of Study Subjects

Study 1: Children and adolescents, 7-17 years of age
Study 2: Children, 7-11 years of age
Study 3: Adolescents, 12-17 years of age
Study 4: Children and adolescents, 7-17 years of age

At least 40% of subjects in Study 4 must be in the 7-11 year-old group, with an even distribution of age ranges. In all 4 studies, the numbers of male and female study subjects should reflect the gender distribution of MDD in the specific age group.

Number of Patients to be Studied

Study 1 must be prospectively powered to target a 95% CI (confidence interval) within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for vortioxetine, with at least 80% power for each of the pediatric patient groups (i.e., pediatric patients 7-11 years of age and adolescents 12-17 years of age). In addition, the full spectrum of age strata in the 7 to 17 continuum must be represented (e.g., 7-9, 10-11, 12-14, 15-17).

Study 2 and Study 3 must include sufficient numbers of patients to provide 85% statistical power to detect a clinically meaningful difference between drug and placebo. You must conduct an interim analysis to estimate variance late in the study, and increase the sample size if necessary to ensure that the study has adequate power (see Statistical Information).

The safety study must include at least 100 patients exposed to vortioxetine for at least 6 months.

Representation of Ethnic and Racial Minorities: The studies must have 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.

Entry Criteria

The studies must include a valid and reliable diagnostic method for recruiting and enrolling children and adolescents meeting DSM-5 criteria for MDD. Given the difficulty in making the diagnosis for screening purposes, a clinical interview of pediatric patients and their caregivers must be conducted by an adequately trained clinician (e.g., a child psychiatrist or other clinician adequately trained to conduct such interviews) to assure accurate diagnosis. The diagnosis must be confirmed using a reliable and valid semi-structured interview.

Study Endpoints

Pharmacokinetic Endpoints

Pharmacokinetic assessments must be conducted with respect to vortioxetine and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected must provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max}, T_{max}, in pediatric subjects in the relevant age range. The pharmacokinetic endpoints for vortioxetine must also include clearance and volume of distribution. A summary (mean, median) of pharmacokinetic parameters such as half-life must also be reported.

Efficacy Endpoints

You must use a scale specific to pediatric MDD and sensitive to the effects of drug treatment of MDD in the target population, e.g., the Children's Depression Rating Scale-Revised (CDRS-R). It is essential to identify a primary outcome (or outcomes, if more than one is considered important) for the controlled efficacy trials; ordinarily this would be the change from baseline to endpoint on the symptom rating scale you have chosen for the studies.

Safety Endpoints

You must perform routine safety assessments at baseline and at appropriate follow-up time points in all studies. The assessments must include physical examination, vital signs (pulse rate and blood pressure), weight, height (as measured by stadiometer), clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; glucose; serum lipids; and urinalysis), ECG, and monitoring for adverse events, including suicidal ideation and suicidal behavior.

Suicidality Assessments in Clinical Studies

There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess this in clinical trials. Given this development, the Division of Psychiatry Products (DPP) has developed a policy regarding how we will address this

issue. All clinical protocols for products developed in DPP, whatever the indication, must include a prospective assessment for suicidality. These assessments must be included in every clinical protocol, at every planned visit, and in every phase of development. For additional information, please see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf.

There are two reasons for implementing this policy. One is to ensure that we collect better data on suicidality than we have in the past, so that in the future we will be able to conduct additional meta-analyses on this matter. A second reason is to ensure that patients in clinical trials who are experiencing suicidality are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidality.

- *Known drug safety concerns and monitoring:* In each of the pediatric studies, you must adequately assess the following safety concerns that were identified in the adult MDD vortioxetine program including nausea, constipation, vomiting, and hyponatremia, as these represent important side effects in pediatric patients.

- *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: once 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(s) 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 compounded 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 compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding 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.

- *Statistical information, including power of studies and statistical assessments:* Studies 2 and 3 must both have detailed SAPs. The preliminary SAPs must be submitted for comment and you must obtain agreement on the final plans prior to initiation of the studies.

  The studies must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably best based on typical effects in adults) at a Type I error rate of 5% (two-sided). You must obtain agreement with the Division on the treatment effect used for sample size calculation prior to initiating the studies. For the purpose of satisfying the Written Request, this treatment effect might, for example, be defined as a 4-unit difference between drug and placebo in the change from baseline in the CDRS-R total score.

  To ensure your studies are adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. Such interim analyses must be performed when the studies are close to completion (for example, when >75% of initially randomized patients have completed/discontinued). You may estimate the variability based on a blinded and pooled analysis of all groups. If you want to perform an interim efficacy assessment at this time or at some other point in time, you must propose an appropriate alpha adjustment method.

- *Pharmacokinetic Analysis in the Pediatric Tolerability and Pharmacokinetic Study:* You must perform a descriptive analysis of the pharmacokinetic parameters.

- *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 vortioxetine 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. 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 the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before March 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.

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 studies 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the 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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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 Public Health Service Act (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 results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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

Sincerely,
{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ELLIS F UNGER
09/24/2015