DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447

NDA APPROVAL

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

Dear Ms. Sambor:

Please refer to your New Drug Application (NDA) dated October 2, 2012, received October 2, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brintellix (vortioxetine) 5 mg, 10 mg, 15 mg, and 20 mg tablets.

We acknowledge receipt of your amendment(s) dated:

October 3, 2012	December 17, 2012	March 7, 2013	May 29, 2013
October 16, 2012 (2)	December 20, 2012	March 12, 2013	May 31, 2013
October 19, 2012	January 17, 2013	March 21, 2013	June 20, 2013
October 26, 2012	January 18, 2013	March 28, 2013	June 28, 2013
November 9, 2012	January 24, 2013	April 8, 2013	July 16, 2013
November 16, 2012	January 30, 2013	April 16, 2013	August 2, 2013
December 7, 2012	February 7, 2013	April 25, 2013	August 12, 2013
December 11, 2012	February 13, 2013 (2)	May, 3, 2013 (2)	August 20, 2013
December 12, 2012	February 19, 2013	May 17, 2013	September 23, 2013

This new drug application provides for the use of Brintellix (vortioxetine) tablets for the treatment of major depressive disorder (MDD).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your September 23, 2013, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Brintellix (vortioxetine) was not referred to an FDA advisory committee because the clinical trial designs are similar to previously approved products for the treatment of major depressive disorder. Additionally, evaluation of the effectiveness and safety data did not raise significant safety or efficacy issues in the adult major depressive disorder population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years because necessary studies are impossible or highly impracticable. This is because of the low prevalence of MDD in this age group.

We are deferring submission of your pediatric studies for ages 7 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2084-1 Deferred pediatric study under PREA for the treatment of major depressive disorder in pediatric patients aged 7 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing vortioxetine in the relevant pediatric population.

Final Protocol Submission:	Submitted 11/18/2011
Trial Completion:	07/2014
Final Report Submission:	02/2015

2084-2 Deferred pediatric study under PREA for the treatment of major depressive disorder in children aged 7 to 11years. Conduct a study to obtain data on the efficacy and safety of vortioxetine in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

Final Protocol Submission:	08/2015
Trial Completion:	10/2018
Final Report Submission:	04/2019

2084-3 Deferred pediatric study under PREA for the treatment of major depressive disorder in adolescents aged 12 to17 years. Conduct a study to obtain data on the efficacy and safety of vortioxetine in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

Final Protocol Submission:	08/2015
Trial Completion:	10/2018
Final Report Submission:	04/2019

Submit the protocols to IND (b) (4) with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing 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 REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk associated with an increase in Brintellix (vortioxetine) exposure in patients with severe hepatic impairment or those taking other drugs that inhibit major transporters.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to evaluate the potential for an unexpected serious risk of increased Brintellix (vortioxetine) exposure in patients with severe hepatic impairment. In addition, we have determined that a non-clinical transporter study should be conducted to assess the potential risk of the co-medications when Brintellix (vortioxetine) is used in combination.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2084-4 In-vivo pharmacokinetic trial in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.

The timetable you agreed to on September 27, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2014
Trial Completion:	09/2015
Final Report Submission:	05/2016

2084-5 In-vitro determination of vortioxetine and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

The timetable you agreed to on September 27, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2014
Study Completion:	05/2015
Final Report Submission:	08/2015

Submit the protocol(s) to your IND 76307, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2084-6 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of vortioxetine in the treatment of adults with major depressive disorder in the US. This trial must include a placebo group and several fixed doses and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of vortioxetine. Because the short-term trials appear to show that higher doses have demonstrated better treatment effects in the US population compared to the rest of the world, it is important to establish the dose-response for maintenance in the US. This trial should randomize patients on stable doses of vortioxetine to several different doses (e.g., 5 mg, 10 mg, and 20 mg) of vortioxetine (and to placebo) during the maintenance phase.

The timetable you agreed to on September 27, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2014
Trial Completion:	04/2019
Final Report Submission:	04/2020

Submit the clinical protocol to your IND 76307 for this product. Submit the postmarketing final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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. 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.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. 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, contact Hiren Patel, PharmD, Regulatory Project Manager, at (301) 796-2087 or hiren.patel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

ROBERT TEMPLE
09/30/2013