CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204447Orig1s009

Trade Name:	TRINTELLIX
Generic or Proper Name:	vortioxetine
Sponsor:	Takeda Pharmaceuticals
Approval Date:	March 10, 2017
Indication:	TRINTELLIX is indicated for the treatment of major depressive disorder (MDD)

CENTER FOR DRUG EVALUATION AND RESEARCH

204447Orig1s009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447/S-009

SUPPLEMENT APPROVAL

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

Dear Ms. Sambor:

Please refer to your Supplemental New Drug Application (sNDA) dated May 10, 2016, received May 10, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trintellix (vortioxetine) 5 mg, 10 mg, and 20 mg tablets.

This Prior Approval supplemental new drug application proposes to add text in the Clinical Studies section of the US package insert regarding vortioxetine's effect on the Clinical Global Impression-Improvement scale as well as to make revisions to product labeling to comply with the Pregnancy and Lactation Labeling Rule.

APPROVAL & LABELING

We have completed our review of this supplemental 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

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).
You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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).

If you have any questions, call Jasmeet (Mona) Kalsi, Regulatory Project Manager, at (240) 402-8977.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MITCHELL V Mathis
03/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s009

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRINTELLIX safely and effectively. See full prescribing information for TRINTELLIX.

TRINTELLIX (vortioxetine) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **TRINTELLIX has not been evaluated for use in pediatric patients (8.4).**

----------INDICATIONS AND USAGE----------
TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) (1, 14).

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dose is 10 mg administered orally once daily without regard to meals (2.1).
- The dose should then be increased to 20 mg/day, as tolerated (2.1).
- Consider 5 mg/day for patients who do not tolerate higher doses (2.1).
- TRINTELLIX can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible (2.3).
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers (2.6).

----------DOSAGE FORMS AND STRENGTHS----------
TRINTELLIX is available as 5 mg, 10 mg and 20 mg immediate release tablets (3).

----------CONTRAINDICATIONS----------
- Hypersensitivity to vortioxetine or any components of the TRINTELLIX formulation (4).
- Monoamine Oxidase Inh bitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX. Do not use TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue (4).

----------WARNINGS AND PRECAUTIONS----------
- Serotonin Syndrome has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with TRINTELLIX, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue TRINTELLIX and initiate supportive treatment. If concomitant use of TRINTELLIX with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).
- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.3).
- Activation of Mania/Hypomania can occur with antidepressant treatment. Screen patients for bipolar disorder (5.4).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.5).
- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.6).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong inhibitors of CYP2D6: Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) is coadministered (2.6 and 7.3).
- Strong CYP Inducers: Consider increasing TRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose (2.7 and 7.3).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Third trimester use may increase risk for persistent pulmonary hypertension and withdrawal in the newborn (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

TRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations (8.4)].*

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD). The efficacy of TRINTELLIX was established in six 6 to 8 week studies (including one study in the elderly) and one maintenance study in adults *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

The recommended starting dose is 10 mg administered orally once daily without regard to meals. Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States. The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials. A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses *[see Clinical Studies (14)].*

2.2 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depression should be followed by several months or longer of sustained pharmacologic therapy. A maintenance study of TRINTELLIX demonstrated that TRINTELLIX decreased the risk of recurrence of depressive episodes compared to placebo.

2.3 Discontinuing Treatment

Although TRINTELLIX can be abruptly discontinued, in placebo-controlled trials patients experienced transient adverse reactions such as headache and muscle tension following abrupt discontinuation of TRINTELLIX 15 mg/day or 20 mg/day. To avoid these adverse reactions, it is recommended that the dose be decreased to 10 mg/day for one week before full discontinuation of TRINTELLIX 15 mg/day or 20 mg/day *[see Adverse Reactions (6)]*.

2.4 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with TRINTELLIX to avoid the risk of Serotonin Syndrome

[see Warnings and Precautions (5.2)]. Conversely, at least 21 days should be allowed after stopping TRINTELLIX before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)].*

2.5 Use of TRINTELLIX with Other MAOIs such as Linezolid or Methylene Blue

Do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4)].*

In some cases, a patient already receiving TRINTELLIX therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, TRINTELLIX should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 21 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with TRINTELLIX may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)].*

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with TRINTELLIX is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)].*

2.6 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors

The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued *[see Drug Interactions (7.3)]*.

2.7 Use of TRINTELLIX in Patients Taking Strong CYP Inducers

Consider increasing the dose of TRINTELLIX when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for greater than 14 days. The maximum recommended dose should not exceed three times the original dose. The dose of TRINTELLIX should be reduced to the original level within 14 days, when the inducer is discontinued *[see Drug Interactions (7.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TRINTELLIX is available as immediate-release, film-coated tablets in the following strengths:

- 5 mg: pink, almond shaped biconvex film coated tablet, debossed with “5” on one side and “TL” on the other side
- 10 mg: yellow, almond shaped biconvex film coated tablet, debossed with “10” on one side and “TL” on the other side
- 20 mg: red, almond shaped biconvex film coated tablet, debossed with “20” on one side and “TL” on the other side

4 CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with TRINTELLIX.
- The use of MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*.

Starting TRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

Table 1. Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	
Increases Compared to Placebo	
<18	14 additional cases
18 - 24	5 additional cases

Decreases Compared to Placebo	
25 - 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that TRINTELLIX is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including TRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants,

fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of TRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. TRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking TRINTELLIX. TRINTELLIX should be discontinued before initiating treatment with the MAOI *[see Contraindications (4) and Dosage and Administration (2.4)]*.

If concomitant use of TRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions (7.2)]*.

5.4 Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in <0.1% of patients treated with TRINTELLIX in pre-marketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use TRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.5 Angle Closure Glaucoma

Angle Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs, including TRINTELLIX, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.6 Hyponatremia

Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with TRINTELLIX in a pre-marketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of TRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications (4)]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.3)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.4)]*
- Hyponatremia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Studies Experience

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 studies of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure

TRINTELLIX was evaluated for safety in 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre-marketing clinical studies; 2616 of those patients were exposed to TRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily and 204 patients were exposed to TRINTELLIX in a 24 week to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily. Patients from the 6 to 8 week studies continued into 12 month open-label studies. A total of 2586 patients were exposed to at least one dose of TRINTELLIX in open-label studies, 1727 were exposed to TRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies

The most commonly observed adverse reactions in MDD patients treated with TRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any TRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 2. Common Adverse Reactions Occurring in ≥2% of Patients Treated with any TRINTELLIX Dose and at Least 2% Greater than the Incidence in Placebo-treated Patients

System Organ Class Preferred Term	TRINTELLIX 5 mg/day	TRINTELLIX 10 mg/day	TRINTELLIX 15 mg/day	TRINTELLIX 20 mg/day	Placebo
	N=1013 %	N=699 %	N=449 %	N=455 %	N=1621 %
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus*	1	2	3	3	1

*includes pruritus generalized

Nausea

Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2)*. It was usually considered mild or moderate in intensity and the median duration was 2 weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of TRINTELLIX treatment with 15 to 20% of patients experiencing nausea after 1 to 2 days of treatment. Approximately 10% of patients taking TRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction

Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

In the MDD 6 to 8 week controlled trials of TRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was

used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed treatment-emergent sexual dysfunction when treated with TRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	**TRINTELLIX 10 mg/day** N=94:86†	**TRINTELLIX 15 mg/day** N=57:67†	**TRINTELLIX 20 mg/day** N=67:59†	**Placebo** N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

*Incidence based on number of subjects with sexual dysfunction during the study / number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

†Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

Adverse Reactions Following Abrupt Discontinuation of TRINTELLIX Treatment

Discontinuation symptoms have been prospectively evaluated in patients taking TRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of TRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests

TRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of TRINTELLIX *[see Warnings and Precautions (5.6)]*. In the 6 month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12 week, open-label phase, there were no clinically important changes in lab test parameters between TRINTELLIX and placebo-treated patients.

Weight

TRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the 6 month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12 week, open-label phase, there was no significant effect on body weight between TRINTELLIX and placebo-treated patients.

Vital Signs
TRINTELLIX has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

Other Adverse Reactions Observed in Clinical Studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Ear and labyrinth disorders — vertigo

Gastrointestinal disorders — dyspepsia

Nervous system disorders — dysgeusia

Vascular disorders — flushing

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TRINTELLIX. 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.

Metabolic disorders — weight gain

Gastrointestinal System — acute pancreatitis

7 DRUG INTERACTIONS

7.1 CNS Active Agents

Monoamine Oxidase Inhibitors
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Dosage and Administration (2.4), Contraindications (4) and Warnings and Precautions (5.2)]*.

Serotonergic Drugs
Based on the mechanism of action of TRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when TRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if TRINTELLIX is co-administered with other serotonergic drugs. Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions (5.2)].*

Other CNS Active Agents
No clinically relevant effect was observed on steady state lithium exposure following coadministration with multiple daily doses of TRINTELLIX. Multiple doses of TRINTELLIX did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam. A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg). Details on the potential pharmacokinetic interactions between TRINTELLIX and bupropion can be found in Section 7.3.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

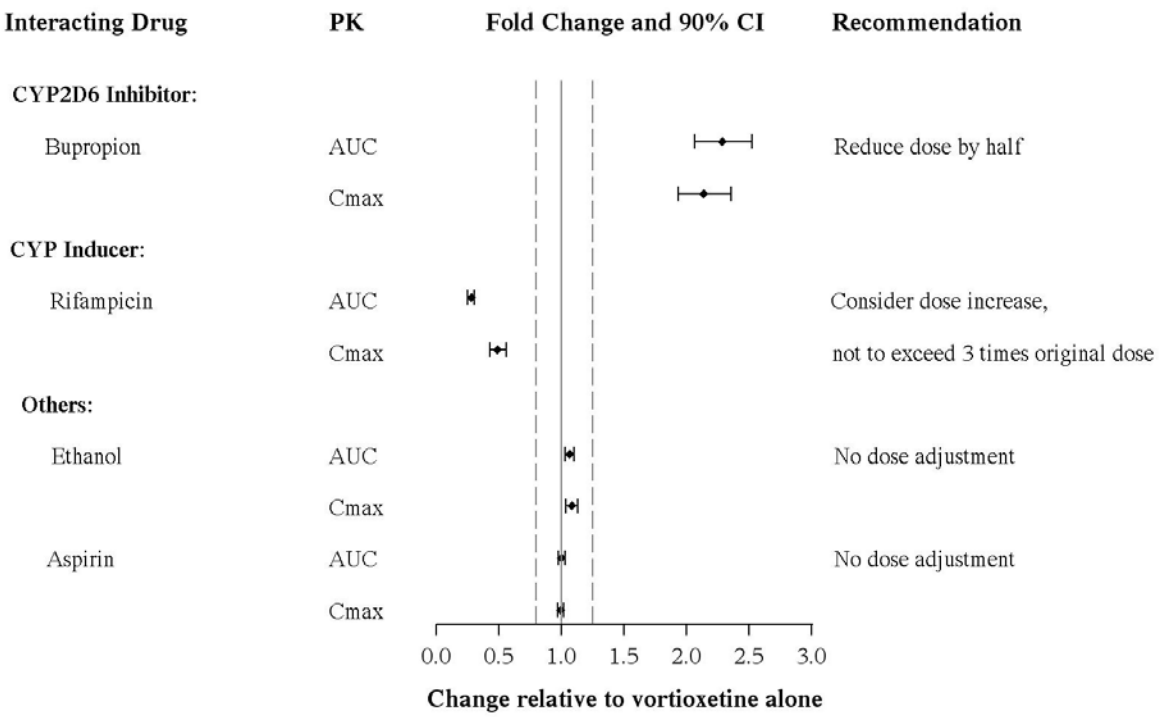
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of TRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin *[see Drug Interactions (7.4)]*. Coadministration of aspirin 150 mg/day with multiple daily doses of TRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Drug Interactions (7.4)]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when TRINTELLIX is initiated or discontinued *[see Warnings and Precautions (5.3)].*

7.3 Potential for Other Drugs to Affect TRINTELLIX

Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the TRINTELLIX dose when a strong CYP inducer (e.g., rifampicin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose *[see Dosage and Administration (2.5 and 2.6)]* (*Figure 1*).

Figure 1. Impact of Other Drugs on Vortioxetine PK



7.4 Potential for TRINTELLIX to Affect Other Drugs

No dose adjustment for the comedications is needed when TRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinide), CYP2C9 (e.g., S-warfarin), CYP2C19 (e.g., diazepam), CYP2D6 (e.g.,

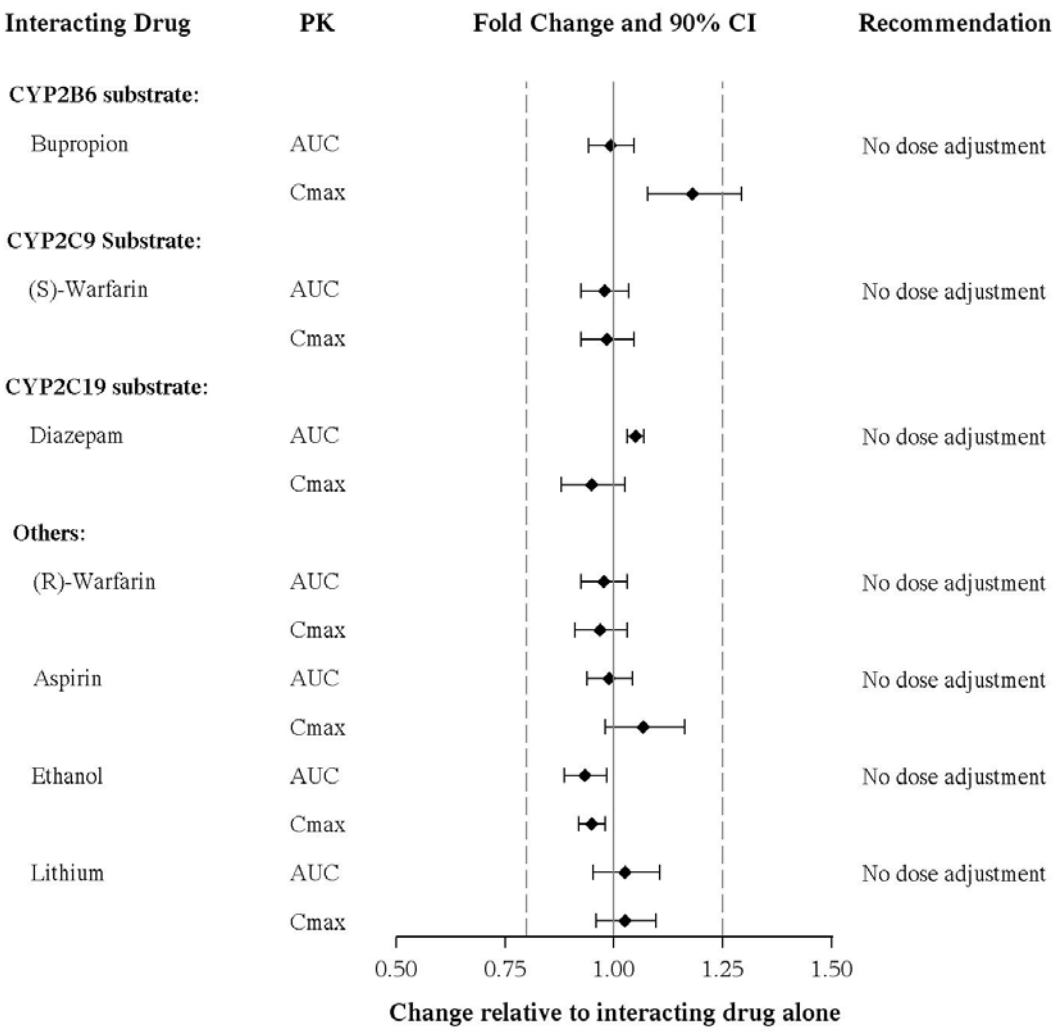
venlafaxine), CYP3A4/5 (e.g., budesonide), and P-gp (e.g., digoxin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

Vortioxetine and its metabolites are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and P-gp. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of TRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of TRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates *(Figure 2).*

Because vortioxetine is highly bound to plasma protein, coadministration of TRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug. However, in a clinical study with coadministration of TRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed *[see Drug Interactions (7.2)].*

Figure 2. Impact of Vortioxetine on PK of Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited human data on TRINTELLIX use during pregnancy to inform any drug-associated risks. However, there are clinical considerations regarding neonates exposed to SSRIs and SNRIs, including TRINTELLIX, during the third trimester of pregnancy *[see Clinical Considerations]*. Vortioxetine administered to pregnant rats and rabbits during the period of organogenesis at doses ≥15 times and 10 times the maximum recommended human dose (MRHD), respectively, resulted in decreased fetal body weight and delayed ossification. No malformations were seen at doses up to 77 times and 58 times the MRHD, respectively. Vortioxetine administered to pregnant rats during gestation and lactation at oral doses ≥20 times the MRHD resulted in a decrease in the number of live-born pups and an increase in early postnatal pup mortality. Decreased pup weight at birth to weaning occurred at 58 times the MRHD and delayed physical development occurred at ≥20 times the MRHD. These effects were not seen at 5 times the MRHD *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Fetal/Neonatal adverse reactions

Exposure to serotonergic antidepressants, including TRINTELLIX, in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN). Monitor neonates who were exposed to TRINTELLIX in the third trimester of pregnancy for PPHN and drug discontinuation syndrome *[see Data]*.

Data

Human Data

Third Trimester Exposure

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. These findings are based on post-marketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or possibly, a drug discontinuation syndrome. In some cases, the clinical picture was consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997-2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs "in early pregnancy" and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs "in early pregnancy" and an antenatal SSRI prescription "in later pregnancy."

Animal Data

In pregnant rats and rabbits, no malformations were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis, in rats and rabbits, respectively. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses of 40 and 120 mg/kg (20 and 58 times the MRHD, respectively) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

8.2 Lactation

Risk Summary

There is no information regarding the presence of vortioxetine in human milk, the effects on the breastfed infant, or the effects on milk production. Vortioxetine is present in rat milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRINTELLIX and any potential adverse effects on the breastfed child from TRINTELLIX or from the underlying maternal condition.

Data

Animal Data

Administration of [^{14}C]-vortioxetine to lactating rats at an oral dose of 20 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis, resulted in drug-related material in milk secretion. Milk to plasma ratio in lactating rats was 1, 1.2, 0.5, and 0.5 at 2, 6, 24, and 72 hours post dose.

8.4 Pediatric Use

Clinical studies on the use of TRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of TRINTELLIX in the pediatric population have not been established.

8.5 Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 3)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs. young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

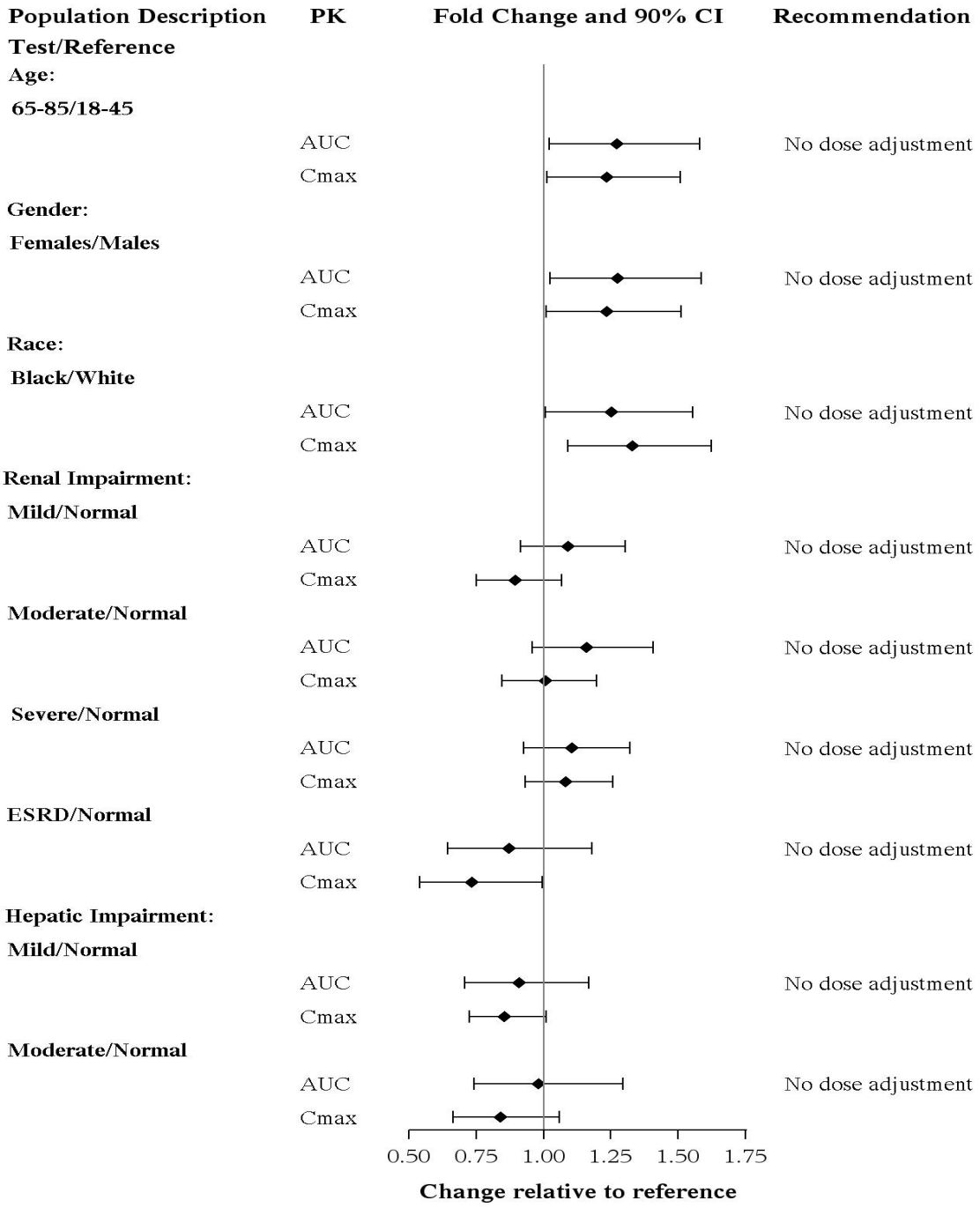
Of the 2616 subjects in clinical studies of TRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.6)].*

8.6 Use in Other Patient Populations

No dose adjustment of TRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment *(Figure 3)*. TRINTELLIX has not been studied in patients with severe hepatic impairment. Therefore, TRINTELLIX is not recommended in patients with severe hepatic impairment.

Figure 3. Impact of Intrinsic Factors on Vortioxetine PK



9 DRUG ABUSE AND DEPENDENCE

TRINTELLIX is not a controlled substance.

10 OVERDOSAGE

10.1 Human Experience

There is limited clinical trial experience regarding human overdosage with TRINTELLIX. In pre-marketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of TRINTELLIX in the dose range of 40 to 75 mg was

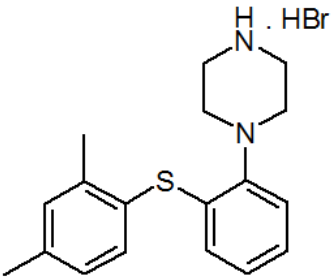
associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

10.2 Management of Overdose

No specific antidotes for TRINTELLIX are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

TRINTELLIX is an immediate-release tablet for oral administration that contains the beta (β) polymorph of vortioxetine hydrobromide (HBr), an antidepressant. Vortioxetine HBr is known chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide. The empirical formula is $C_{18}H_{22}N_2S$, HBr with a molecular weight of 379.36 g/mol. The structural formula is:



Vortioxetine HBr is a white to very slightly beige powder that is slightly soluble in water.

Each TRINTELLIX tablet contains 6.355 mg, 12.71 mg or 25.42 mg of vortioxetine HBr equivalent to 5 mg, 10 mg, or 20 mg of vortioxetine, respectively. The inactive ingredients in TRINTELLIX tablets include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating which consists of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg and 20 mg) and iron oxide yellow (10 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

12.2 Pharmacodynamics

Vortioxetine binds with high affinity to the human serotonin transporter (Ki=1.6 nM), but not to the norepinephrine (Ki=113 nM) or dopamine (Ki>1000 nM) transporters. Vortioxetine potently and selectively inhibits reuptake of serotonin (IC50=5.4 nM). Vortioxetine binds to 5-HT3 (Ki=3.7 nM), 5-HT1A (Ki=15 nM), 5-HT7 (Ki=19 nM), 5-HT1D (Ki=54 nM), and 5-HT1B (Ki=33 nM), receptors and is a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist.

In humans, the mean 5-HT transporter occupancy, based on the results from 2 clinical PET studies using 5-HTT ligands ([^{11}C]-MADAM or [^{11}C]-DASB), was approximately 50% at 5 mg/day, 65% at 10 mg/day and approximately 80% at 20 mg/day in the regions of interest.

Effect on Cardiac Repolarization

The effect of vortioxetine 10 mg and 40 mg administered once daily on QTc interval was evaluated in a randomized, double-blind, placebo-, and active-controlled (moxifloxacin 400 mg), four-treatment-arm parallel study in 340 male subjects. In the study the upper bound of the one-sided 95% confidence interval for the QTc was below 10 ms, the threshold for regulatory concern. The oral dose of 40 mg is sufficient to assess the effect of metabolic inhibition.

Effect on Driving Performance

In a clinical study in healthy subjects, TRINTELLIX did not impair driving performance, or have adverse psychomotor or cognitive effects following single and multiple doses of 10 mg/day.

12.3 Pharmacokinetics

Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine (2.5 mg to 60 mg) are linear and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately 66 hours, and steady-state plasma concentrations are typically achieved within two weeks of dosing.

Absorption

The maximal plasma vortioxetine concentration (C_{max}) after dosing is reached within 7 to 11 hours postdose (T_{max}). Steady-state mean C_{max} values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. Absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed.

Distribution

The apparent volume of distribution of vortioxetine is approximately 2600 L, indicating extensive extravascular distribution. The plasma protein binding of vortioxetine in humans is 98%, independent of plasma concentrations. No apparent difference in the plasma protein binding between healthy subjects and subjects with hepatic (mild, moderate) or renal (mild, moderate, severe, ESRD) impairment is observed.

Metabolism and Elimination

Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers.

Following a single oral dose of [^{14}C]-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. Negligible amounts of unchanged vortioxetine were excreted in the urine up to 48 hours. The presence of hepatic (mild or moderate) or renal impairment (mild, moderate, severe and ESRD) did not affect the apparent clearance of vortioxetine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which CD-1 mice and Wistar rats were given oral doses of vortioxetine up to 50 and 100 mg/kg/day for male and female mice, respectively, and 40 and 80 mg/kg/day for male and female rats, respectively, for two years. The doses in the

two species were approximately 12, 24, 20, and 39 times, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

In rats, the incidence of benign polypoid adenomas of the rectum was statistically significantly increased in females at doses 39 times the MRHD, but not at 15 times the MRHD. These were considered related to inflammation and hyperplasia and possibly caused by an interaction with a vehicle component of the formulation used for the study. The finding did not occur in male rats at 20 times the MRHD.

In mice, vortioxetine was not carcinogenic in males or females at doses up to 12 and 24 times, respectively, the MRHD.

Mutagenicity

Vortioxetine was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay in cultured human lymphocytes, and an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Treatment of rats with vortioxetine at doses up to 120 mg/kg/day had no effect on male or female fertility, which is 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of TRINTELLIX in treatment for MDD was established in six 6 to 8 week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly) and one maintenance study in adult inpatients and outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD.

Adults (aged 18 years to 75 years)

The efficacy of TRINTELLIX in patients aged 18 years to 75 years was demonstrated in five 6 to 8 week, placebo-controlled studies (Studies 1 to 5 in *Table 4*). In these studies, patients were randomized to TRINTELLIX 5 mg, 10 mg, 15 mg or 20 mg or placebo once daily. For patients who were randomized to TRINTELLIX 15 mg/day or 20 mg/day, the final doses were titrated up from 10 mg/day after the first week.

The primary efficacy measures were the Hamilton Depression Scale (HAMD-24) total score in Study 2 and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in all other studies. In each of these studies, at least one dose group of TRINTELLIX was superior to placebo in improvement of depressive symptoms as measured by mean change from baseline to endpoint visit on the primary efficacy measurement *(see Table 4)*. Subgroup analysis by age, gender or race did not suggest any clear evidence of differential responsiveness. Two studies of the 5 mg dose in the U.S. (not represented in *Table 4*) failed to show effectiveness.

Elderly Study (aged 64 years to 88 years)

The efficacy of TRINTELLIX for the treatment of MDD was also demonstrated in a randomized, double-blind, placebo-controlled, fixed-dose study of TRINTELLIX in elderly patients (aged 64 years to 88 years) with MDD (Study 6 in *Table 4*). Patients meeting the diagnostic criteria for recurrent MDD with at least one previous major depressive episode before the age of 60 years and without comorbid cognitive impairment (Mini Mental State Examination score <24) received TRINTELLIX 5 mg or placebo.

Table 4. Primary Efficacy Results of 6 Week to 8 Week Clinical Trials

Study No. [Primary Measure]	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
Study 1 [MADRS] Non-US Study	TRINTELLIX (5 mg/day)‡	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	TRINTELLIX (10 mg/day)‡	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Placebo	105	33.9 (2.7)	-14.5 (1.0)	--
Study 2 [HAMD-24] Non-US Study	TRINTELLIX (5 mg/day)	139	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	TRINTELLIX (10 mg/day)‡	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	139	32.7 (4.4)	-11.3 (0.7)	--
Study 3 [MADRS] Non-US Study	TRINTELLIX (15 mg/day) ‡	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	TRINTELLIX (20 mg/day) ‡	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Placebo	158	31.5 (3.6)	-11.7 (0.8)	--
Study 4 [MADRS] US Study	TRINTELLIX (15 mg/day)	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	TRINTELLIX (20 mg/day) ‡	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Placebo	153	31.5 (4.2)	-12.8 (0.8)	--
Study 5 [MADRS] US Study	TRINTELLIX (10 mg/day)	154	32.2 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	TRINTELLIX (20 mg/day) ‡	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)
	Placebo	155	32.0 (4.0)	-10.8 (0.8)	--
Study 6 (elderly) [HAMD-24] US and Non-US	TRINTELLIX (5 mg/day) ‡	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Placebo	145	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
†Difference (drug minus placebo) in least-squares mean change from baseline.
‡Doses that are statistically significantly superior to placebo after adjusting for multiplicity.

TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is a clinician's impression of how much the patient's clinical condition has improved or worsened relative to baseline on a scale of 1 (very much improved) to 7 (very much worse).

Time Course of Treatment Response

In the 6 to 8 week placebo-controlled studies, an effect of TRINTELLIX based on the primary efficacy measure was generally observed starting at Week 2 and increased in subsequent weeks with the full antidepressant effect of TRINTELLIX generally not seen until Study Week 4 or later. *Figure 4* depicts time course of response in U.S. based on the primary efficacy measure (MADRS) in Study 5.

Figure 4. Change from Baseline in MADRS Total Score by Study Visit (Week) in Study 5

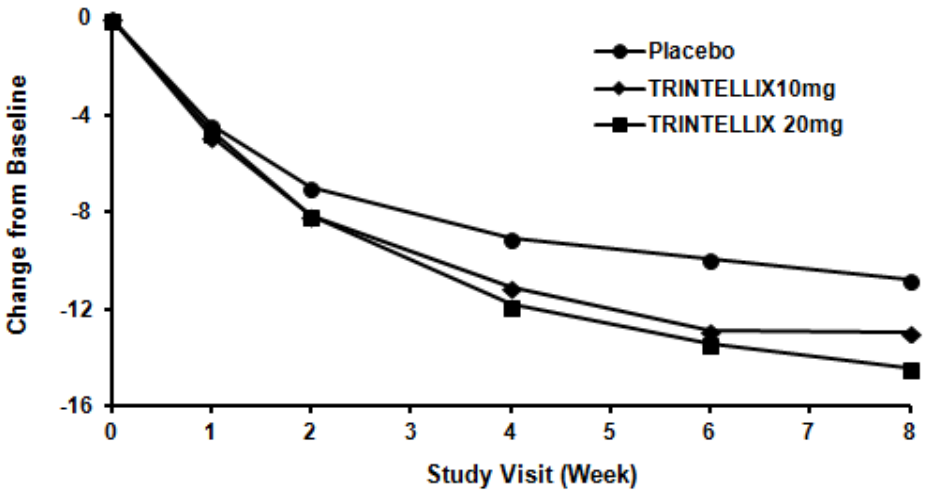
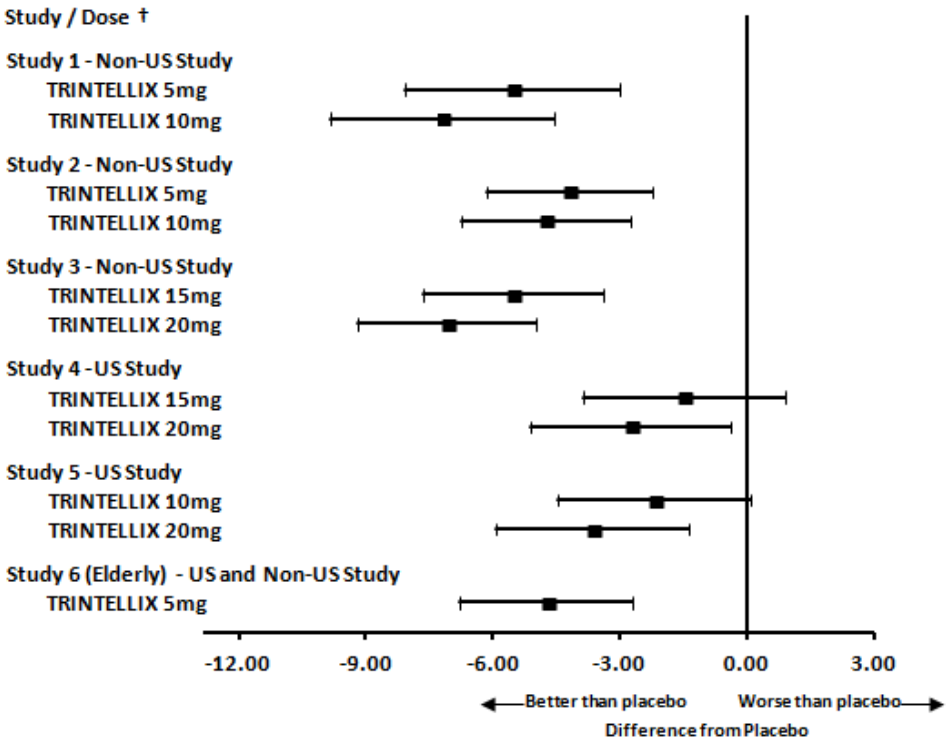


Figure 5. Difference from Placebo in Mean Change from Baseline in MADRS Total Score at Week 6 or Week 8



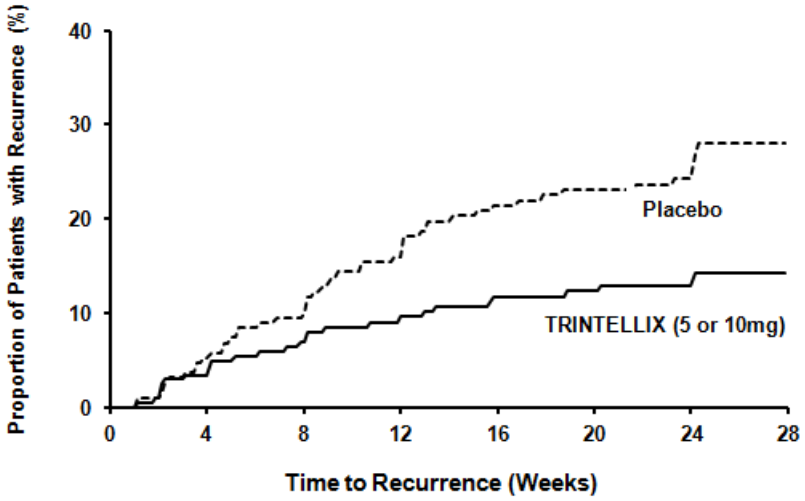
†Results (point estimate and unadjusted 95% confidence interval) are from mixed model for repeated measures (MMRM) analysis. In Studies 1 and 6, the primary analysis was not based on MMRM and in Studies 2 and 6 the primary efficacy measure was not based on MADRS.

Maintenance Study

In a non-US maintenance study (Study 7 in *Figure 6*), 639 patients meeting DSM-IV-TR criteria for MDD received flexible doses of TRINTELLIX (5 mg or 10 mg) once daily during an initial 12 week open-label treatment phase; the dose of TRINTELLIX was fixed during Weeks 8 to 12. Three hundred ninety six (396) patients who were in remission (MADRS total score ≤10 at both Weeks 10 and 12) after open-label treatment were randomly assigned to continuation of a fixed dose of TRINTELLIX at the final dose they responded to (about 75% of patients were on 10 mg/day) during the open-label phase or to placebo for 24 to 64 weeks. Approximately 61%

of randomized patients satisfied remission criterion (MADRS total score ≤10) for at least 4 weeks (since Week 8), and 15% for at least 8 weeks (since Week 4). Patients on TRINTELLIX experienced a statistically significantly longer time to have recurrence of depressive episodes than did patients on placebo. Recurrence of depressive episode was defined as a MADRS total score ≥22 or lack of efficacy as judged by the investigator.

Figure 6. Kaplan-Meier Estimates of Proportion of Patients with Recurrence (Study 7)



16 HOW SUPPLIED/STORAGE AND HANDLING

TRINTELLIX tablets are available as follows:

Features	Strengths			
	5 mg	**10 mg**		**20 mg**
Color	pink	yellow		red
Debossment	"5" on one side of tablet "TL" on other side of tablet	"10" on one side of tablet "TL" on other side of tablet		"20" on one side of tablet "TL" on other side of tablet
Presentations and NDC Codes				
Bottles of 30	64764-720-30	64764-730-30		64764-750-30
Bottles of 90	64764-720-90	64764-730-90		64764-750-90
Bottles of 500	64764-720-77	64764-730-77		64764-750-77

Storage: Store at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients and their caregivers about the benefits and risks associated with treatment with TRINTELLIX and counsel them in its appropriate use. Advise patients and their caregivers

to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk
Advise patients and caregivers to look for the emergence of suicidal ideation and behavior, especially early during treatment and when the dose is adjusted up or down *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Discontinuation of Treatment
Patients who are on TRINTELLIX 15 mg/day or 20 mg/day may experience headache, muscle tension, mood swings, sudden outburst of anger, dizziness and runny nose if they abruptly stop their medicine. Advise patients not stopping TRINTELLIX without talking to their healthcare provider *[see Adverse Reactions (6)]*.

Concomitant Medication
Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications because of a potential for interactions. Instruct patients not to take TRINTELLIX with an MAOI or within 14 days of stopping an MAOI and to allow 21 days after stopping TRINTELLIX before starting an MAOI *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2), and Drug Interactions (7.1)]*.

Serotonin Syndrome
Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of TRINTELLIX and triptans, tricyclic antidepressants, fentanyl, Lithium, tramadol, tryptophan supplements, and St. John's Wort supplements *[see Warnings and Precautions (5.2) and Drug Interactions (7.1, 7.2)]*.

Abnormal Bleeding
Caution patients about the increased risk of abnormal bleeding when TRINTELLIX is given with NSAIDs, aspirin, warfarin, or other drugs that affect coagulation *[see Warnings and Precautions (5.3)]*.

Activation of Mania/Hypomania
Advise patients and their caregivers to look for signs of activation of mania/hypomania *[see Warnings and Precautions (5.4)]*.

Angle Closure Glaucoma
Patients should be advised that taking TRINTELLIX can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.5)]*.

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking TRINTELLIX *[see Warnings and Precautions (5.6)]*.

Nausea
Advise patients that nausea is the most common adverse reaction, and is dose related. Nausea commonly occurs within the first week of treatment, then decreases in frequency but can persist in some patients.

Alcohol

A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg/day) did not increase the impairment of mental and motor skills caused by alcohol.

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise a pregnant woman or a woman planning to become pregnant that TRINTELLIX may cause withdrawal symptoms in the newborn or persistent pulmonary hypertension of the newborn (PPHN) *[see Use in Specific Populations (8.1)]*.

Distributed and marketed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

Marketed by:
Lundbeck
Deerfield, IL 60015

LUN205 R12

MEDICATION GUIDE

TRINTELLIX (trin'-TELL-ix)

(vortioxetine) Tablets

What is the most important information I should know about TRINTELLIX?

TRINTELLIX and other antidepressant medicines may cause serious side effects.

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.**
2. **Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions**. **Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions?**
   - Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- attempts to commit suicide
- thoughts about suicide or dying
- feeling agitated, restless, angry or irritable
- other unusual changes in behavior or mood
- acting on dangerous impulses
- new or worse depression
- trouble sleeping
- panic attacks
- acting aggressive, being angry or violent
- new or worse anxiety
- an extreme increase in activity or talking (mania)
- new or worse irritability

What is TRINTELLIX?

TRINTELLIX is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD).

It is important to talk with your healthcare provider about the risks of treating depression and also the risk of not treating it. You should discuss all treatment choices with your healthcare provider.

- Talk to your healthcare provider if you do not think that your condition is getting better with TRINTELLIX treatment.

Do not take TRINTELLIX if you:

- are allergic to vortioxetine, or any of the ingredients in TRINTELLIX. See the end of this Medication Guide for a complete list of ingredients in TRINTELLIX.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 21 days of stopping TRINTELLIX.
- Do not start TRINTELLIX if you stopped taking an MAOI in the last 14 days.

Before taking TRINTELLIX, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have or had seizures or convulsions
- have mania or bipolar disorder (manic depression)

- have low salt (sodium) levels in your blood
- have or had bleeding problems
- drink alcohol
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if TRINTELLIX will harm your unborn baby. Taking TRINTELLIX while pregnant in your third trimester may cause your newborn baby to have withdrawal symptoms that causes a certain type of breathing problem called Persistent Pulmonary Hypertension of the Newborn (PPHN).
- are breastfeeding or plan to breastfeed. It is not known if TRINTELLIX passes into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take TRINTELLIX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TRINTELLIX and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.

Especially tell your healthcare provider if you take:

- medicines used to treat migraine headache (e.g. triptans)
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), buspirone, or antipsychotics
- MAOIs (including linezolid, an antibiotic)
- Tramadol or fentanyl
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- aspirin
- warfarin (Coumadin, Jantoven)
- diuretics
- rifampicin
- carbamazepine
- phenytoin
- quinidine

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before you take TRINTELLIX with any of these medicines, talk to your healthcare provider about serotonin syndrome. See **"What are the possible side effects of TRINTELLIX?"**

How should I take TRINTELLIX?

- Take TRINTELLIX exactly as your healthcare provider tells you to take it.
- Take TRINTELLIX at about the same time each day.
- Your healthcare provider may need to change the dose of TRINTELLIX until it is the right dose for you.
- Do not start or stop taking TRINTELLIX without talking to your healthcare provider first. Suddenly stopping TRINTELLIX when you take higher doses may cause you to have side effects
  - o Headache
  - o Stiff muscles
  - o mood swings
  - o sudden outburst of anger
  - o dizziness or feeling lightheaded
  - o runny nose
- TRINTELLIX may be taken with or without food.

  If you take too much TRINTELLIX, call the Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What are the possible side effects of TRINTELLIX?

TRINTELLIX may cause serious side effects, including:

- **See "What is the most important information I should know about TRINTELLIX?"**
- **serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when medicines such as TRINTELLIX are taken with certain other medicines. Symptoms of serotonin syndrome may

include:

- agitation, hallucinations, coma or other changes in mental status
- problems controlling your movements or muscle twitching
- fast heartbeat
- high or low blood pressure
- sweating or fever
- nausea or vomiting
- diarrhea
- muscle stiffness or tightness
- **abnormal bleeding or bruising.** TRINTELLIX may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.
- **hypomania** (manic episodes). Symptoms of manic episodes include:

o greatly increased energy	o racing thoughts	o unusually grand ideas	o reckless behavior
o severe problems sleeping	o talking more or faster than usual	o excessive happiness or irritability	

- **visual problems**
  - o eye pain
  - o changes in vision
  - o swelling or redness in or around the eye

  Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
- **low levels of salt (sodium) in your blood**. Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet. Symptoms of severe or sudden cases of low salt levels in your blood may include: hallucinations (seeing or hearing things that are not real), fainting, seizures and coma. If not treated, severe low sodium levels can cause death.

Common side effects in people who take TRINTELLIX include:

- nausea
- constipation
- vomiting

These are not all the possible side effects of TRINTELLIX. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store TRINTELLIX?

Store TRINTELLIX at room temperature between 59°F to 86°F (15°C to 30°C).

Keep TRINTELLIX and all medicines out of the reach of children.

General information about the safe and effective use of TRINTELLIX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRINTELLIX for a condition for which it was not prescribed. Do not give TRINTELLIX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about TRINTELLIX that is written for healthcare professionals.

What are the ingredients in TRINTELLIX?

Active ingredient: vortioxetine hydrobromide

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating consisting of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg and 20 mg) and iron oxide yellow (10 mg)

Distributed and Marketed by:
Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015

Marketed by:
Lundbeck, Deerfield, IL 60015

For more information, go to www.TRINTELLIX.com or call 1-877-TAKEDA-7 (1-877-825-3327).

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: March 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s009

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	February 13, 2017
From	Jasmine Gatti, MD MA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	sNDA 204447 Supplement 009
Applicant	Takeda Phramaceutical
Date of Submission	May 10, 2016
PDUFA Goal Date	March 10, 2017
Proprietary Name / Non-Proprietary Name	Vortioxetine Trintellix
Dosage form(s) / Strength(s)	10mg, 15mg, 20mg oral tablets daily
Applicant Proposed Indication(s)/Population(s)	Major Depression Adults
Recommendation on Regulatory Action	*Approve*

1. Benefit-Risk Assessment

Relying on two Phase 3, eight week, randomized placebo controlled studies in adults with moderate to severe Major Depressive Disorder (MDD) treated with Trintellix (vortioxetine), the Sponsor requests that the Clinical Global Impression-Improvement scale (CGI-I) information be added to the *Clinical Studies* section of the label. Study 202 studied the flexible doses of vortioxetine 10 mg and 20 mg daily versus placebo and duloxetine 60 mg daily with a primary endpoint of the change from baseline to Week 8 in the Digit Symbol Substitution Test (DSST) and Study 13267A studied the fixed doses 15 mg and 20 mg daily versus placebo and duloxetine 60 mg daily with a primary endpoint of the change from baseline to Week 8 in the Montgomery and Åsberg Depression Rating Scale (MADRS).

In both studies, the CGI-I measured efficacy in the key secondary endpoint of the change from baseline to the end of Week 8 of treatment, as part of a hierarchical testing plan. These two studies demonstrated statistical significance for CGI-I for doses of vortioxetine of 10 mg to 20 mg compared with placebo in adult patients with MDD. The 20 mg dose showed numerical superiority to the 15 mg dose. The benefits of vortioxetine treatment based on CGI-I at a dose of 10 mg to 20 mg in adults with Major Depressive Disorder are felt to outweigh the risks. This CDTL recommends the addition to the Trintellix label of the CGI-I information.

2. Background

Vortioxetine is a serotonin reuptake inhibitor that acts as a potent and selective inhibitor of the serotonin transporter, with additional activities at some serotonin receptors: antagonist at 5-HT3, 5-HT7, and 5-HT1D; partial agonist at 5-HT1B; agonist at 5-HT1A.[1]

[1] Other available selective serotonin reuptake inhibitors (SSRIs) used to treat depression in adults include:

The Sponsor would like to add the following CGI-I scale[2] data from Study 202 and Study 13267A to the *Clinical Studies* section of the label:

"Trintellix was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is (b) (4)

(b) (4)

- In the September 13, 2013 NDA approval letter for vortioxetine tablets (trade name Brintellix™ at that time) , the drug was approved for the treatment of Major Depressive Disorder in adults at the doses of 5 mg, 10 mg, 15mg, and 20 mg tablets. Pediatric population was fully waived (≤ 17 years of age).

- During the review of NDA 204447, the FDA recommended not including CGI-I-related information in labeling, stating that, for a key secondary endpoint to be included it must be pre-specified and the positive findings required replication within a testing strategy.

- Given the positive results from Study 13267A and Study 202, the sponsor seeks to add CGI-I data to the Clinical Studies of the label.

- The CGI-I was included as a key secondary endpoint in vortioxetine clinical trials because it complements information captured by the MADRS and provides a brief, stand-alone assessment of the clinician's view of the patient's global functioning.

Other Regulatory Background

The Sponsor's annual report (September 30, 2015 to September 29, 2016) noted that the 15 mg capsule was removed from the market (summary of labeling changes, section 1.13.4). The rationale for this removal was not mentioned.

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fluoxetine (Prozac®, Selfemra®), paroxetine (Paxil®, Pexeva®), sertraline (Zoloft®), citalopram (Celexa®) fuovoxamine (Luvox®) and escitalopram (Lexapro®).

[2] The CGI-I has two parts: CG-I Severity (ranks severity of illness) and the CGI-I which is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1=very much improved, 2=much improved, 3=minimally improved, 4+no change, 5= minimally worse, 6= much worse, or 7=very much worse.

In April 29, 2016, a change in the proprietary name to Trintellix from Brintellix, in order to reduce medication errors (with the brand name of the approved product Brilinta) was approved.

In a correspondence sent to the Sponsor dated March 28, 2016, DPP stated that "the data from Studies 14122 (FOCUS) and 202 (CONNECT) did not demonstrate substantial evidence of improvement in cognitive dysfunction associated with MDD". Several recommendations were given. One of them was to conduct a study similar to Study 202 using a functional outcome measure in addition to DSST as a co-primary endpoint. Inclusion of an active comparator would not be required, but could provide valuable information.[3]

In July 14, 2014, a labeling change was approved to include the risk of angle-closure glaucoma.

3. Product Quality

Studies 202 and 13267A were conducted in accordance with Good Clinical Practices. No inspections were performed for this supplement. Financial disclosure certification summaries were included in this submission for the principal investigator and all the sub-investigators in all the sites in the United States and internationally. None of them had any financial disclosures.

4. Nonclinical Pharmacology/Toxicology

Refer to NDA 204447. No new information submitted.

5. Clinical Pharmacology

No new information from the original NDA 203447 was submitted.

6. Clinical Microbiology

Refer to NDA 204447. No new information submitted.

7. Clinical/Statistical- Efficacy

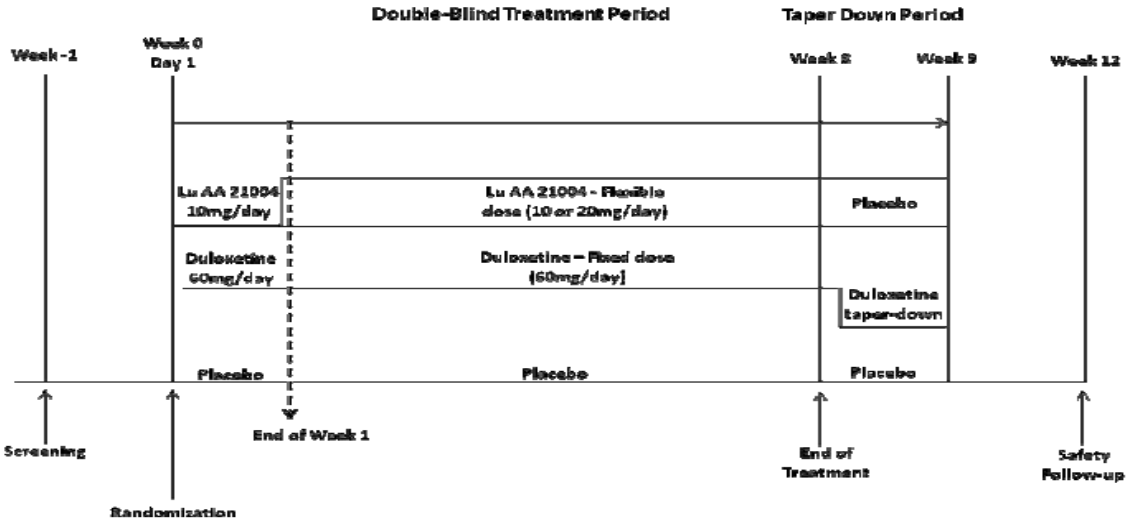
Superiority over placebo at week 8 on the key secondary endpoint of CGI-I was demonstrated for the efficacy of vortioxetine at oral doses of 10, 15 and 20 mg daily compared to placebo and duloxetine 60mg in patients ages 18 to 75 years old with MDD in two efficacy trials (Study 202 and Study 13267A) conducted in Bulgaria, Finland, Germany, Poland, Russian Federation, Ukraine and the United States. The studies are described in *Table 1*[4] followed by the study design of 202 in *Figure 1*.

[3] Farchione T. DPP Cross-Discipline Team Leader Review, NDA 20447, DARRTS, 3/28/16.

Table 1: Clinical Trials	
Phase/Trial	**Description**
Phase 3	
Study 202	8-week, randomized, double-blind, parallel-group, placebo controlled, active reference (duloxetine 60 mg/day), 80 sites worldwide, flexible-dose (vortioxetine 10 and 20 mg/day). N=602 adults randomized
Phase 3	
13267-A	8-week, randomized, double-blind, parallel group, placebo-controlled, active reference (duoloxetine 60 mg/day), 72 sites worldwide, fixed dose (vortioxetine 15 and 20 md/day). N=600 adults randomized

STUDY 202

Figure 1: Study 202 Sponsor Design Schematic



Source: Sponsor's Study Design Schematic, Clinical Study Report (LuAA21004-202, Page 26)

Study 202 included subjects with an acute major depressive episode (MDE) who had been prescribed treatment for a prior episode of depression as confirmed using the Mini International Neuropsychiatric Interview and who had moderate to severe depression. Also included were both genders between 18-64 years of age who had a MADRS total score ≥26 (at Screening and Baseline) and reported cognitive dysfunction (such as difficulty concentrating, slowed thinking, and difficulty in learning new things or remembering things). Subjects were excluded if they had psychiatric disorders other than MDD, current diagnosis of alcohol or other substance abuse, or had a significant risk of suicide or had a score ≥5 on item 10 (suicidal thoughts) of the MADRS or had a suicide attempt in the last 6 months. Additionally, patients with significant neurological disorder or unstable thyroid condition were excluded (*See Gonzalez p.15*[4]). Subjects were started on vortioxetine 10 mg daily with possible titration

[4] Gonzalez G. DPP Medical Officer Review of NDA 20447/S009: Trintellix Tablets in Adults for MDD, 2/10/17.

up to 20 mg after Week 1. The duloxetine arm received a fixed dose of 60 mg daily. Medication could be taken with or without food. CGI-I assessments were performed at Visit 3 (end of week 1), Visit 4 (end of week 4) and at completion/termination (end of week 8).

In Study 202, 12% of subjects had a mean age of 45 years with 79% being ≤55 years of age. Nearly 65% of the subjects were female, 86% were Caucasian (including Hispanic), 13% were Black, 1% were Asian, and only 0.5% were American Indian or Alaskan Native. There were no significant differences among the treatment groups in any category. In Study 202, of 885 subjects screened, 602 were randomized (completed study: PBO, N= 164 (84.5%); drug, N= 168 (84.8%); duloxetine, N=176 (83.8%)) (*See Gonzalez, Figure 2: Disposition of Subjects and p.17 for Protocol Violations/Deviations*.[4]) The incidence of disposition of subjects and major protocol deviations was similar across treatment groups.

The CGI-I efficacy results in Study 202 using a heirarchical plan and MMRM, demonstrated superiority as difference in Least Square (LS) mean from placebo at flexible doses 10/20mg compared to duloxetine [vortioxetine: -0.29 (p-value= 0.017, α=0.05) versus duloxetine -0.40 (p-value< 0.001)]. According to the clinical reviewer, the Sponsor did not provide a separate analysis of the 10 mg dose[4] (*See Table 3* for details of the hierarchical testing plan/statistical significance[5]). Analysis of CGI-I (baseline and end of week 1, 4 and 8) score: CGI-I response was defined as a CGI-I score ≤ 2 so that at Week 8, response rates were 49% (82/167) for placebo, 58% (101/175) for vortioxetine, and 64% (120/187) for duloxetine[4].

Table 2: Study 202: Sponsor's Key Secondary Efficacy Results

[5] All confidence intervals, statistical tests, and resulting p-values were reported as nominal 2-sided and assessed at the 5% significance level. No adjustments were made for multiplicity. For continuous variables, descriptive statistics included the number of subjects (n), mean, SD or SE as appropriate, minimum, median, and maximum. The full analysis set (FAS) included all subjects who were randomized, received at least 1 dose of study drug, and had at least 1 valid post-baseline value for assessment of primary efficacy. In FAS efficacy summaries, subjects were analyzed by the treatment to which they were randomized. *From Gonzalez review section 6.1.1.*

Table 2.c Primary and Key Secondary Efficacy Results (FAS)—Study 202

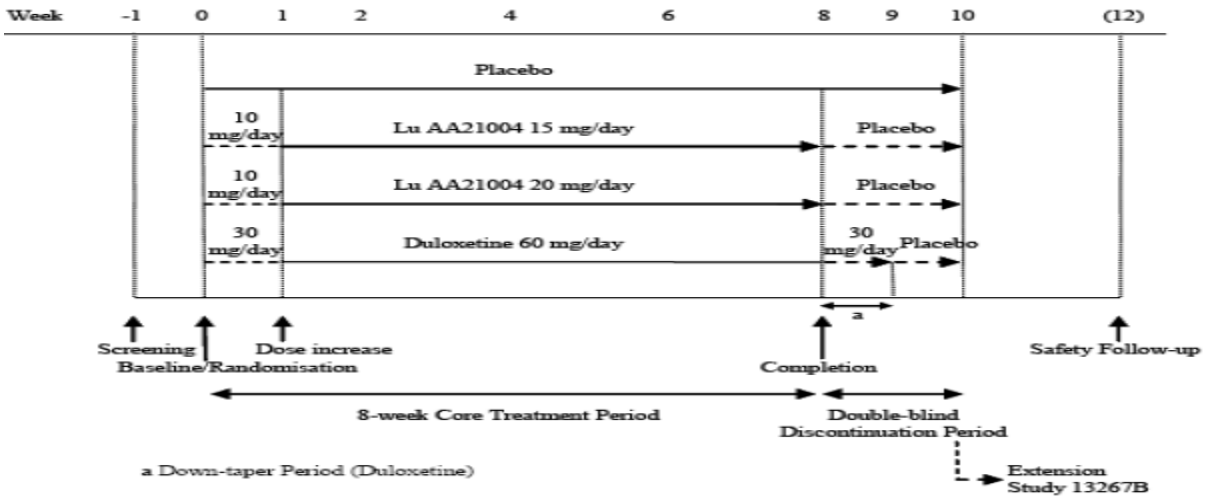
	Difference From Placebo at Week 8					
	Vortioxetine 10 to 20 mg/day			Duloxetine 60 mg/day (a)		
	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
Primary endpoint						
Δ DSST number of correct symbols (b) (c) (ANCOVA [OC] [d])	1.75	(0.28, 3.21)	0.019	1.21	(-0.23, 2.65)	0.099
Key secondary endpoints						
Δ PDQ (e) (f) subscore (MMRM)	-2.6	(-4.1, -1.0)	0.001	-3.0	(-4.5,-1.5)	<0.001
CGI-I score (MMRM)	-0.29	(-0.528, -0.052)	0.017	-0.40	(-0.638, -0.169)	<0.001

Source: Study 202, Tables 15.2.1.1.2, 15.2.13.3.5, 15.2.11.1.5.
Δ = change from Baseline.
(a) Not part of the testing strategy.
(b) Primary efficacy analysis.
(c) A positive LS mean value indicates advantages compared to placebo.
(d) OC = LOCF, as the DSST was only assessed at Baseline and at Week 8 (Completion/Early Termination).
(e) PDQ attention/concentration and planning/organization combined subscore.
(f) A negative LS mean value indicates advantages compared to placebo.
Note: Hierarchical testing in 1 sequence (10 to 20 mg/day), at α = 0.05.

STUDY 13267A

In Study 13267A, 600 adult patients with MDD (N=151 per vortioxetine group; N=158 PBO; N=147 duloxetine) were studied in 72 sites (2 in Belgium, 2 in Estonia, 7 in Finland, 10 in France, 7 in Germany, 5 in Latvia, 3 in Lithuania, 2 in Norway, 10 in Russian Federation, 6 in Slovakia, 2 in South Africa, 4 in Sweden, and 12 in Ukraine). Inclusion criteria were similar to Study 202 with major differences in CGI-S score≥4, duration of MDD > 3months, resistant to two antidepressant treatments of ≥ 6 weeks duration each, and ages between 18 to 75 years of age, inclusive. Excluded were a history of moderate or severe head trauma and other neurological disorders. There was no major difference in mean age, gender or race across the treatment groups. See *See Gonzalez, Table 7:Demographics*

Figure 4: Sponsor Study 13267A Study Design



Source: Sponsor's Study Design, Integrated Clinical Study Report (Study 13267A, Page 28)

The patients were randomized (1:1:1:1) to placebo, 15mg or 20mg of vortioxetine, or duloxetine 60 mg for 8 weeks. Those receiving a dose of vortioxetine 10 mg during Week 1, were then up-titrated from Weeks 2 to 8 to either 15 or 20 mg and discontinued to placebo in Week 9 and 10. Those in the duloxetine arm received a dose of 30 mg during Week 1, then were up-titrated from Weeks 2 to 8, to 60 mg. Week 9 they down-tapered to duloxetine 30mg and in Week 10, they received placebo.(*See Gonzalez for details*.)The statistical strategy, a hierarchical step-down testing strategy was defined *a priori and* was the same as in Study 202[6].

Table 8: Testing Strategy Results –Study 13267A

[6] 1) Change from baseline at Week 8 in MADRS total score (primary endpoint); 2) Response (defined as >50% decrease from baseline in MADRS total score) at Week 8; 3) CGI-I score at Week 8. Change from baseline at Week 8 in MADRS total score in patients with a baseline HAM-A total score ≥20; 4) Remission (defined as a MADRS total score ≤10) at Week 8; 5) Change from baseline at Week 8 in SDS total score

	Difference From Placebo		P-value	
	Lu AA21004		Lu AA21004	
Endpoint (Week 8)	15 mg	20 mg	15 mg	20 mg
Δ MADRS total score (a)	-5.5 ± 1.1	-7.1 ± 1.1	<0.001	<0.001
MADRS response (b)	24.8%	29.3%	<0.001	<0.001
CGI-I score (c)	-0.7 ± 0.1	-1.0 ± 0.1	<0.001	<0.001
Δ MADRS total score in subjects with a HAM-A total score ≥20 at Baseline	-5.2 ± 1.5	-6.4 ± 1.6	<0.001	<0.001
MADRS remission (b)	15.9%	19.4%	0.002	<0.001
Δ SDS total score	-3.2 ± 1.2	-3.9 ± 1.1	0.005	<0.001

Source: Study 13267A Tables 30, 41, 78, 88, 96, and 105.
Hierarchical testing in 2 parallel sequences, each at α = 0.025; values are mean ± SE.
(a) Primary efficacy analysis; Lu AA21004 15 mg and Lu AA21004 20 mg were tested in parallel at α = 0.025.
(b) Logistic regression analyses for response and remission (LOCF); values are percentage point differences from placebo.
(c) Treatment difference from placebo in mean CGI-I score at Week 8.

The primary efficacy analysis showed that vortioxetine in doses of 15 and 20mg were statistically significant and superior to placebo (p <0.001) in the mean change from baseline in MADRS total score at Week 8, with a treatment difference to placebo of -5.5 (15mg) and -7.1 (20mg) (FAS, MMRM) and the mean CGI-I score (week 8) at 15mg to separate from placebo by -0.7 and at the 20mg dose by -1.0 (both with p-values<0.001) .

For the CGI-I results, the 20 mg was numerically superior to the 15 mg dose, but both were statistically significant compared to placebo[7].

Table 3: Summary of CGI-I Positive Results in Study 202 and 13267A from Sponsor

Study	Dose (a)	Difference From PBO (CGI-I)	95% CI	Nominal p-value (b)	Comments About Statistical Significance
202	10/20 mg	-0.29	(-0.53, -0.05)	0.017	Primary analysis method = MMRM CGI-I was included in a planned hierarchical testing plan (α set at 0.05) as the third endpoint in the sequence. Based on the study analyses (MMRM), the primary endpoint and all key secondary endpoints, including CGI-I, were significant at α=0.05 for treatment.
13267A	15 mg	-0.69	(-0.94, -0.44)	<0.001	Primary analysis method = MMRM CGI-I was included in a planned hierarchical testing plan with separate sequences per dose (α set at 0.025) as the third endpoint in the sequences. Based on the study analyses (MMRM), the primary endpoint and all key secondary endpoints, including CGI-I, were significant at α=0.025 for each dose.
	20 mg	-0.95	(-1.20, -0.70)	<0.001	

[7] The positive results were confirmed by all the sensitivity analyses (FAS, LOCF and OC, ANCOVA; PPS, MMRM). Duloxetine also separated from placebo in all the primary and key secondary analyses (nominal p <0.001). *From Gonzalez Section 6.2.4.*

8. Safety

Because this is an efficacy supplement, the safety data has been previously reviewed.

9. Advisory Committee Meeting

There was no advisory committee meeting.

10. Pediatrics

In February 20, 2015, a notification was send to the Sponsor stating that due to the inadequate proposed pediatric study request submitted, the Division was unable to issue a Written Request.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

Labeling meetings were held on October 18, 2016 and November 14, 2016. Further negotiations are still in progress. Currently, the following is included in the *Clinical Trials* section and *Section 6.2*:
"TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is a clinician's impression of how much the patient's clinical condition has improved or worsened relative to baseline on a scale of 1 (very much improved) to 7 (very much worse)".

Section 6.2 Postmarketing Experience
Metabolic Disorders- weight gain
Gastrointestinal System- acute pancreatitis

13. Postmarketing Recommendations

There are no Risk Evaluation and Management Strategies, postmarketing requirements and commitments norrecommendations.

14. Recommended Comments to the Applicant

None

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

/s/

JASMINE C GATTI
03/10/2017

MITCHELL V Mathis
03/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s009

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	204447/s-009
Priority or Standard	Standard
Submit Date(s)	May 10, 2016
Received Date(s)	May 10, 2016
PDUFA Goal Date	March 10, 2017
Division / Office	DPP/ODE 1
Reviewer Name(s)	Graciela M. Gonzalez, MD
Review Completion Date	March 1, 2017
Established Name	Vortioxetine
Proposed Brand Name	Trintellix
Therapeutic Class	Antidepressant
Applicant	Takeda Pharmaceutical
Formulation(s)	Immediate Release Tablet
Dosing Regimen	10mg,15mg, 20mg (oral) daily
Indication(s)	Major Depressive Disorder
Intended Population(s)	Adult Patients

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1 Recommendations/Risk Benefit Assessment

The purpose of this supplemental NDA application is to request inclusion in labeling of data related to the effect of vortioxetine treatment on global functioning in depression as assessed by the Clinical Global Impression-Improvement (CGI-I) scale. The data the Applicant wishes to include in the Clinical Studies section of the package label comes from two Phase 3, eight week, placebocontrolled studies in adults with Major Depressive Disorder (MDD) in which the CGI-I was a pre-specified secondary endpoint:

- Study 202 (n=602, 80 worldwide sites, fixed dose of vortioxetine 10 mg and 20 mg Q day versus placebo). The primary endpoint in this study was the change from baseline to Week 8 in the Digit Symbol Substitution Test (DSST).

- Study 13267A (n=600, 72 worldwide sites, flexible dose 15 mg and 20 mg Q day versus placebo). The primary endpoint in this study was the change from baseline to Week 8 in the Montgomery and Åsberg Depression Rating Scale (MADRS).

Both studies used duloxetine 60 mg per day as a comparator drug.

In both studies the CGI-I was included to measure efficacy in their key secondary endpoint (the change from baseline to the end of Week 8 of treatment) as part of a hierarchal testing plan.

These two studies demonstrated statistical significance for CGI-I versus placebo for doses of vortioxetine of 10 mg, 15mg, and 20 mg in adult patients meeting criteria for MDD.

1.1 Recommendation on Regulatory Action

I recommend that this supplement be approved and labeling be updated. The Applicant has demonstrated that vortioxetine is superior to placebo as measured by the CGI-I.

1.2 Risk Benefit Assessment

Vortioxetine is an approved antidepressant indicated for the treatment of MDD. The addition of CGI-I data to labeling does not alter the benefit/risk assessment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations are necessary.

1.4 Recommendations for Postmarket Requirements and Commitments

No recommendations are necessary.

2 Introduction and Regulatory Background

2.1 Product Information

Vortioxetine was discovered and patented by H. Lundbeck A/S (Lundbeck) and co-developed with Takeda Pharmaceutical Company Ltd. (Takeda) for the treatment of major depressive disorder (MDD).

Vortioxetine is indicated for the treatment of major depressive disorder (MDD). The efficacy of vortioxetine was established in six 6- to 8-week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly) and one maintenance study in adult inpatients and outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD.

The mechanism of the antidepressant effect of Lu AA21004 is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of 5-HT. It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism.

2.2 Currently Available Treatments for Proposed Indications

Several selective serotonin reuptake inhibitors (SSRIs) are approved for the treatment of MDD. Among the SSRIs, the following products include CGI data (either CGI-I or CGI-Severity) in Section 14 of their product labeling: fluoxetine (Prozac, Sarafem), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and vilazodone (Viibryd).

2.3 Availability of Proposed Active Ingredient in the United States

Vortioxetine was approved in the United States for the treatment of MDD in adults on September 13, 2013.

2.4 Important Safety Issues with Consideration to Related Drugs

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation, and vomiting. Other common adverse reactions include diarrhea, dry mouth, flatulence, dizziness, abnormal dreams, and pruitis. Vortioxetine is also associated with both male and female sexual dysfunction.

Vortioxetine labeling also includes the following Warnings and Precautions:

- Clinical Worsening and Suicide Risk
- Serotonin Syndrome

- Abnormal Bleeding
- Activation of Mania/Hypomania
- Angle Closure Glaucoma
- Hyponatremia

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

In the original NDA approval letter for vortioxetine tablets (trade name Brintellix at that time) dated September 13, 2013, the drug was approved for the treatment of Major Depressive Disorder in adults at the doses of 5 mg, 10 mg, 15mg, and 20 mg tablets.

During the review of New Drug Application (NDA) 204447, the Food and Drug administration (FDA) recommended not including CGI-Irelated information from the package insert, stating that for a key secondary endpoint to be described in the package insert it must be pre-specified and the positive findings have to be replicated within a testing strategy.

In the recently completed Study 202, CGI-I was included as a key secondary endpoint and vortioxetine separated from placebo on this endpoint. Given the positive and now replicated results, the Applicant seeks to add CGI-I data to the Clinical Studies section of the package insert using data from Study 13267A and Study 202.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was well organized and the information was easy to find. The reporting, interpretation and verification of the data were accurate. The confidentiality of records was protected. No request for additional information was needed.

3.2 Compliance with Good Clinical Practices

The Studies 202 and 13267A were conducted in accordance with Good Clinical Practices.

No inspections were performed for this supplement.

3.3 Financial Disclosures

In accordance with 21 CFR 314.50(k), financial disclosure certification summaries were included in this submission for the principal investigator and all the sub-investigators at all the sites in the United States and in different countries around the world. None of the investigators had any financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to original NDA #: 204447. No new CMC information was included with this submission.

4.2 Clinical Microbiology

Refer to original NDA #: 204447. No new clinical microbiology information was included with this submission.

4.3 Preclinical Pharmacology/Toxicology

Refer to original NDA #: 204447. No new pharmacology/toxicology information was included with this submission.

4.4 Clinical Pharmacology

Refer to original NDA #: 204447. No new clinical pharmacology information was included with this submission.

4.4.1 Mechanism of Action

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

4.4.2 Pharmacodynamics

Refer to original NDA #: 204447. No new pharmacodynamic information was included with this submission.

4.4.3 Pharmacokinetics

Refer to original NDA #: 204447. No new pharmacokinetic information was included with this submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trial

Table 1: Phase 3 Clinical Trials

Table 1: Clinical Trials	
Phase/Trial	**Description**
Phase 3	
Study 202	8-week, randomized, double-blind, parallel-group, placebo controlled, active reference (duloxetine 60 mg/day), 80 sites worldwide, flexible-dose (vortioxetine 10 and 20 mg/day). N=602 adults randomized
Phase 3	
13267-A	8-week, randomized, double-blind, parallel group, placebo-controlled, active reference (duoloxetine 60 mg/day), 72 sites worldwide, fixed dose (vortioxetine 15 and 20 md/day). N=600 adults randomized

5.2 Review Strategy

This review is focused on the key secondary endpoints of the two studies 202 and 13267A and the inclusion of the CGI-I data as a secondary assessment of efficacy.

6 Review of Efficacy

6.1 Efficacy Summary

The efficacy of vortioxetine for the treatment of MDD has been established in prior applications. Here, the Applicant has provided data to support inclusion of CGI-I data in Section 14 of labeling. Adult patients receiving vortioxetine 10 to 20 mg experienced significantly greater improvement in CGI-I scores in both Study 202 and Study 13267A than patients receiving placebo.

Table 2: Summary of CGI Positive Results in Study 202 and Study 13267A

Study	Dose (a)	Difference From PBO (CGI-I)	95% CI	Nominal p-value (b)	Comments About Statistical Significance
202	10/20 mg	-0.29	(-0.53, -0.05)	0.017	Primary analysis method = MMRM CGI-I was included in a planned hierarchical testing plan (α set at 0.05) as the third endpoint in the sequence. Based on the study analyses (MMRM), the primary endpoint and all key secondary endpoints, including CGI-I, were significant at α=0.05 for treatment.
13267A	15 mg	-0.69	(-0.94, -0.44)	<0.001	Primary analysis method = MMRM CGI-I was included in a planned hierarchical testing plan with separate sequences per dose (α set at 0.025) as the third endpoint in the sequences. Based on the study analyses (MMRM), the primary endpoint and all key secondary endpoints, including CGI-I, were significant at α=0.025 for each dose.
	20 mg	-0.95	(-1.20, -0.70)	<0.001	

Source: Applicant's Table of Summary of CGI-I Positive Results in Study 202 and 13267

6.2 Indication

Under this supplemental NDA application, Takeda Pharmaceutical is seeking the addition of labeling language to describe that vortioxetine is superior to placebo on the CGI-I in adult patients with MDD using two studies (Studies 202 and 13267A) that demonstrated statistical significance for CGI-I versus placebo, for doses of 10 to 20 mg.

6.2.1 Study Summaries

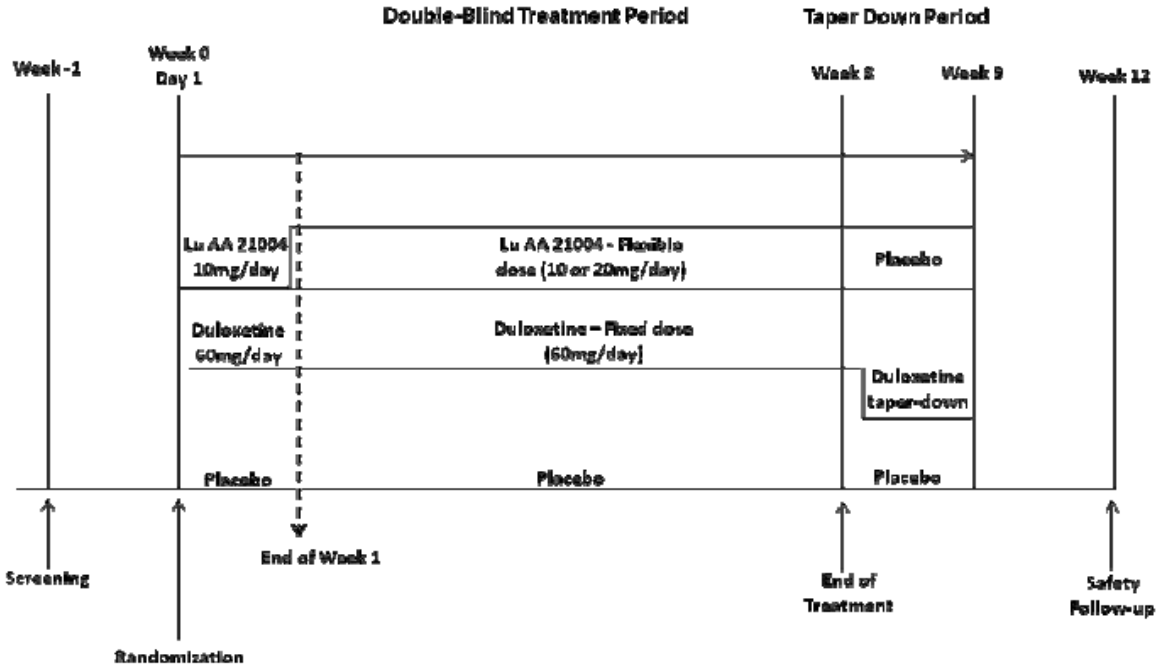
Study 202

Study Design

The study was a Phase 3, 80 site (Bulgaria, Finland, Germany, Poland, Russian Federation, Ukraine and the United States), randomized, double-blind, placebo- and active-controlled (duloxetine 60 mg daily), 8-week study, with flexible doses of vortioxetine (10 mg daily or 20 mg daily) in adult patients with MDD.

For the study design schematic see Figure 1below.

Figure 1: Design Schematics



Source: Clinical Study Report (Sttudy 202), Page 26

Inclusion and Exclusion Criteria:

Subjects meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for MDD were eligible for inclusion.
Subjects were required to have a diagnosis of acute (major depressive episode (MDE) in the context of recurrent MDD and to have received prescribed treatment for a previous episode of depression. Previous MDE was to be confirmed using the Mini International Neuropsychiatric Interview (MINI) and attempts were to be made to document previous MDEs through review of medical records. Subjects were also required to have moderate to severe depression. Milder forms of depression were excluded as high placebo response rates and spontaneous remission rates are believed to account for the lack of drug-placebo difference in mild depression. Also, duration of at least 3 months for the current episode was required. Men and women between 18 to 64 years of age, who had a MADRS total score ≥26 at both the Screening and Baseline visits and reported subjective cognitive dysfunction (such as difficulty concentrating, slow thinking, and difficulty in learning new things or remembering things) were included.

Any current psychiatric disorder other than MDD was exclusionary as well as current diagnosis of alcohol or other substance abuse or dependence that had not been in sustained remission for at least 2 years prior to Screening, or if the subject had a significant risk of suicide according to the investigator's clinical judgment or had a score

≥5 on item 10 (suicidal thoughts) of the MADRS or had made a suicide attempt in the previous 6 months. Additionally, the presence or history of a clinically significant neurological disorder or unstable thyroid condition was exclusionary..

All subjects were started on vortioxetine 10 mg daily and were able to have their dosage flexibly increased to 20 mg after the end of Week 1. The subjects in the duloxetine arm received a fixed dose of 60 mg daily.

Table 3: Schedule of Efficacy Assessment

Visit	Screening	Baseline	Treatment Period		Safety Phone Call (a)	Completion/ Early Termination (b)	End of Taper-Down Period (c)	Safety Follow- up (d)
Visit Number	1	2	3	4	5	6	7	8
Day/End of Week	Days -10 to -2	Day 1	End of Week 1	End of Week 4	End of Week 6	End of Week 8	End of Week 9	End of Week 12
Visit Window (e) (days relative to which visit)			± 1	± 3	± 3	± 3	± 3	±5
Efficacy Assessments								
Neuropsychological tests: DSST, TMT A, TMT B, Stroop test, GMLT, DET, IDN, One-Back	X (g)	X				X		
MADRS	X	X	X	X		X		
CGI-S		X	X	X		X		
CGI-I			X	X		X		
PDQ		X		X		X		
CPFQ		X		X		X		
UPSA-VIM/UPSA-B (h)		X				X		
WLQ (i)		X				X		

DSST-Digit Symbol Subs itution Test, TMT A and B-Trail Making Test Part A and Part B, Stroop test-Stroop Color Naming Test, GMLT-Groton Maxe learning Test, DET- Detection Task, IDN- Identification Task, MADRS- Montgomery-Asberg Depression Scale, CGI-I- Clinical Global Impressions Improvement, PDQ-Perceived Deficits Ques ionnaire, UPSA-VIM/UPSA-B- University of San Diego Performance-Based Skills Assessments-Validation of Immediate Measures/University of San Diego Performance-Based Skills Assessment- Brief, WLQ-Working Limita ion Questionnaire
Source: Clinical Study Report (Study 202), Page 45

Prohibited Concomitant Medications:

Antipsychotics, antidepressants, anxiolytics, psychoactive herbal remedies, mood stabilizers, psychostimulants, tryptophan, sedatives, hypnotics, or medications that alter the concentration of serotonin in the brain (such as: meperidine, tramadol, St. John's wort, triptans, or street drugs like cocaine, etc.), nonsteroidal anti-inflammatory drugs and anticoagulants.

Statistical Analysis Plan:

Primary Endpoint: The change from baseline to Week 8 in DSST total number of correct symbols.

Secondary Endpoints: The pre-specified key secondary efficacy parameters were change from baseline to week 8 in PDQ attention/concentration and planning/organization sub-score; CGI-I at week 8.

All tabulations of analysis results included summaries for the following treatment groups: placebo, vortioxetine, and duloxetine.
All confidence intervals, statistical tests, and resulting p-values were reported as nominal 2-sided and assessed at the 5% significance level.
To control two-sided type I error of overall efficacy in Study 202, the primary and key efficacy endpoints were tested sequentially at significance level of 0.05 in the following order:

1. Change from baseline to Week 8 in DSST total number correct symbols.
2. Change from baseline to Week 8 in the PDQ attention/concentration and planning/organization sub-score.
3. CGI-I at Week 8.

The full analysis set (FAS) included all subjects who were randomized, received at least one dose of study drug, and had at least one valid post-baseline value for assessment of primary efficacy. In FAS efficacy summaries, subjects were analyzed by the treatment to which they were randomized.

Demographics

Mean (SD) age was 45 years of age (12%) with the majority (79%) $\leq$55 years of age. Nearly two-thirds of the subjects were female (65%). Most of the subjects (86%) were Caucasian (including Hispanic), 13% were Black, 1% were Asian, and only 3 subjects (0.5%) were American Indian or Alaskan Native. Mean (SD) BMI was 29 (7%). Half of the subjects had never smoked and 16% no longer smoked. There were no significant differences among the treatment groups in any demographic category.

Subject Disposition

The categories included all subjects who were randomized (those not treated, discontinued from the study, or those that completed the study). Post-randomization discontinuation reasons included: adverse events, major protocol deviations, lost to follow-up, lack of efficacy, voluntary withdrawal, study termination, and pregnancy. See Figure 2 below.

Figure 2: Disposition of Subjects (All Randomized Subjects)

Number of Subjects Screened=885

No. of subjects randomized – 602

No. of subjects not randomized=283

	Pbo	Lu	Du
Completed the study	164 (84.5)	168 (84.8)	176 (83.8)
Prematurely discontinued study	30 (15.5)	30 (15.2)	34 (16.2)

Primary reason for discontinuation from study (b):	Pbo	Lu	Du
Lost to follow-up	6 (3.1)	10 (5.1)	8 (3.8)
Voluntary withdrawal	8 (4.1)	9 (4.5)	6 (2.9)
Pretreatment event or adverse event	6 (3.1)	6 (3.0)	12 (5.7)
Major protocol deviation	4 (2.1)	3 (1.5)	3 (1.4)
Lack of efficacy	6 (3.1)	1 (0.5)	5 (2.4)
Other reason(s) (c)	0	1 (0.5)	0

Primary reason for discontinuation prior to treatment (a):	Total
Did not meet inclusion criteria	210 (23.7)
Met exclusion criteria	50 (5.6)
Other	22 (2.5)
Lost to follow up	17 (1.9)
Withdrew consent	16 (1.8)
Pretreatment event/adverse event	3 (0.3)
Major protocol deviation	2 (0.2)
Study termination	2 (0.2)

Pbo=placebo. Lu=Lu AA21004. Du=Duloxetine.
(a) More than 1 reason for discontinuation could have been reported for a subject at the Screening visit.
(b) Primary reasons for study discontinuation are mutually exclusive and exhaustive categories for randomized subjects.
(c) Other reason for study discontinuation: In the Lu AA21004 group, 1 subject (b) (6) discontinued the study on Day 7 because of the serious illness of a family member (Appendix 16.2.1.2).
Note: Reasons for study discontinuation are listed in descending order in the Lu AA21004 treatment group.

Source: Clinical Study Report (Study 202), Page 82

Protocol Violations/Deviations:

Seventy-five subjects had at least one major protocol deviation: 24 subjects (12.1%) in the vortioxetine group, 23 subjects (11.0%) in the duloxetine group, and 28 subjects (14.4%) in the placebo group.
A total of 10 subjects (1.7%) discontinued the study for major protocol deviations.
The incidence of major protocol deviations was similar across treatment groups for each category of major protocol deviation. There is no reason to believe that any of these protocol deviations could have biased the efficacy results of the study.

Analysis of Primary Endpoint

The vortioxetine group was statistically significantly better than placebo in the change from baseline in DSST total number of correct symbols score group (LS mean = 1.75, p=0.019. The difference between the duloxetine and placebo groups was not statistically significant (p=0.099).

Analysis of Secondary Endpoints

Both vortioxetine and duloxetine showed statistically significant improvement in the PDQ attention/concentration and planning/organization sub-score from placebo at Week 8 (vortioxetine, LS mean = -2.6, p = 0.001; duloxetine, LS mean = -3.0, p< 0.001). Treatment with vortioxetine and duloxetine also produced a statistically significant improvement in CGI-I score compared to placebo at week 8 (vortioxetine, LS mean = -0.29, p = 0.017; duloxetine, LS mean = -0.40, p < 0.001). The focus of this supplement is the CGI-I.

Table 4: Primary and Key Secondary Efficacy Analysis at Week 8, Difference from Placebo Hierarchical Testing) (FAS)

	Lu AA21004	
Efficacy Variable	**Difference From Placebo LS Mean (SE)**	**P-value**
DSST total number of correct symbols (OC)(a)	1.75 (0.744)	0.019
PDQ attention/concentration and planning/organization subscore (MMRM)	-2.6 (0.78)	0.001
CGI-I (MMRM)	-0.290 (0.1211)	0.017

Source: Table 15.2.1.1.2, Table 15.2.13.3.5, Table 15.2.11.1.5.
(a) primary efficacy analysis.

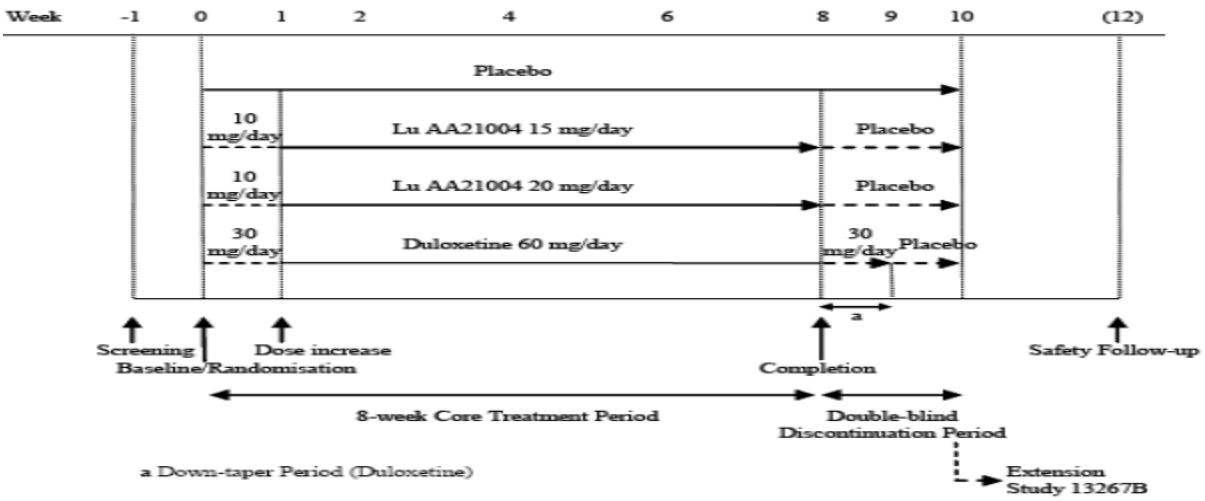
Source: Clinical Study Report (Study 202.), Page 94.

Study 13267A

Study Design

Study 13267A was a randomized, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating vortioxetine 15 and 20 mg/d in 600 adult patients with MDD (151 patients per vortioxetine group). The study was conducted in 72 sites around the world (2 in Belgium, 2 in Estonia, 7 in Finland, 10 in France, 7 in Germany, 5 in Latvia, 3 in Lithuania, 2 in Norway, 10 in Russian Federation, 6 in Slovakia, 2 in South Africa, 4 in Sweden, and 12 in Ukraine).

Figure 3: Study Design



Source: Integrated Clinical Study Report (Study 13267A), Page 28

The following periods were defined:

- Screening Period – from screening to randomization 8-week (1 to 0 week)
- Core Treatment Period – 8-week double-blind period with vortioxetine (15 mg/day or 20mg/day), duloxetine (60mg/day), or placebo (Weeks 1 to 8)
- Discontinuation Period I – 1-week double-blind down-taper period with either duloxetine 30mg/day for those randomized to duloxetine or placebo for those randomized to any of the other three treatment groups (Week 8 to 9)
- Discontinuation Period II – 1-week double-blind period with placebo after Discontinuation Period I (Week 9 to10)
- Safety Follow-up Period – 4-week period after completion/withdrawal (Weeks 9 to 12)

Inclusion and Exclusion Criteria

Patients with moderate to severe recurrent MDD (baseline MADRS total score ≥ 26 and CGI-S score ≥ 4) based on DSM-IV-TR criteria were eligible for inclusion. Subjects' diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI). Subjects were required to have > 3 months duration of symptoms with inadequate response to two antidepressant treatments of ≥ 6 weeks duration each.

Men and women (ages ≥18 and ≤ 75 years) were included in the study.
Patients with current psychiatric disorders other than MDD were excluded, as well as patients with a diagnosis of alcohol or other substance abuse, history of moderate or severe head trauma, other neurological disorders or systemic medical diseases, or who were judged to be at risk of harm to self or others.

Study Treatment:

The patients were randomized equally (1:1:1:1) to placebo, vortioxetine 15mg/day, vortioxetine 20mg/day, or duloxetine 60 mg/day for 8 weeks of double-blind treatment. Patients randomized to treatment with vortioxetine received a dose of 10 mg/day during Week 1 (up-titration); from Weeks 2 to 8 they received a dose of either 15 or 20 mg/day. Patients randomized to treatment with duloxetine received a dose of 30 mg/day during Week 1 (up-titration); from Weeks 2 to 8, they received a dose of 60 mg/day.

Table 5: Dose Titration Schedules

Week	IMP Dispensed Day/Visit	Dosing Time[a]	Placebo Group	Lu AA21004 15mg Group	Lu AA21004 20mg Group	Duloxetine Group
Week 1	Day 0/Visit 2	Morning	placebo	10mg	10mg	30mg
Weeks 2 to 8	Day 7/Visit 3	Morning	placebo	15mg	20mg	60mg
	Day 14/Visit 4	Morning	placebo	15mg	20mg	60mg
	Day 28/Visit 5	Morning	placebo	15mg	20mg	60mg
	Day 42/Visit 6	Morning	placebo	15mg	20mg	60mg
Week 9	Day 56/Visit 7	Morning	placebo	placebo	placebo	30mg
Week 10	Day 63/Visit 8	Morning	placebo	placebo	placebo	placebo

a The first dose from the dispensed IMP was to be taken the day after the visit.

Source: Integrated Clinical Study Report (Study 13267A), Page 34

Table 6: Schedule of Efficacy Assessments

Period	8-week Core Treatment Period					Safety Follow-up
Visit	3	4	5	6	Completion	10
End of Week	1	2	4	6	8	12
Day	7	14	28	42	56	84
Eficacy Assessments						
MADRS, CGI-S	X	X	X	X	X	
HAM-A	X	X	X	X	X	
CGI-I	X	X	X	X	X	

MADRS=Montgomery and Asberg Depression Rating Scale, CGI-S=Clinical Global Impression Safety Scale
HAM-A= Hamilton Anxiety Rating Scale, CGI-I=Clinical Global Impression Improvement Scale

Prohibited Concomitant Medications:

Same as in Study 202, listed above.

Subject Discontinuation and Withdrawal:

After completion of the 8-week Core Treatment Period, the patients entered a 2-week, double-blind Discontinuation Period: patients on placebo remained on placebo; patients on vortioxetine 15 or 20 mg/day switched abruptly to placebo; and patients on duloxetine (60 mg/day) received duloxetine 30 mg/day during the first week and placebo during the second week. The same treatment regimen was offered to patients who withdrew from the study. Potential discontinuation symptoms were evaluated during the Discontinuation Period. Patients who did not continue into extension Study 13267B were scheduled for a Safety Follow-up Visit/Contact 4 weeks after the Completion/Withdrawal Visit.

Statistical Analysis Plan:

Primary Endpoint: Change from baseline to Week 8 on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Key Secondary Endpoints: Sheehan Disability Scale (SDS) total score and CGI-I score.

To adjust for multiplicity, Vortioxetine 15 and 20 mg/day were tested separately versus placebo at a Bonferroni-corrected significance level of 0.05/2 = 0.025. There were two parallel testing sequences for the 15 mg and 20 mg doses, respectively. Focusing only on the accepted key secondary endpoints, for each of the dose groups, the primary and key secondary endpoints were hierarchically ordered as follows:

1. Change from baseline to Week 8 in MADRS total score (primary)
2. CGI-I score at Week 8
3. Change from baseline to Week 8 in SDS total score

6.3.2 Demographics

Table 7: Demographics

		PBO		DUL		AA21004_15		AA21004_20		Total	
Number of Patients		158		147		151		151		607	
Age	N	158		147		151		151		607	
	Mean	48.13		45.57		47.02		46.15		46.74	
	SD	13.11		13.55		14.61		13.43		13.68	
	Min	21.00		19.00		18.00		18.00		18.00	
	Max	74.00		74.00		74.00		73.00		74.00	
	Median	49.00		46.00		47.00		46.00		47.00	
Sex n (%)	M	48	(30.4)	45	(30.6)	54	(35.8)	60	(39.7)	207	(34.1)
	F	110	(69.6)	102	(69.4)	97	(64.2)	91	(60.3)	400	(65.9)
Race n (%)	White	156	(98.7)	144	(98.0)	150	(99.3)	146	(96.7)	596	(98.2)
	Black	2	(1.3)	3	(2.0)	0	(0.0)	2	(1.3)	7	(1.2)
	Asian	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.2)
	Other	0	(0.0)	0	(0.0)	1	(0.7)	2	(1.3)	3	(0.5)

13267A FINAL ST_DE01 19JUN2012:19:44:17 SADs Build Number: 240

PBL=Placebo, Dul=Duloxetine, 15=15 mg, 20=mg.

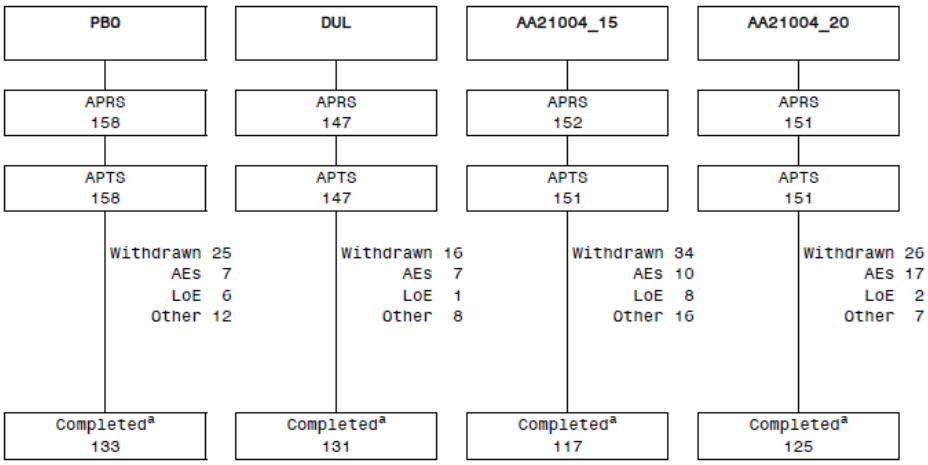
Source: Integrated Clinical Study Report (Study 13267A), Page 69

There was no major difference in mean age, gender or race across the treatment groups.

6.3.3 Subject Disposition

Same as in Study 202 (page 16 of this review).

Table 8: Subject Disposition



Source: Clinical Study Report (Study 13267A), page 64

6.3.4. Analysis of Primary and Secondary Endpoints:

A hierarchical step-down testing strategy was defined *a priori* and comprised the primary efficacy analysis, as well as the key secondary efficacy analyses under multiplicity control.

The primary efficacy analysis showed that vortioxetine in doses of 15 and 20mg/day was statistically significantly superior to placebo (p <0.001) as measured by the mean change from baseline in MADRS total score at Week 8, with a treatment difference to placebo of -5.5 (15mg) and -7.1 (20mg) (FAS, MMRM).

Table 9: Testing Strategy Results-Study 13267A

	Difference From Placebo		P-value	
	Lu AA21004		Lu AA21004	
Endpoint (Week 8)	15 mg	20 mg	15 mg	20 mg
Δ MADRS total score (a)	-5.5 ± 1.1	-7.1 ± 1.1	<0.001	<0.001
MADRS response (b)	24.8%	29.3%	<0.001	<0.001
CGI-I score (c)	-0.7 ± 0.1	-1.0 ± 0.1	<0.001	<0.001
Δ MADRS total score in subjects with a HAM-A total score ≥20 at Baseline	-5.2 ± 1.5	-6.4 ± 1.6	<0.001	<0.001
MADRS remission (b)	15.9%	19.4%	0.002	<0.001
Δ SDS total score	-3.2 ± 1.2	-3.9 ± 1.1	0.005	<0.001

Source: Study 13267A Tables 30, 41, 78, 88, 96, and 105.
Hierarchical testing in 2 parallel sequences, each at α = 0.025; values are mean ± SE.
(a) Primary efficacy analysis; Lu AA21004 15 mg and Lu AA21004 20 mg were tested in parallel at α = 0.025.
(b) Logistic regression analyses for response and remission (LOCF); values are percentage point differences from placebo.
(c) Treatment difference from placebo in mean CGI-I score at Week 8.

The mean CGI-I score (week 8) at 15mg separated from placebo by -0.7 and at the 20mg dose by -1.0 (both with p-values<0.001). The 20 mg was numerically superior to the 15 mg dose, but both were statistically significant compared to placebo.

7 Review of Safety

7.1 Safety Summary

The safety data review for Study 13267A will not be included in this supplement review.The data from that study was reviewed with the original NDA application.

Study 202 is reviewed below; in general, the rates of adverse events in the studies supporting this supplemental application are similar to those listed in the current product label. No new safety signals were identified.

7.2 Review of the Safety Database—Study 202

7.2.1 Overall Exposure

The treatment groups were comparable regarding the mean number of weeks of exposure to study drug, which ranged from 7.4 to 7.7 weeks; the median number of weeks of exposure was 8 weeks across all three treatment groups.

Table 10: Overall Exposure, Study 202

Duration of exposure (weeks)	Placebo (N=191)	Lu AA21004 (N=196)	Duloxetine (N=207)
N	191	196	207
Mean (SD)	7.51 (1.803)	7.68 (1.439)	7.41 (1.839)
Median	8.00	8.00	8.00
Minimum - Maximum	0.1 - 10.1	0.4 – 10.0	0.4 – 9.1
Duration of exposure categories:			
1 – 6 days	2 (1.0)	2 (1.0)	4 (1.9)
7 – 13 days	7 (3.7)	2 (1.0	6 (2.9)
14 – 27 days	5 (2.6)	3 (1.5)	6 (2.9)
28 – 41 days	5 (2.6)	10 (5.1)	7 (3.4)
42 – 55 days	39 (20.4)	41 (20.9)	48 (23.2)
≥ 56 days	133 (69.6)	138 (70.4)	136 (65.7)

Source: Clinical Study Report (Study 202), page 113

Table 11: Treatment Emergent Adverse Events, Study 202

	Placebo (N=191)		Vortioxetine 10 or 20 mg (N=196)		Duloxetine 60 mg (N=207)	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAE	162	85 (44.5)	235	117 (59.7)	323	119 (57.5)
Leading to discontinuation		7 (3.7)		7 (3.6)		13 (6.3)
Serious TEAEs		2 (1.0)		1 (0.5)		1 (0.5)
Deaths		0		0		0

Source: Study 202, Table 12.c.

Nausea was the most common treatment-emergent adverse event (TEAE) during the 8-week Treatment Period in the vortioxetine treatment group [approximately 20% of subjects when treated with flexible dose (10 or 20 mg)].This incidence is consistent with previous vortioxetine studies.

7.3 Safety Results

7.3.1 Deaths

There were no deaths reported in either study 202 or 14122A.

7.3.2 Serious Adverse Events

A total of 4 subjects (0.7%), 1 subject (0.5%) in the vortioxetine group and 1 subject (0.5%) in the duloxetine group compared with 2 subjects (1.0%) in the placebo group, had a total of 5 serious TEAEs during the study. The only SAE in the vortioxetine group was a 56yo male with a history of two previous suicide attempts reported on the Baseline C-SSRS who was hospitalized on Study Day 19 for a life-threatening suicide attempt.

7.3.2 Dropouts and/or Discontinuations Due to Adverse Effects

A total of 27 subjects (4.5%) discontinued the study because of a TEAE, 7 subjects (3.6%) in the vortioxetine group and 13 subjects (6.3%) in the duloxetine group, compared with 7 subjects (3.7%) in the placebo group. The most frequently reported TEAEs that led to study discontinuation were nausea, fatigue, and depression, each occurring in 4 subjects (0.7%) and distributed among the treatment groups. All other TEAEs that led to study discontinuation occurred at an incidence of 0.5% (1 subject).

8 Postmarket Experience

Since initial approval, additional safety information regarding angle-closure glaucoma, weight gain, and acute pancreatitis has been added to this product's labeling.

9 Appendices

9.1 Labeling Recommendations

The Applicant proposed the following addition to the product label in Section 14:

> TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is (b) (4) [redacted]

The final agreed upon language is as follows:

> TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is a clinician's impression of how much the patient's clinical condition has improved or worsened relative to baseline on a scale of 1 (very much improved) to 7 (very much worse).

9.2 Advisory Committee Meeting

No Advisory Committee meeting was held.

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

/s/

GRACIELA M GONZALEZ
03/10/2017

JASMINE C GATTI
03/10/2017

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	204447/s-009
Priority or Standard	Standard
Submit Date(s)	May 10, 2016
Received Date(s)	May 10, 2016
PDUFA Goal Date	March 10, 2017
Division / Office	DPP/ODE 1
Reviewer Name(s)	Graciela M. Gonzalez, MD
Review Completion Date	March 1, 2017
Established Name	Vortioxetine
Proposed Brand Name	Trintellix
Therapeutic Class	Antidepressant
Applicant	Takeda Pharmaceutical
Formulation(s)	Immediate Release Tablet
Dosing Regimen	10mg,15mg, 20mg (oral) daily
Indication(s)	Major Depressive Disorder
Intended Population(s)	Adult Patients

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1 Recommendations/Risk Benefit Assessment

The purpose of this supplemental NDA application is to request inclusion in labeling of data related to the effect of vortioxetine treatment on global functioning in depression as assessed by the Clinical Global Impression-Improvement (CGI-I) scale. The data the Applicant wishes to include in the Clinical Studies section of the package label comes from two Phase 3, eight week, placebocontrolled studies in adults with Major Depressive Disorder (MDD) in which the CGI-I was a pre-specified secondary endpoint:

- Study 202 (n=602, 80 worldwide sites, fixed dose of vortioxetine 10 mg and 20 mg Q day versus placebo). The primary endpoint in this study was the change from baseline to Week 8 in the Digit Symbol Substitution Test (DSST).

- Study 13267A (n=600, 72 worldwide sites, flexible dose 15 mg and 20 mg Q day versus placebo). The primary endpoint in this study was the change from baseline to Week 8 in the Montgomery and Åsberg Depression Rating Scale (MADRS).

Both studies used duloxetine 60 mg per day as a comparator drug.

In both studies the CGI-I was included to measure efficacy in their key secondary endpoint (the change from baseline to the end of Week 8 of treatment) as part of a hierarchal testing plan.

These two studies demonstrated statistical significance for CGI-I versus placebo for doses of vortioxetine of 10 mg, 15mg, and 20 mg in adult patients meeting criteria for MDD.

1.1 Recommendation on Regulatory Action

I recommend that this supplement be approved and labeling be updated. The Applicant has demonstrated that vortioxetine is superior to placebo as measured by the CGI-I.

1.2 Risk Benefit Assessment

Vortioxetine is an approved antidepressant indicated for the treatment of MDD. The addition of CGI-I data to labeling does not alter the benefit/risk assessment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations are necessary.

1.4 Recommendations for Postmarket Requirements and Commitments

No recommendations are necessary.

2 Introduction and Regulatory Background

2.1 Product Information

Vortioxetine was discovered and patented by H. Lundbeck A/S (Lundbeck) and co-developed with Takeda Pharmaceutical Company Ltd. (Takeda) for the treatment of major depressive disorder (MDD).

Vortioxetine is indicated for the treatment of major depressive disorder (MDD). The efficacy of vortioxetine was established in six 6- to 8-week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly) and one maintenance study in adult inpatients and outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD.

The mechanism of the antidepressant effect of Lu AA21004 is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of 5-HT. It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism.

2.2 Currently Available Treatments for Proposed Indications

Several selective serotonin reuptake inhibitors (SSRIs) are approved for the treatment of MDD. Among the SSRIs, the following products include CGI data (either CGI-I or CGI-Severity) in Section 14 of their product labeling: fluoxetine (Prozac, Sarafem), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and vilazodone (Viibryd).

2.3 Availability of Proposed Active Ingredient in the United States

Vortioxetine was approved in the United States for the treatment of MDD in adults on September 13, 2013.

2.4 Important Safety Issues with Consideration to Related Drugs

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation, and vomiting. Other common adverse reactions include diarrhea, dry mouth, flatulence, dizziness, abnormal dreams, and pruitis. Vortioxetine is also associated with both male and female sexual dysfunction.

Vortioxetine labeling also includes the following Warnings and Precautions:

- Clinical Worsening and Suicide Risk
- Serotonin Syndrome

- Abnormal Bleeding
- Activation of Mania/Hypomania
- Angle Closure Glaucoma
- Hyponatremia

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

In the original NDA approval letter for vortioxetine tablets (trade name Brintellix at that time) dated September 13, 2013, the drug was approved for the treatment of Major Depressive Disorder in adults at the doses of 5 mg, 10 mg, 15mg, and 20 mg tablets.

During the review of New Drug Application (NDA) 204447, the Food and Drug administration (FDA) recommended not including CGI-Irelated information from the package insert, stating that for a key secondary endpoint to be described in the package insert it must be pre-specified and the positive findings have to be replicated within a testing strategy.

In the recently completed Study 202, CGI-I was included as a key secondary endpoint and vortioxetine separated from placebo on this endpoint. Given the positive and now replicated results, the Applicant seeks to add CGI-I data to the Clinical Studies section of the package insert using data from Study 13267A and Study 202.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was well organized and the information was easy to find. The reporting, interpretation and verification of the data were accurate. The confidentiality of records was protected. No request for additional information was needed.

3.2 Compliance with Good Clinical Practices

The Studies 202 and 13267A were conducted in accordance with Good Clinical Practices.

No inspections were performed for this supplement.

3.3 Financial Disclosures

In accordance with 21 CFR 314.50(k), financial disclosure certification summaries were included in this submission for the principal investigator and all the sub-investigators at all the sites in the United States and in different countries around the world. None of the investigators had any financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to original NDA #: 204447. No new CMC information was included with this submission.

4.2 Clinical Microbiology

Refer to original NDA #: 204447. No new clinical microbiology information was included with this submission.

4.3 Preclinical Pharmacology/Toxicology

Refer to original NDA #: 204447. No new pharmacology/toxicology information was included with this submission.

4.4 Clinical Pharmacology

Refer to original NDA #: 204447. No new clinical pharmacology information was included with this submission.

4.4.1 Mechanism of Action

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

4.4.2 Pharmacodynamics

Refer to original NDA #: 204447. No new pharmacodynamic information was included with this submission.

4.4.3 Pharmacokinetics

Refer to original NDA #: 204447. No new pharmacokinetic information was included with this submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trial

Table 1: Phase 3 Clinical Trials

Table 1: Clinical Trials	
Phase/Trial	**Description**
Phase 3	
Study 202	8-week, randomized, double-blind, parallel-group, placebo controlled, active reference (duloxetine 60 mg/day), 80 sites worldwide, flexible-dose (vortioxetine 10 and 20 mg/day). N=602 adults randomized
Phase 3	
13267-A	8-week, randomized, double-blind, parallel group, placebo-controlled, active reference (duoloxetine 60 mg/day), 72 sites worldwide, fixed dose (vortioxetine 15 and 20 md/day). N=600 adults randomized

5.2 Review Strategy

This review is focused on the key secondary endpoints of the two studies 202 and 13267A and the inclusion of the CGI-I data as a secondary assessment of efficacy.

6 Review of Efficacy

6.1 Efficacy Summary

The efficacy of vortioxetine for the treatment of MDD has been established in prior applications. Here, the Applicant has provided data to support inclusion of CGI-I data in Section 14 of labeling. Adult patients receiving vortioxetine 10 to 20 mg experienced significantly greater improvement in CGI-I scores in both Study 202 and Study 13267A than patients receiving placebo.

Table 2: Summary of CGI Positive Results in Study 202 and Study 13267A

Study	Dose (a)	Difference From PBO (CGI-I)	95% CI	Nominal p-value (b)	Comments About Statistical Significance
202	10/20 mg	-0.29	(-0.53, -0.05)	0.017	Primary analysis method = MMRM CGI-I was included in a planned hierarchical testing plan (α set at 0.05) as the third endpoint in the sequence. Based on the study analyses (MMRM), the primary endpoint and all key secondary endpoints, including CGI-I, were significant at α=0.05 for treatment.
13267A	15 mg	-0.69	(-0.94, -0.44)	<0.001	Primary analysis method = MMRM CGI-I was included in a planned hierarchical testing plan with separate sequences per dose (α set at 0.025) as the third endpoint in the sequences. Based on the study analyses (MMRM), the primary endpoint and all key secondary endpoints, including CGI-I, were significant at α=0.025 for each dose.
	20 mg	-0.95	(-1.20, -0.70)	<0.001	

Source: Applicant's Table of Summary of CGI-I Positive Results in Study 202 and 13267

6.2 Indication

Under this supplemental NDA application, Takeda Pharmaceutical is seeking the addition of labeling language to describe that vortioxetine is superior to placebo on the CGI-I in adult patients with MDD using two studies (Studies 202 and 13267A) that demonstrated statistical significance for CGI-I versus placebo, for doses of 10 to 20 mg.

6.2.1 Study Summaries

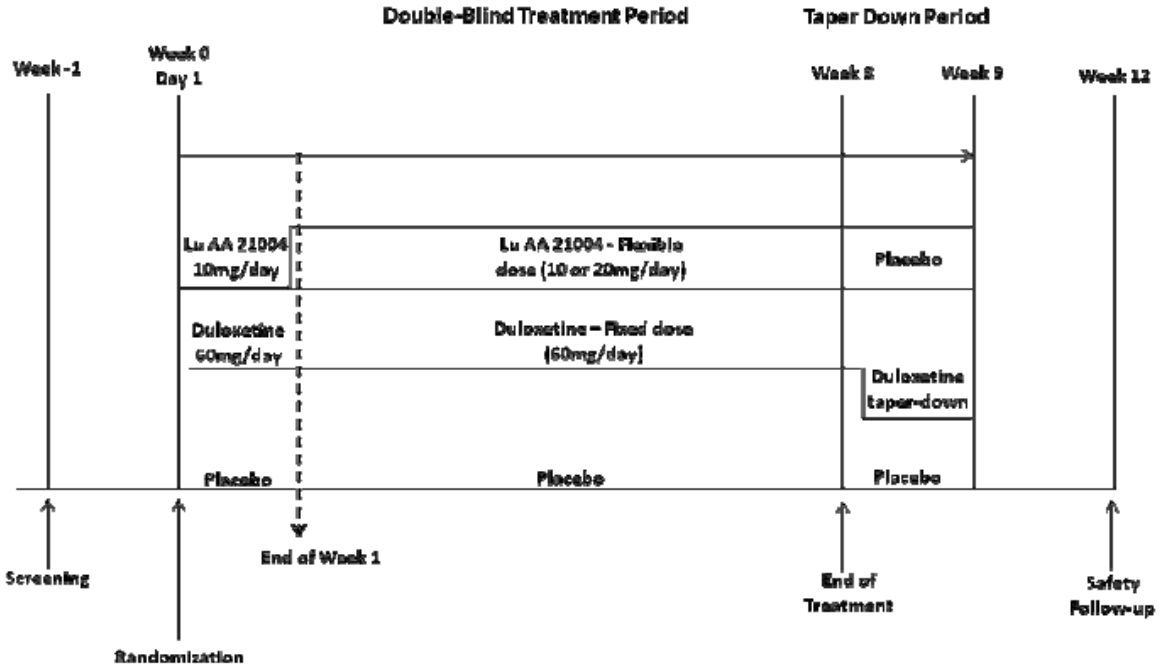
Study 202

Study Design

The study was a Phase 3, 80 site (Bulgaria, Finland, Germany, Poland, Russian Federation, Ukraine and the United States), randomized, double-blind, placebo- and active-controlled (duloxetine 60 mg daily), 8-week study, with flexible doses of vortioxetine (10 mg daily or 20 mg daily) in adult patients with MDD.

For the study design schematic see Figure 1below.

Figure 1: Design Schematics



Source: Clinical Study Report (Sttudy 202), Page 26

Inclusion and Exclusion Criteria:

Subjects meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for MDD were eligible for inclusion.
Subjects were required to have a diagnosis of acute (major depressive episode (MDE) in the context of recurrent MDD and to have received prescribed treatment for a previous episode of depression. Previous MDE was to be confirmed using the Mini International Neuropsychiatric Interview (MINI) and attempts were to be made to document previous MDEs through review of medical records. Subjects were also required to have moderate to severe depression. Milder forms of depression were excluded as high placebo response rates and spontaneous remission rates are believed to account for the lack of drug-placebo difference in mild depression. Also, duration of at least 3 months for the current episode was required. Men and women between 18 to 64 years of age, who had a MADRS total score ≥26 at both the Screening and Baseline visits and reported subjective cognitive dysfunction (such as difficulty concentrating, slow thinking, and difficulty in learning new things or remembering things) were included.

Any current psychiatric disorder other than MDD was exclusionary as well as current diagnosis of alcohol or other substance abuse or dependence that had not been in sustained remission for at least 2 years prior to Screening, or if the subject had a significant risk of suicide according to the investigator's clinical judgment or had a score

≥5 on item 10 (suicidal thoughts) of the MADRS or had made a suicide attempt in the previous 6 months. Additionally, the presence or history of a clinically significant neurological disorder or unstable thyroid condition was exclusionary..

All subjects were started on vortioxetine 10 mg daily and were able to have their dosage flexibly increased to 20 mg after the end of Week 1. The subjects in the duloxetine arm received a fixed dose of 60 mg daily.

Table 3: Schedule of Efficacy Assessment

Visit	Screening	Baseline	Treatment Period		Safety Phone Call (a)	Completion/ Early Termination (b)	End of Taper-Down Period (c)	Safety Follow- up (d)
Visit Number	1	2	3	4	5	6	7	8
Day/End of Week	Days -10 to -2	Day 1	End of Week 1	End of Week 4	End of Week 6	End of Week 8	End of Week 9	End of Week 12
Visit Window (e) (days relative to which visit)			± 1	± 3	± 3	± 3	± 3	±5
Efficacy Assessments								
Neuropsychological tests: DSST, TMT A, TMT B, Stroop test, GMLT, DET, IDN, One-Back	X (g)	X				X		
MADRS	X	X	X	X		X		
CGI-S		X	X	X		X		
CGI-I			X	X		X		
PDQ		X		X		X		
CPFQ		X		X		X		
UPSA-VIM/UPSA-B (h)		X				X		
WLQ (i)		X				X		

DSST-Digit Symbol Subs itution Test, TMT A and B-Trail Making Test Part A and Part B, Stroop test-Stroop Color Naming Test, GMLT-Groton Maxe learning Test, DET- Detection Task, IDN- Identification Task, MADRS- Montgomery-Asberg Depression Scale, CGI-I- Clinical Global Impressions Improvement, PDQ-Perceived Deficits Ques ionnaire, UPSA-VIM/UPSA-B- University of San Diego Performance-Based Skills Assessments-Validation of Immediate Measures/University of San Diego Performance-Based Skills Assessment- Brief, WLQ-Working Limita ion Questionnaire
Source: Clinical Study Report (Study 202), Page 45

Prohibited Concomitant Medications:

Antipsychotics, antidepressants, anxiolytics, psychoactive herbal remedies, mood stabilizers, psychostimulants, tryptophan, sedatives, hypnotics, or medications that alter the concentration of serotonin in the brain (such as: meperidine, tramadol, St. John's wort, triptans, or street drugs like cocaine, etc.), nonsteroidal anti-inflammatory drugs and anticoagulants.

Statistical Analysis Plan:

Primary Endpoint: The change from baseline to Week 8 in DSST total number of correct symbols.

Secondary Endpoints: The pre-specified key secondary efficacy parameters were change from baseline to week 8 in PDQ attention/concentration and planning/organization sub-score; CGI-I at week 8.

All tabulations of analysis results included summaries for the following treatment groups: placebo, vortioxetine, and duloxetine.
All confidence intervals, statistical tests, and resulting p-values were reported as nominal 2-sided and assessed at the 5% significance level.
To control two-sided type I error of overall efficacy in Study 202, the primary and key efficacy endpoints were tested sequentially at significance level of 0.05 in the following order:

1. Change from baseline to Week 8 in DSST total number correct symbols.
2. Change from baseline to Week 8 in the PDQ attention/concentration and planning/organization sub-score.
3. CGI-I at Week 8.

The full analysis set (FAS) included all subjects who were randomized, received at least one dose of study drug, and had at least one valid post-baseline value for assessment of primary efficacy. In FAS efficacy summaries, subjects were analyzed by the treatment to which they were randomized.

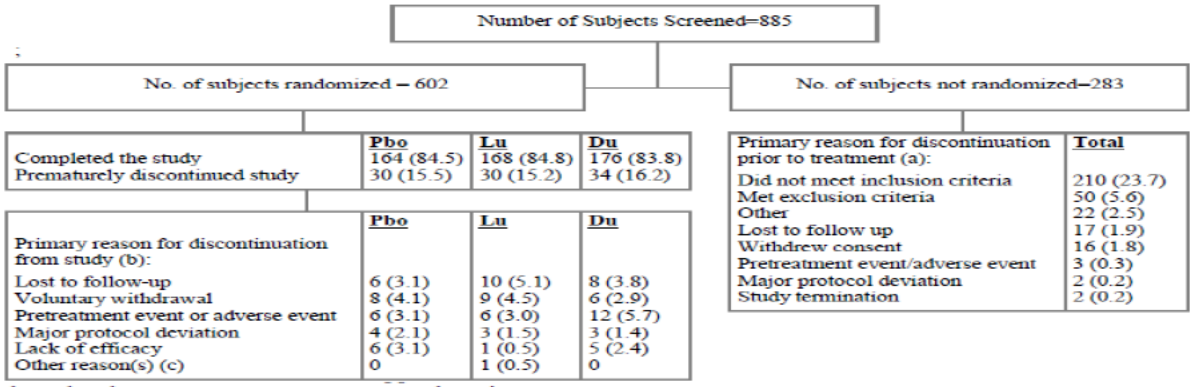
Demographics

Mean (SD) age was 45 years of age (12%) with the majority (79%) $\leq$55 years of age. Nearly two-thirds of the subjects were female (65%). Most of the subjects (86%) were Caucasian (including Hispanic), 13% were Black, 1% were Asian, and only 3 subjects (0.5%) were American Indian or Alaskan Native. Mean (SD) BMI was 29 (7%). Half of the subjects had never smoked and 16% no longer smoked. There were no significant differences among the treatment groups in any demographic category.

Subject Disposition

The categories included all subjects who were randomized (those not treated, discontinued from the study, or those that completed the study). Post-randomization discontinuation reasons included: adverse events, major protocol deviations, lost to follow-up, lack of efficacy, voluntary withdrawal, study termination, and pregnancy. See Figure 2 below.

Figure 2: Disposition of Subjects (All Randomized Subjects)



	Pbo	Lu	Du
Completed the study	164 (84.5)	168 (84.8)	176 (83.8)
Prematurely discontinued study	30 (15.5)	30 (15.2)	34 (16.2)

Primary reason for discontinuation from study (b):	Pbo	Lu	Du
Lost to follow-up	6 (3.1)	10 (5.1)	8 (3.8)
Voluntary withdrawal	8 (4.1)	9 (4.5)	6 (2.9)
Pretreatment event or adverse event	6 (3.1)	6 (3.0)	12 (5.7)
Major protocol deviation	4 (2.1)	3 (1.5)	3 (1.4)
Lack of efficacy	6 (3.1)	1 (0.5)	5 (2.4)
Other reason(s) (c)	0	1 (0.5)	0

Primary reason for discontinuation prior to treatment (a):	Total
Did not meet inclusion criteria	210 (23.7)
Met exclusion criteria	50 (5.6)
Other	22 (2.5)
Lost to follow up	17 (1.9)
Withdrew consent	16 (1.8)
Pretreatment event/adverse event	3 (0.3)
Major protocol deviation	2 (0.2)
Study termination	2 (0.2)

Pbo=placebo. Lu=Lu AA21004. Du=Duloxetine.
(a) More than 1 reason for discontinuation could have been reported for a subject at the Screening visit.
(b) Primary reasons for study discontinuation are mutually exclusive and exhaustive categories for randomized subjects.
(c) Other reason for study discontinuation: In the Lu AA21004 group, 1 subject (b) (6) discontinued the study on Day 7 because of the serious illness of a family member (Appendix 16.2.1.2).
Note: Reasons for study discontinuation are listed in descending order in the Lu AA21004 treatment group.

Source: Clinical Study Report (Study 202), Page 82

Protocol Violations/Deviations:

Seventy-five subjects had at least one major protocol deviation: 24 subjects (12.1%) in the vortioxetine group, 23 subjects (11.0%) in the duloxetine group, and 28 subjects (14.4%) in the placebo group.
A total of 10 subjects (1.7%) discontinued the study for major protocol deviations.
The incidence of major protocol deviations was similar across treatment groups for each category of major protocol deviation. There is no reason to believe that any of these protocol deviations could have biased the efficacy results of the study.

Analysis of Primary Endpoint

The vortioxetine group was statistically significantly better than placebo in the change from baseline in DSST total number of correct symbols score group (LS mean = 1.75, p=0.019. The difference between the duloxetine and placebo groups was not statistically significant (p=0.099).

Analysis of Secondary Endpoints

Both vortioxetine and duloxetine showed statistically significant improvement in the PDQ attention/concentration and planning/organization sub-score from placebo at Week 8 (vortioxetine, LS mean = -2.6, p = 0.001; duloxetine, LS mean = -3.0, p< 0.001). Treatment with vortioxetine and duloxetine also produced a statistically significant improvement in CGI-I score compared to placebo at week 8 (vortioxetine, LS mean = -0.29, p = 0.017; duloxetine, LS mean = -0.40, p < 0.001). The focus of this supplement is the CGI-I.

Table 4: Primary and Key Secondary Efficacy Analysis at Week 8, Difference from Placebo Hierarchical Testing) (FAS)

	Lu AA21004	
Efficacy Variable	**Difference From Placebo LS Mean (SE)**	**P-value**
DSST total number of correct symbols (OC)(a)	1.75 (0.744)	0.019
PDQ attention/concentration and planning/organization subscore (MMRM)	-2.6 (0.78)	0.001
CGI-I (MMRM)	-0.290 (0.1211)	0.017

Source: Table 15.2.1.1.2, Table 15.2.13.3.5, Table 15.2.11.1.5.
(a) primary efficacy analysis.

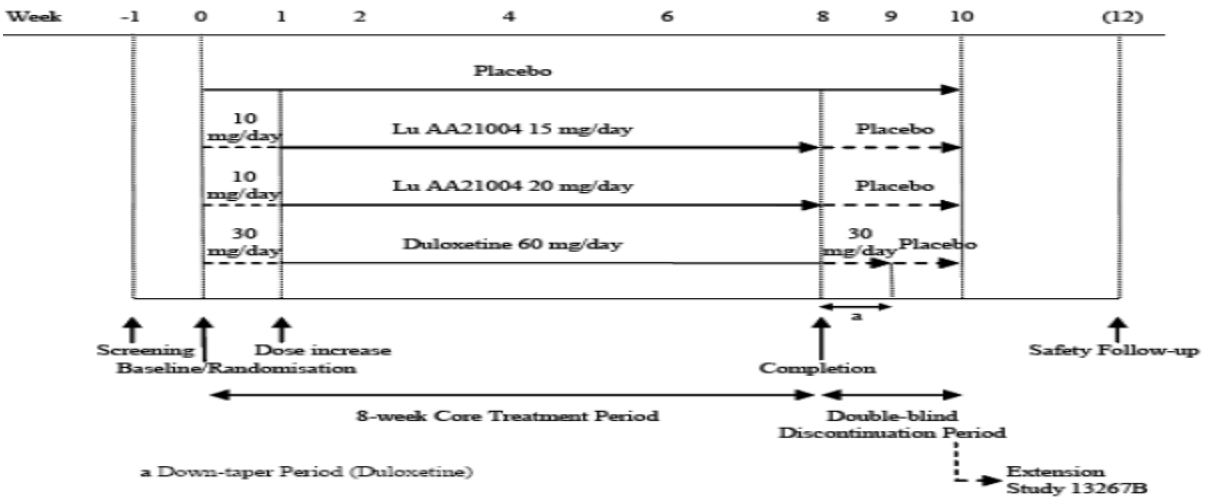
Source: Clinical Study Report (Study 202.), Page 94.

Study 13267A

Study Design

Study 13267A was a randomized, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating vortioxetine 15 and 20 mg/d in 600 adult patients with MDD (151 patients per vortioxetine group). The study was conducted in 72 sites around the world (2 in Belgium, 2 in Estonia, 7 in Finland, 10 in France, 7 in Germany, 5 in Latvia, 3 in Lithuania, 2 in Norway, 10 in Russian Federation, 6 in Slovakia, 2 in South Africa, 4 in Sweden, and 12 in Ukraine).

Figure 3: Study Design



Source: Integrated Clinical Study Report (Study 13267A), Page 28

The following periods were defined:

- Screening Period – from screening to randomization 8-week (1 to 0 week)
- Core Treatment Period – 8-week double-blind period with vortioxetine (15 mg/day or 20mg/day), duloxetine (60mg/day), or placebo (Weeks 1 to 8)
- Discontinuation Period I – 1-week double-blind down-taper period with either duloxetine 30mg/day for those randomized to duloxetine or placebo for those randomized to any of the other three treatment groups (Week 8 to 9)
- Discontinuation Period II – 1-week double-blind period with placebo after Discontinuation Period I (Week 9 to10)
- Safety Follow-up Period – 4-week period after completion/withdrawal (Weeks 9 to 12)

Inclusion and Exclusion Criteria

Patients with moderate to severe recurrent MDD (baseline MADRS total score ≥ 26 and CGI-S score ≥ 4) based on DSM-IV-TR criteria were eligible for inclusion. Subjects' diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI). Subjects were required to have > 3 months duration of symptoms with inadequate response to two antidepressant treatments of ≥ 6 weeks duration each.

Men and women (ages ≥18 and ≤ 75 years) were included in the study.
Patients with current psychiatric disorders other than MDD were excluded, as well as patients with a diagnosis of alcohol or other substance abuse, history of moderate or severe head trauma, other neurological disorders or systemic medical diseases, or who were judged to be at risk of harm to self or others.

Study Treatment:

The patients were randomized equally (1:1:1:1) to placebo, vortioxetine 15mg/day, vortioxetine 20mg/day, or duloxetine 60 mg/day for 8 weeks of double-blind treatment. Patients randomized to treatment with vortioxetine received a dose of 10 mg/day during Week 1 (up-titration); from Weeks 2 to 8 they received a dose of either 15 or 20 mg/day. Patients randomized to treatment with duloxetine received a dose of 30 mg/day during Week 1 (up-titration); from Weeks 2 to 8, they received a dose of 60 mg/day.

Table 5: Dose Titration Schedules

Week	IMP Dispensed Day/Visit	Dosing Time[a]	Placebo Group	Lu AA21004 15mg Group	Lu AA21004 20mg Group	Duloxetine Group
Week 1	Day 0/Visit 2	Morning	placebo	10mg	10mg	30mg
Weeks 2 to 8	Day 7/Visit 3	Morning	placebo	15mg	20mg	60mg
	Day 14/Visit 4	Morning	placebo	15mg	20mg	60mg
	Day 28/Visit 5	Morning	placebo	15mg	20mg	60mg
	Day 42/Visit 6	Morning	placebo	15mg	20mg	60mg
Week 9	Day 56/Visit 7	Morning	placebo	placebo	placebo	30mg
Week 10	Day 63/Visit 8	Morning	placebo	placebo	placebo	placebo

a The first dose from the dispensed IMP was to be taken the day after the visit.

Source: Integrated Clinical Study Report (Study 13267A), Page 34

Table 6: Schedule of Efficacy Assessments

Period	8-week Core Treatment Period					Safety Follow-up
Visit	3	4	5	6	Completion	10
End of Week	1	2	4	6	8	12
Day	7	14	28	42	56	84
Eficacy Assessments						
MADRS, CGI-S	X	X	X	X	X	
HAM-A	X	X	X	X	X	
CGI-I	X	X	X	X	X	

MADRS=Montgomery and Asberg Depression Rating Scale, CGI-S=Clinical Global Impression Safety Scale
HAM-A= Hamilton Anxiety Rating Scale, CGI-I=Clinical Global Impression Improvement Scale

Prohibited Concomitant Medications:

Same as in Study 202, listed above.

Subject Discontinuation and Withdrawal:

After completion of the 8-week Core Treatment Period, the patients entered a 2-week, double-blind Discontinuation Period: patients on placebo remained on placebo; patients on vortioxetine 15 or 20 mg/day switched abruptly to placebo; and patients on duloxetine (60 mg/day) received duloxetine 30 mg/day during the first week and placebo during the second week. The same treatment regimen was offered to patients who withdrew from the study. Potential discontinuation symptoms were evaluated during the Discontinuation Period. Patients who did not continue into extension Study 13267B were scheduled for a Safety Follow-up Visit/Contact 4 weeks after the Completion/Withdrawal Visit.

Statistical Analysis Plan:

Primary Endpoint: Change from baseline to Week 8 on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Key Secondary Endpoints: Sheehan Disability Scale (SDS) total score and CGI-I score.

To adjust for multiplicity, Vortioxetine 15 and 20 mg/day were tested separately versus placebo at a Bonferroni-corrected significance level of 0.05/2 = 0.025. There were two parallel testing sequences for the 15 mg and 20 mg doses, respectively. Focusing only on the accepted key secondary endpoints, for each of the dose groups, the primary and key secondary endpoints were hierarchically ordered as follows:

1. Change from baseline to Week 8 in MADRS total score (primary)
2. CGI-I score at Week 8
3. Change from baseline to Week 8 in SDS total score

6.3.2 Demographics

Table 7: Demographics

		PBO		DUL		AA21004_15		AA21004_20		Total	
Number of Patients		158		147		151		151		607	
Age	N	158		147		151		151		607	
	Mean	48.13		45.57		47.02		46.15		46.74	
	SD	13.11		13.55		14.61		13.43		13.68	
	Min	21.00		19.00		18.00		18.00		18.00	
	Max	74.00		74.00		74.00		73.00		74.00	
	Median	49.00		46.00		47.00		46.00		47.00	
Sex n (%)	M	48	(30.4)	45	(30.6)	54	(35.8)	60	(39.7)	207	(34.1)
	F	110	(69.6)	102	(69.4)	97	(64.2)	91	(60.3)	400	(65.9)
Race n (%)	White	156	(98.7)	144	(98.0)	150	(99.3)	146	(96.7)	596	(98.2)
	Black	2	(1.3)	3	(2.0)	0	(0.0)	2	(1.3)	7	(1.2)
	Asian	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.2)
	Other	0	(0.0)	0	(0.0)	1	(0.7)	2	(1.3)	3	(0.5)

13267A FINAL ST_DE01 19JUN2012:19:44:17 SADs Build Number: 240

PBL=Placebo, Dul=Duloxetine, 15=15 mg, 20=mg.

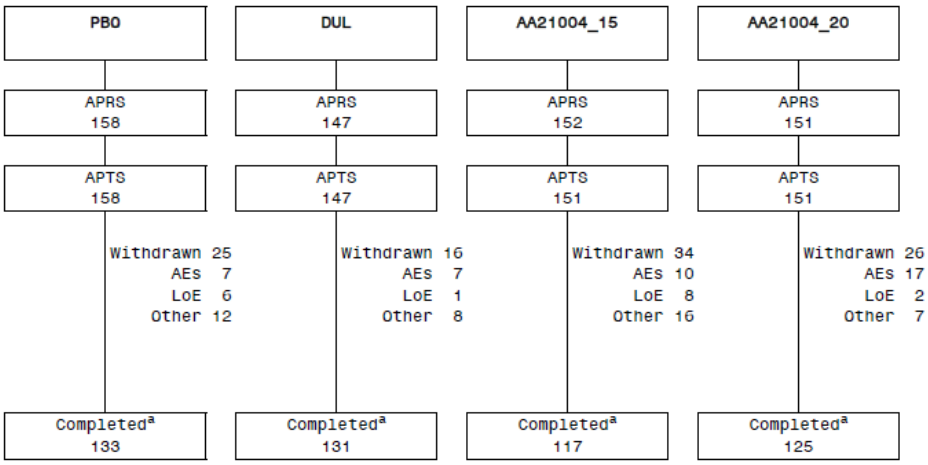
Source: Integrated Clinical Study Report (Study 13267A), Page 69

There was no major difference in mean age, gender or race across the treatment groups.

6.3.3 Subject Disposition

Same as in Study 202 (page 16 of this review).

Table 8: Subject Disposition



Source: Clinical Study Report (Study 13267A), page 64

6.3.4. Analysis of Primary and Secondary Endpoints:

A hierarchical step-down testing strategy was defined *a priori* and comprised the primary efficacy analysis, as well as the key secondary efficacy analyses under multiplicity control.

The primary efficacy analysis showed that vortioxetine in doses of 15 and 20mg/day was statistically significantly superior to placebo (p <0.001) as measured by the mean change from baseline in MADRS total score at Week 8, with a treatment difference to placebo of -5.5 (15mg) and -7.1 (20mg) (FAS, MMRM).

Table 9: Testing Strategy Results-Study 13267A

	Difference From Placebo		P-value	
	Lu AA21004		Lu AA21004	
Endpoint (Week 8)	15 mg	20 mg	15 mg	20 mg
Δ MADRS total score (a)	-5.5 ± 1.1	-7.1 ± 1.1	<0.001	<0.001
MADRS response (b)	24.8%	29.3%	<0.001	<0.001
CGI-I score (c)	-0.7 ± 0.1	-1.0 ± 0.1	<0.001	<0.001
Δ MADRS total score in subjects with a HAM-A total score ≥20 at Baseline	-5.2 ± 1.5	-6.4 ± 1.6	<0.001	<0.001
MADRS remission (b)	15.9%	19.4%	0.002	<0.001
Δ SDS total score	-3.2 ± 1.2	-3.9 ± 1.1	0.005	<0.001

Source: Study 13267A Tables 30, 41, 78, 88, 96, and 105.
Hierarchical testing in 2 parallel sequences, each at α = 0.025; values are mean ± SE.
(a) Primary efficacy analysis; Lu AA21004 15 mg and Lu AA21004 20 mg were tested in parallel at α = 0.025.
(b) Logistic regression analyses for response and remission (LOCF); values are percentage point differences from placebo.
(c) Treatment difference from placebo in mean CGI-I score at Week 8.

The mean CGI-I score (week 8) at 15mg separated from placebo by -0.7 and at the 20mg dose by -1.0 (both with p-values<0.001). The 20 mg was numerically superior to the 15 mg dose, but both were statistically significant compared to placebo.

7 Review of Safety

7.1 Safety Summary

The safety data review for Study 13267A will not be included in this supplement review.The data from that study was reviewed with the original NDA application.

Study 202 is reviewed below; in general, the rates of adverse events in the studies supporting this supplemental application are similar to those listed in the current product label. No new safety signals were identified.

7.2 Review of the Safety Database—Study 202

7.2.1 Overall Exposure

The treatment groups were comparable regarding the mean number of weeks of exposure to study drug, which ranged from 7.4 to 7.7 weeks; the median number of weeks of exposure was 8 weeks across all three treatment groups.

Table 10: Overall Exposure, Study 202

Duration of exposure (weeks)	Placebo (N=191)	Lu AA21004 (N=196)	Duloxetine (N=207)
N	191	196	207
Mean (SD)	7.51 (1.803)	7.68 (1.439)	7.41 (1.839)
Median	8.00	8.00	8.00
Minimum - Maximum	0.1 - 10.1	0.4 – 10.0	0.4 – 9.1
Duration of exposure categories:			
1 – 6 days	2 (1.0)	2 (1.0)	4 (1.9)
7 – 13 days	7 (3.7)	2 (1.0	6 (2.9)
14 – 27 days	5 (2.6)	3 (1.5)	6 (2.9)
28 – 41 days	5 (2.6)	10 (5.1)	7 (3.4)
42 – 55 days	39 (20.4)	41 (20.9)	48 (23.2)
≥ 56 days	133 (69.6)	138 (70.4)	136 (65.7)

Source: Clinical Study Report (Study 202), page 113

Table 11: Treatment Emergent Adverse Events, Study 202

	Placebo (N=191)		Vortioxetine 10 or 20 mg (N=196)		Duloxetine 60 mg (N=207)	
	Events	Subjects	Events	Subjects	Events	Subjects
Any TEAE	162	85 (44.5)	235	117 (59.7)	323	119 (57.5)
Leading to discontinuation		7 (3.7)		7 (3.6)		13 (6.3)
Serious TEAEs		2 (1.0)		1 (0.5)		1 (0.5)
Deaths		0		0		0

Source: Study 202, Table 12.c.

Nausea was the most common treatment-emergent adverse event (TEAE) during the 8-week Treatment Period in the vortioxetine treatment group [approximately 20% of subjects when treated with flexible dose (10 or 20 mg)].This incidence is consistent with previous vortioxetine studies.

7.3 Safety Results

7.3.1 Deaths

There were no deaths reported in either study 202 or 14122A.

7.3.2 Serious Adverse Events

A total of 4 subjects (0.7%), 1 subject (0.5%) in the vortioxetine group and 1 subject (0.5%) in the duloxetine group compared with 2 subjects (1.0%) in the placebo group, had a total of 5 serious TEAEs during the study. The only SAE in the vortioxetine group was a 56yo male with a history of two previous suicide attempts reported on the Baseline C-SSRS who was hospitalized on Study Day 19 for a life-threatening suicide attempt.

7.3.2 Dropouts and/or Discontinuations Due to Adverse Effects

A total of 27 subjects (4.5%) discontinued the study because of a TEAE, 7 subjects (3.6%) in the vortioxetine group and 13 subjects (6.3%) in the duloxetine group, compared with 7 subjects (3.7%) in the placebo group. The most frequently reported TEAEs that led to study discontinuation were nausea, fatigue, and depression, each occurring in 4 subjects (0.7%) and distributed among the treatment groups. All other TEAEs that led to study discontinuation occurred at an incidence of 0.5% (1 subject).

8 Postmarket Experience

Since initial approval, additional safety information regarding angle-closure glaucoma, weight gain, and acute pancreatitis has been added to this product's labeling.

9 Appendices

9.1 Labeling Recommendations

The Applicant proposed the following addition to the product label in Section 14:

> TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is (b) (4) [redacted]

The final agreed upon language is as follows:

> TRINTELLIX was superior to placebo on the Clinical Global Impression of Improvement (CGI-I) scale, which is a clinician's impression of how much the patient's clinical condition has improved or worsened relative to baseline on a scale of 1 (very much improved) to 7 (very much worse).

9.2 Advisory Committee Meeting

No Advisory Committee meeting was held.

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

/s/

GRACIELA M GONZALEZ
03/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s009

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	204,447/S-009
Drug Name:	Lu AA21004
Indication:	Major Depressive Disorder
Applicant:	Takeda Global Research and Development Center
Date(s):	Submission Date: May 10, 2016
	PDUFA Date: March 10, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewers:	Semhar Ogbagaber, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., HM James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Graciela M. Gonzalez, M.D.
Project Manager:	Jasmeet Kalsi, Pharm. D.

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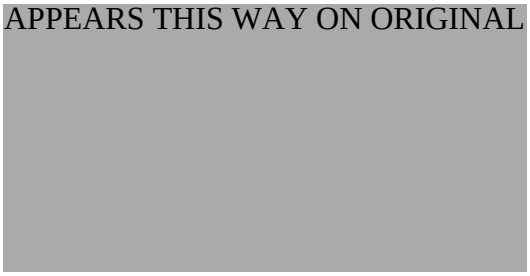

1 EXECUTIVE SUMMARY

The purpose of this supplemental NDA application by Takeda Global Research and Development Center is to add text in the Clinical Studies section of the US package insert (USPI) regarding effect of vortioxetine (Brintellix) on the Clinical Global Impression Improvement (CGI-I) scale. Vortioxetine was approved by the US FDA for the treatment of Major Depressive Disorder (MDD) on September 30, 2013 under NDA 204447. The CGI-I provides a clinician's view of a patient's improvement in global clinical condition as compared to baseline measures. Data to support a claim for labeling purposes are extracted from two positive studies: 13267A and 202. Study 13267A was reviewed under the original NDA 204447 for the treatment of MDD and Study 202 was reviewed under supplement S-006 for the treatment of cognitive dysfunction associated with MDD.

Controlling for the family-wise type I error, the two studies demonstrated formal statistical significance for CGI-I versus placebo. Supportive evidence collected from studies 305, 316, 11492A, and 12541A were also presented to show nominal significance of CGI-I. However, formal statistical significance could not be established. CGI-I was a part of the hierarchical testing plan for doses 5 mg and 10 mg in study 305 and doses 10 mg and 20 mg for study 316. The statistical testing did not proceed to test the significance of CGI-I in the pre-specified sequences because preceding endpoints were found to be not significant for the doses of interest. On the other hand, CGI-I was only stated as a secondary endpoint in studies 11492A and 12541A and hence was not part of the overall type I error control plan.

Please refer to the statistical reviews by the FDA on 06/05/2013[1] and 01/06/2016[2] for details concerning studies 13267A and 202, respectively.

2 INTRODUCTION

2.1 Overview

Vortioxetine (Brintellix) was approved on September 30, 2013 for the treatment of MDD under the original NDA 204447. In principle, for a new molecular entity to support a labeling description, replication of positive findings is required whether for the primary or the key secondary efficacy endpoint. Study 13267A was the only one of the positive studies under the original NDA which showed superiority of vortioxetine over placebo on key secondary endpoint CGI-I on 15 mg and 20 mg per day fixed doses. Accordingly, the sponsor submitted an international pivotal study (Study 202) in support of a supplemental New Drug Application (sNDA 204447) that demonstrated statistical significance of vortioxetine on CGI-I.

As Study 202 was ongoing, the sponsor met with the FDA on February 25, 2014 to obtain a feedback on the vortioxetine program on cognitive dysfunction in MDD and attain an agreement

[1] DARRTS Reference ID 3319841

[2] DARRTS Reference ID 3868611

on their clinical program to include CGI-I in the Clinical Studies Section of the vortioxetine package insert. Takeda formally added CGI-I as a key secondary endpoint which was included in the overall hierarchical testing strategy in Study 202. Vortioxetine separated statistically significantly from placebo on this endpoint.

Table 1 below summarizes sponsor's testing strategy in six (6) positive studies that included CGI-I in the multiple testing procedures. The hierarchical testing strategies were predefined in the SAP. The testing was conducted in a single sequence (Studies 11492A, 305, 202, and 12541A) or two parallel sequences (Studies 13267A and 316) for multiple doses. Each hypothesis in a single sequence was tested at significance level of 0.05 while each hypothesis in the parallel sequence was tested at a Bonferroni-corrected significance level of 0.025. Testing stopped as soon as the previous hypothesis in a hierarchy would be rejected. Although Study 315 is not included in Table 1, CGI-I was also a key secondary endpoint in this study which investigated doses 15 mg and 20 mg. However, CGI-I was not statistically significant for both doses. Table 1 included positive studies on the primary efficacy parameter as well as a statistically significant CGI-I on at least one of the vortioxetine doses.

The basis for sponsor's label claim of CGI-I is based on two positive studies (13267A and 202) that showed statistically significant separation between investigated dose groups and placebo. As a consequence, much emphasis in this review is put on the results of the two studies. Investigation of CGI-I in studies 11492A and 12541A are purely exploratory but are presented by the sponsor as supportive evidence of efficacy.

Table 1: Sponsor's Hierarchical Testing Strategies in the Short-Term Studies

Study	Testing Strategy
202	Hierarchical testing in 1 sequence (10 to 20 mg/day); α = 0.05—at Week 8: Δ DSST number of correct symbols score (ANCOVA, OC) (a) Δ PDQ attention/concentration and planning /organization combined subscore (MMRM) CGI-I score (b) (MMRM)
13267A	Hierarchical testing in 2 parallel sequences (15 and 20 mg); each at α = 0.025,—at Week 8: Δ MADRS total score (MMRM) Response—defined as ≥50% reduction in MADRS total score (LOCF) CGI-I score (MMRM) Δ MADRS total score in subjects with a HAM-A total score ≥20 at Baseline (MMRM) Remission—defined as a MADRS total score ≤10 (LOCF) Δ SDS total score (MMRM)
11492A	Hierarchical testing in 1 sequence; α = 0.05 (ANCOVA, LOCF) Δ MADRS total score at Week 6: 10 mg Δ MADRS total score at Week 6: 5 mg Δ MADRS total score at Week 1: 10 mg Δ MADRS total score at Week 1: 5 mg
305	Hierarchical testing in 1 sequence; α = 0.05—at Week 8: Δ HAM-D24 total score—10 mg (MMRM) Δ SDS total score—10 mg (MMRM) CGI-I score—10 mg (MMRM) Response—defined as a ≥50% reduction in HAM-D24 total score—10 mg (LOCF) Δ HAM-D24 total score in subjects with a HAM-A total score ≥20 at Baseline—10 mg (MMRM) Remission—defined as a MADRS total score ≤10—10 mg (LOCF) Δ HAM-D24 total score—5 mg (MMRM) Δ SDS total score—5 mg (MMRM) CGI-I score—5 mg (MMRM) Response—defined as a ≥50% reduction in HAM-D24 total score—5 mg (LOCF) Δ HAM-D24 total score in subjects with a HAM-A total score ≥20 at Baseline—5 mg (MMRM) Remission—defined as a MADRS total score ≤10—5 mg (LOCF)
316	Hierarchical testing in 2 parallel sequences (10 and 20 mg); each at α = 0.025,—at Week 8: Δ MADRS total score (MMRM) Response—defined as ≥50% reduction in MADRS total score (LOCF) CGI-I score (MMRM) Δ MADRS total score in subjects with a HAM-A total score ≥20 at Baseline (MMRM) Remission—defined as a MADRS total score ≤10 (LOCF) Δ SDS total score (MMRM)
12541A	Hierarchical testing in 1 sequence (5 mg); α = 0.05 (ANCOVA, LOCF) Δ HAM-D24 total score at Week 8, 6, 4, 2, and 1

α =level of statistical significance, Δ=change in, ANCOVA=analysis of covariance, HAM-24= 24-item Hamilton Depression Scale, OC=observed case, PDQ= Perceived Deficits Questionnaire.

Source: Sponsor's CGI-I Justification Report (Page 10)

2.2 Data Sources

Sponsor's primary analysis data and SAS program listings for the two pivotal studies are available in the following directory of the CDER' electronic document room (EDR):

\\Cdsesub1\evsprod\NDA204447\0000\m5\datasets\ and
\\Cdsesub1\evsprod\NDA204447\0078\m5\datasets\.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data satisfying and acceptable for the review analysis.

3.2 Evaluation of Efficacy

Pivotal studies 13267A and 202 provided evidence to describe CGI-I endpoint in the Clinical Studies section of the US package insert to support claim of global clinical improvement in adult MDD patients.

3.2.1 Study Design and Endpoints

3.2.1.1 Study 13267A

Efficacy Analyses Methods (Primary and Key Secondary Efficacy)
The primary efficacy parameter was change from baseline to Week 8 on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) total score. The sponsor's primary analysis method was a Mixed Model Repeated Measures (MMRM) with unstructured covariance structure to model the within- subject variation. The least square comparison of MADRS total score vortioxetine 15 mg/day and 20 mg/day versus placebo at Week 8 was based on completely observed data (OC). The model included treatment, site, visit, and treatment-by-visit interaction, baseline MADRS total score and baseline MADRS total score-by-visit interaction.

The FDA advice letter on September 14, 2010 determined that the only accepted key secondary endpoints were Sheehan Disability Scale (SDS) total score and CGI-I score. MMRM was also used as the primary analysis method.

Multiple Testing Procedure
To adjust for multiplicity, Vortioxetine 15 and 20 mg/day were tested separately versus placebo at a Bonferroni-corrected significance level of 0.05/2 = 0.025. There were two parallel testing sequences for the 15 mg and 20 mg doses, respectively. Focusing only on the accepted key secondary endpoints, for each of the dose groups, the primary and key secondary endpoints were hierarchically ordered as follows:

1. Change from baseline to Week 8 in MADRS total score (primary)
2. CGI-I score at Week 8
3. Change from baseline to Week 8 in SDS total score

The testing procedure stops as soon as there was no statistically significant difference ($p > 0.025$) between vortioxetine (10 mg, 20 mg/day) and placebo.

3.2.1.2 Study 202

Efficacy Analyses Methods (Primary and Key Secondary Efficacy)
The change from baseline in DSST total number of correct symbols to Week 8 was analyzed using analysis of covariance (ANCOVA), with treatment and pooled center as fixed factors, baseline DSST total number of correct symbols as covariate. Vortioxetine is flexibly dosed, 10 mg to 20 mg per day, in this study.

The pre-specified key secondary efficacy parameters were change from baseline to week 8 in PDQ attention/concentration and planning/organization sub-score; CGI-I at week 8.

Efficacy of vortioxetine in key secondary endpoints was evaluated using MMRM model with unstructured covariance structure. The model included the following terms: treatment, pooled site, baseline, visit, baseline-by-visit interaction, and treatment-by-visit interaction.

Multiple Testing Procedure
To control two-sided type I error of overall efficacy in Study 202, the primary and key efficacy endpoints were tested sequentially at significance level of 0.05 in the following order:

1. Change from baseline to Week 8 in DSST total number correct symbols.
2. Change from baseline to Week 8 in the PDQ attention/concentration and planning/organization sub-score.
3. CGI-I at Week 8.

3.2.2 Statistical Methodologies

Please refer to the formal statistical reviews, cited in Section 2.1, for details of the statistical methodologies as pre-specified in the sponsor's statistical analyses plans.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Please refer to the statistical reviews.

3.2.4 Results and Conclusions

Study 13267A (outside North America)
Primary Endpoint
The results of the primary efficacy analysis are presented in Table 2. The least squares (LS) mean difference for change from baseline in MADRS total score was statistically significantly superior to placebo for both dose groups: -5.5 ($P < 0.0001$) for 15 mg and -7.1 ($P < 0.0001$) for 20 mg.

Table 2. MADRS Total Score Change From Baseline at Week 8 (FAS, MMRM)

MADRS Total Score	Placebo	Duloxetine	Lu AA21004

	(N=158)	(N=146)	15mg (N=149)	20mg (N=151)
Mean Baseline Score (SD*)	31.5 (3.6)	31.2 (3.5)	31.8 (3.4)	31.2 (3.4)
LS Mean Change from Baseline (SE#)	-11.7 (0.76)	-21.2 (0.77)	-17.2 (0.79)	-18.8 (0.78)
LS Mean Difference from Placebo (SE)	-	-9.5 (1.07)	-5.5 (1.09)	-7.1 (1.08)
p-value	-	<0.0001	<0.0001	<0.0001

Source: Sponsor's results included in Original NDA Statistical Review (NDA 204447), confirmed by this reviewer.
* Standard deviation, # Standard error

Sponsor-Proposed Key Secondary Endpoints

Only CGI-I and SDS are accepted as legitimate key secondary endpoints. Table 3 below shows that both doses of vortioxetine were statistically significantly superior to placebo in CGI-I score and change from baseline in SDS score at Bonferroni-corrected alpha level.

Table 3. Sponsor-Proposed Key Secondary Endpoints at Week 8 (LS Mean Difference (SE#) from Placebo).

Efficacy variable	Duloxetine		Lu AA21004 15mg		Lu AA21004 20mg	
	Difference	p-value	Difference	p-value	Difference	p-value
MADRS response %	41.7 %	<0.001	24.7%	<0.001	29.3%	<0.001
CGI-I score	-1.1 (0.13)	<0.001	-0.7 (0.13)	<0.001	-1.0 (0.13)	<0.001
Δ MADRS total score (baseline HAM-A ≥20)*	-8.7	<0.001	-5.2	0.001	-6.4	<0.001
MADRS remission %	35.1 %	<0.001	15.9%	0.002	19.4%	<0.001
Δ SDS total score	-6.9 (1.13)	<0.001	-3.2 (1.16)	0.005	-3.9 (1.11)	0.001

Source: Sponsor's results included in Original NDA Statistical Review (NDA 204447), confirmed by this reviewer.
Standard error
* Subgroup of patients with baseline HAM-A total score ≥20

Table 4: Sponsor's Analysis Results of CGI-I (FAS, MMRM)

	Placebo N=157	Vortioxetine (15 mg) N=148	Vortioxetine (20 mg) N=150	Duloxetine N=145
CGI-S Baseline				
N	158	149	151	146
Mean (SD*)	4.85 (0.69)	4.86 (0.62)	4.80 (0.70)	4.79 (0.69)
Value at Week 8				
N	130	118	125	131
LS◊ mean (SE#)	2.86 (0.09)	2.18 (0.09)	1.92 (0.09)	1.75 (0.09)
P-value, active vs placebo		<0.0001	<0.0001	<0.0001
LS◊ Mean Differences (SE#) from placebo	--	-1.1 (0.13)	-0.7 (0.13)	-1.0 (0.13)
95% CI for Differences	--	(-0.94, -0.44)	(-1.20, -0.70)	(-1.36, -0.87)

Source: Clinical Study Report for Original NDA (Page 307, 309)
* Standard Deviation, # Standard Error, ◊ Least Squares

The sponsor conducted sensitivity analysis using ANCOVA (LOCF, OC) and results were consistent with MMRM (FAS).

Table 5: Sponsor's Analysis Results of SDS (FAS, MMRM)

	Placebo N=115	Vortioxetine (15 mg) N=97	Vortioxetine (20 mg) N=107	Duloxetine N=99
Baseline				
N	115	97	107	99
Mean (SD*)	19.83 (6.00)	20.56 (5.32)	20.70 (4.76)	20.54 (4.37)
Change from Baseline at Week 8				
N	81	65	80	79
LS◊ mean (SE#)	-4.46 (0.82)	-7.70 (0.89)	-8.38 (0.85)	-11.39 (0.85)
P-value, active vs placebo		0.0054	0.0005	<0.0001
LS◊ Mean Differences (SE#) from placebo	--	-3.24 (1.16)	-3.92 (1.11)	-6.93 (1.13)
95% CI for Differences	--	(-5.51, -0.97)	(-6.11, -1.73)	(-9.16, -4.70)

Source: Clinical Study Report for Original NDA (Page 341-342)
* Standard Deviation, #Standard Error, ◊Least Squares

Reviewer's Conclusion for Study 13267A

Both doses of vortioxetine were statistically significantly better than placebo at week 8, in the mean treatment effect on the change from baseline in MADRS total score, mean CGI-I score, and mean change from baseline in SDS score.

Study 202

Primary Efficacy Endpoint

As shown in Table 6, vortioxetine group was statistically significantly better than placebo in the change from baseline in DSST total number of correct symbols score group (LS mean = 1.75, p=0.019. The difference between the duloxetine and placebo groups was not statistically significant (p=0.099).

Table 6: Sponsor's Analysis Results of DSST Total Number of Correct Symbols (FAS, ANCOVA)

	Placebo N=167	Vortioxetine N=175	Duloxetine N=187
Baseline			
N	167	175	187
Mean (SD*)	43.0 (12.28)	42.1 (11.93)	42.8 (12.20)
Change from Baseline at Week 8			
N	167	175	187
LS◊ mean (SE#)	2.85 (0.54)	4.60 (0.53)	4.06 (0.51)
P-value, active vs placebo		0.019	0.099
LS◊ Mean Differences (SE#) from placebo	--	1.75 (0.744)	1.21 (0.73)
95% CI for Differences	--	(0.28, 3.21)	(-0.23, 2.65)

Source: Supplemental NDA Review (NDA 204447-S06)* Standard Deviation, #Standard Error, ◊Least Squares

Key Secondary Endpoints

Both vortioxetine and duloxetine showed statistically significant improvement in the PDQ attention/concentration and planning/organization sub-score from placebo at Week 8 (vortioxetine, LS mean = -2.6, p = 0.001; duloxetine, LS mean = -3.0, p< 0.001). Treatment with vortioxetine and duloxetine also produced a statistically significant improvement in CGI-I score compared to placebo at week 8 (vortioxetine, LS mean = -0.29, p = 0.017; duloxetine, LS mean = -0.40, p < 0.001). Details are displayed in Table 7 and Table 8.

Table 7: Sponsor's Analysis Results of PDQ Attention/Concentration and Planning/Organization Subscore (FAS, MMRM)

	Placebo N=167	Vortioxetine N=175	Duloxetine N=187
Baseline			
N	167	175	187
Mean (SD[*])	25.6 (5.7)	25.4 (5.9)	23.8 (6.82)
Change from Baseline at Week 8			
N	160	169	179
LS[◊] mean (SE[#])	-6.3 (0.57)	-8.9 (0.55)	-9.3 (0.53)
P-value, active vs placebo		0.001	<0.001
LS[◊] Mean Differences (SE[#]) from placebo	--	-2.6 (0.78)	-3.0 (0.77)
95% CI for Differences	--	(-4.1, -1.0)	(-4.5, -1.5)

Source: Supplemental NDA Review (NDA 204447-S06)
[*] Standard Deviation, [#]Standard Error, [◊]Least Squares

Table 8: Sponsor's Analysis Results of CGI-I Score (FAS, MMRM)

	Placebo N=167	Vortioxetine N=175	Duloxetine N=187
CGI-S Baseline			
N	167	175	187
Mean (SD[*])	4.6 (0.59)	4.6 (0.62)	4.6 (0.59)
Value at Week 8			
N	161	169	179
LS[◊] mean (SE[#])	2.64 (0.087)	2.35 (0.085)	2.23 (0.083)
P-value, active vs placebo		0.017	0.001
LS[◊] Mean Differences (SE[#]) from placebo	--	-0.29 (0.12)	-0.40 (0.12)
95% CI for Differences	--	(-0.53, -0.05)	(-0.64, -0.17)

Source: Supplemental NDA Review (NDA 204447-S06)
[*] Standard Deviation, [#]Standard Error, [◊]Least Squares

The sponsor conducted ANCOVA (LOCF, OC) and efficacy conclusions remained consistent with MMRM.

In both studies, there was not substantial dropout in key secondary efficacy endpoints. Results from alternative efficacy analyses methods were consistent with the pre-specified methods.

Reviewer's Conclusion for Study 202

Vortioxetine was statistically significantly superior to placebo in the mean change from baseline at week 8 in DSST. Similarly, vortioxetine separated statistically significantly from placebo, in the mean CGI-I score at week 8, in the mean change from baseline at week 8 in PDQ.

3.3 Evaluation of Safety

Safety evaluation was not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to previous NDA reviews for the subgroup analysis by age and sex.

4.2 Other Special/Subgroup Populations: U.S. versus Non U.S.

Please refer to previous NDA reviews for subgroup analysis by region.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no particular statistical issues in this review.

5.2 Collective Evidence

Under the original NDA 204447, the sponsor submitted 10 short-term controlled studies (9 adult studies and 1 elderly study) and one maintenance study to gain approval of vortioxetine for the treatment of Major Depressive Disorder (MDD). In 6 studies (11492A, 305, 13267A, 315, 316, 12541A) out of the 10, vortioxetine showed superiority over placebo on at least one of the investigated doses. The primary efficacy parameters specified in these studies were either MADRS (studies 11492A, 13267A, 315, 316) or HAM-D24 (studies 305 and 12541A).

Statistically significant treatment effect of vortioxetine versus placebo was shown in at least one trial in dose groups 5mg (studies 11492A, 12541A), 10mg (studies 11492A, 305), 15mg (study 13267A), and 20mg (studies 13267A, 315, 316). Efficacy of 15mg dose was only demonstrated in Study 13267A which was conducted outside of North America. As summarized in Table 1 multiple key secondary endpoints were considered. However, the FDA advised in a letter dated September 14, 2010 that only CGI-I or SDS were acceptable as key secondary endpoints. CGI-I was assessed in all positive efficacy studies while SDS was not assessed in in the two positive exploratory studies, 11492A and 12541A. In studies 11492A and 12541A, CGI-I was considered a supportive secondary endpoint. The vortioxetine clinical program included CGI-I as a key secondary endpoint in Study 202 under sNDA 204447 to establish a label change by including it in the Clinical Studies section of the package insert.

Results of vortioxetine in CGI-I are summarized in Table 9 and Table 10 wherein statistical comparisons of different doses of vortioxetine and placebo across positive studies are displayed. In five of the short-term studies, CGI-I score was considered a key secondary endpoint. In Study 202, the mean CGI-I showed statistical significance in favor of vortioxetine (flexible doses 10 mg to 20 mg per day) at endpoint. Also, Study 13267A showed statistically significant treatment differences between the two investigated doses (15mg and 20mg per day) and placebo.

As summarized in Table 9, although the three investigated doses (1mg, 5mg, and 10mg) had nominal p-values <0.001 for CGI-I results, it should be noted that Study 305 provided only supportive evidence as the multiplicity testing procedure in the pre-specified hierarchy stopped before CGI-I could be tested. SDS which preceded CGI-I in the testing rank was found to be non-significant. The four key secondary endpoints were to be tested sequentially in parallel within each dose starting from 10mg dose. The testing stopped at SDS, so no subsequent key secondary endpoints could be tested.

Exploratory studies 11492A (5mg, 10mg), 12541A (5mg) showed nominally statistically significant p-values for CGI-I, favoring vortioxetine doses versus placebo. The results, however, served only as supportive evidence as there was no formal statistical testing that incorporates multiplicity adjustment. Also, in studies 305 (5mg and 10mg) and 316 (20mg), vortioxetine doses demonstrated nominal statistically significant improvement versus placebo on CGI-I though not formally tested against placebo since it did not separate on the preceding endpoints in the hierarchy.

Table 9. Summary Results of CGI-I Analysis for Positive Acute Efficacy Studies

Study Number	CGI Endpoint status	Dose				
		1mg	5mg	10mg	15mg	20mg
11492A	**Exploratory**					
LS mean difference (SE)			-0.6 (0.16)	-0.6 (0.16)		
p-value (unadjusted)			<0.001	<0.001		
Significance (based on MCP)			N/A	N/A		
305	**Key Secondary**					
LS mean difference (SE)		-0.5(0.13)	-0.5 (0.13)	-0.6 (0.13)		
p-value (unadjusted)		<0.001	<0.001	<0.001		
Significance (based on MCP)*		N/A	No*	No*		
13267A	**Key Secondary**					
LS mean difference (SE)					-0.7 (0.13)	-1.0 (0.13)
p-value (unadjusted)					<0.001	<0.001
Significance (based on MCP)					**Yes**	**Yes**
315	**Key**					

	Secondary					
LS mean difference (SE)					-0.1 (0.14)	-0.2 (0.14)
p-value (unadjusted)					0.400	0.177
Significance (based on MCP)					**No**	**No**
316	**Key Secondary**					
LS mean difference (SE)				-0.2 (0.13)		-0.3 (0.13)
p-value (unadjusted)				0.119		0.024
Significance (based on MCP)				**No**		**No**[#]
12541A	**Exploratory**					
LS mean difference (SE)			-0.6 (0.13)			
p-value (unadjusted)			<0.0001			
Significance (based on MCP)			N/A			

Source: Reviewer's Summary

[*]Since 10mg dose failed to beat placebo in the first key secondary variable in the sequence (SDS), the formal testing was stopped according to the pre-specified hierarchical testing. None of the subsequent endpoints in the pre-specified testing hierarchy are considered statistically significantly different from placebo.

[#]Since 20mg dose failed to beat placebo in the first key secondary variable in the sequence (MADRS response rate at Week 8), the formal testing was stopped according to the pre-specified hierarchical testing. None of the subsequent endpoints in the pre-specified testing hierarchy are considered statistically significantly different from placebo.

Table 10. Summary Results of CGI-I Analysis for Positive Acute Efficacy Study 202

Study Number	CGI Endpoint status	Flexible Dose 10mg to 20 mg
202	**Key Secondary**	
LS mean difference (SE)		-0.29(0.12)
p-value (unadjusted)		0.017
Significance (based on MCP)		**Yes**

Source: Reviewer's Summary

5.3 Conclusions and Recommendations

In Study 13267A, vortioxetine (15mg, and 20mg) has shown statistically significant treatment effect with respect to placebo in MADRS, SDS, and CGI-I. In study 202, treatment effect of vortioxetine (flexible10-20 mg) has demonstrated superiority to placebo in DSST, CGI-I, and PDQ in treatment of cognitive dysfunction in adult patient population with MDD. Vortioxetine's efficacy has been evidenced in both short-term clinical trials.

In summary, sufficient data from the two confirmatory studies supported that efficacy of viortioxetine on CGI-I was replicated.

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/s/

SEMHAR B OGBAGABER
01/25/2017

PEILING YANG
01/25/2017

HSIEN MING J HUNG
01/25/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s009

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date:	February 14, 2017
From:	Tamara Johnson, MD, MS Team Leader, Maternal Health Division of Pediatric and Maternal Health
Through:	Lynne Yao, MD Division Director Division of Pediatric and Maternal Health
To:	Division of Psychiatry Products (DPP)
Drug:	Trintellix (vortioxetine)
NDA:	204447, S-009
Applicant:	Takeda Pharmaceuticals USA, Inc.
Drug Class:	antidepressant
Indication:	For treatment of major depressive disorder (MDD)
Subject:	Pregnancy and Lactation Labeling Rule (PLLR) Conversion
Submission Date:	May 10, 2016
Consult Date:	July 13, 2016
Consult Request:	Assistance with labeling revision consistent with PLLR

PURPOSE

The purpose of the memorandum is to acknowledge the input of the Division of Pediatric and Maternal Health (DPMH) on labeling recommendations in order to bring the Trintellix labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format and content requirements.

BACKGROUND

The Pregnancy and Lactation Labeling Rule

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect.[1] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and 17 of the Trintellix labeling for compliance with the PLLR. DPMH labeling recommendations were conveyed to DPP in November 2016. DPMH agrees with the PLLR labeling for Trintellix and refers the reader to the final NDA action for the final labeling.

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

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/s/

TAMARA N JOHNSON
02/14/2017

LYNNE P YAO
02/14/2017

Kalsi, Jasmeet (Mona)

From: Kalsi, Jasmeet (Mona)
Sent: Tuesday, October 04, 2016 2:51 PM
To: Sambor, Joanna
Cc: Kiedrow, Keith; Patel, Hiren; David, Paul A; Hardeman, Steven D; Kalsi, Jasmeet (Mona)
Subject: NDA 204447/S-009 Information Request

Hi Joanna,

This e-mail is in reference to your efficacy supplement submitted on May 10, 2016. The review team has requested the following information:

Please provide the full article that is excerpted in your IR response dated June 22, 2016. Comment from 5.3.5.3:

- *"An excerpt of the literature articles has been provided in these search reports. The full literature articles are not provided in this submission but are available upon request."*

Please submit by COB 10/5/16.

Thanks,
Mona

Jasmeet (Mona) Kalsi, PharmD
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Psychiatry Products

U.S. Food and Drug Administration
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov

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/s/

JASMEET K KALSI
10/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: **Division of Pharmacovigilance**

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Jasmeet (Mona) Kalsi, PharmD, RPM, Division of Psychiatry Products (DPP)/240-402-8977
Graciela Gonzalez, MD, Clinical Reviewer, MO, DPP
Jasmine Gatti, MD, Clinical Reviewer TL, MO, DPP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/2/16		**204447/S-009**	**Efficacy Supplement**	**5/10/16**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Trintellix (vortioxetine)	**Standard**	**Antidepressant**	**10/3/16**

NAME OF FIRM: **Takeda Pharmaceuticals**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DPP is reviewing an NDA efficacy supplement for the drug Trintellix (vortioxetine- NDA-204447/s-009). The Sponsor would like to add the CGI-I data to their label as an indicator that Trintellix is superior to placebo. A 915 review was done and its cutoff date was 4/30/2015. We will appreciate if you could review FAERS and the literature in regard to the postmarket safety experience from the cutoff date from the last 915 to present. Thank you very much for your assistance.

EDR link: \\Cdsesub1\evsprod\NDA204447\0116

Please let me know if you would like to be invited to the Mid-Cycle Meeting on October 4, 2016

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Jasmeet Kalsi, RPM	☒ DARRTS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

JASMEET K KALSI
09/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Jasmeet (Mona) Kalsi, RPM, Division of Psychiatry Products (DPP)/

240-402-8977

Graciela Gonzalez, MD, Clinical Reviewer, MO, DPP

Jasmine Gatti, MD, Clinical Reviewer TL, MO, DPP

REQUEST DATE:

7/21/16

NDA/BLA NO.:

204447/S-009

TYPE OF DOCUMENTS:

(PLEASE CHECK OFF BELOW)

NAME OF DRUG:

Trintellix (vortioxetine)

PRIORITY CONSIDERATION:

Standard

CLASSIFICATION OF DRUG:

Anti-depressant

DESIRED COMPLETION DATE

(Generally 2 Weeks after receiving substantially complete labeling)

January 23, 2017

SPONSOR:

Takeda Pharmaceuticals USA, Inc.

PDUFA Date: March 10, 2017

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

☒ PATIENT PACKAGE INSERT (PPI)

☒ MEDICATION GUIDE

☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

☐ ORIGINAL NDA/BLA/ANDA

☒ EFFICACY SUPPLEMENT

☐ SAFETY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ MANUFACTURING (CMC) SUPPLEMENT

☐ PLR CONVERSION

REASON FOR LABELING CONSULT

☐ INITIAL PROPOSED LABELING

☒ LABELING REVISION

EDR link to submission:

\\Cdsesub1\evsprod\NDA204447\0123

SharePoint: sNDA 204447/s-009

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

- Filing/Planning Meeting: June 30, 2016
- Mid-Cycle Meeting: October 4, 2016
- Label Planning Meeting: October 18, 2016
- Labeling Meetings (subject to change):
  - 1: October 31, 2016
  - 2: November 14, 2016
  - 3: November 30, 2016
- Wrap-up Meeting: February 1, 2017

SIGNATURE OF REQUESTER

Jasmeet Kalsi

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

JASMEET K KALSI
07/22/2016

MITCHELL V Mathis
07/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☒ Both ☐	FROM *(Name, Office/Division, and Phone Number of Requestor)*: Jasmeet (Mona) Kalsi, RPM, Division of Psychiatry Products (DPP)/ 240-402-8977 Graciela Gonzalez, MD, Clinical Reviewer, MO, DPP Jasmine Gatti, MD, Clinical Reviewer TL, MO, DPP

DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7/12/16		204447/S-009	Submissions of labeling in PLLR format to an efficacy supplement	May 10, 2016

NAME OF DRUG	NAME OF FIRM	CLASSIFICATION OF DRUG	PDUFA Goal Date
Trintellix (vortioxetine)	Takeda Pharmaceuticals USA, Inc.	Antidepressant	March 10, 2017

Requested Consult Completion Date: January 23, 2017	☐ Urgent* (< 14 days)	☐ Priority (14-29 days)	☒ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): \\Cdsesub1\evsprod\NDA204447\0123	Materials to be reviewed: SharePoint: sNDA 204447/s-009

1. Please briefly describe the submission including drug's indication(s):
Trintellix (vortioxetine) is approved for the treatment of major depressive disorder (MDD). During the review of the NDA 204447, the Agency recommended to not include the Clinical Global Impression – Improvement (CGI-I) related information in the package insert unless the key secondary endpoint to be described in the package insert was pre-specified and the positive findings were replicated within a testing strategy. Takeda completed Study 202 and CGI-I was included as a key secondary endpoint. Vortioxetine was separated from placebo on this endpoint. With the positive results, the sponsor seeks to add CGI-I data to the Clinical Studies section of the package insert.

2. Describe in detail the reason for your consult. Include specific questions:
Please review all applicable sections of the labeling that was recently submitted in PLLR format.

3. Meeting dates:
- Mid-Cycle Meeting: October 4, 2016
- Label Planning Meeting: October 18, 2016
- Labeling Meetings (subject to change):
  - 1: October 31, 2016
  - 2: November 14, 2016
  - 3: November 30, 2016
- Wrap-up Meeting: February 1, 2017

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):
Last consult sent on 3/7/13 and completed on 8/19/13 by Tammie Brent Howard.

Review team: Project Manager: Jasmeet (Mona) Kalsi Clinical reviewer & Team Leader: Graciela Gonzalez (reviewer) and Jasmine Gatti (TL) Pharmacology/Toxicology reviewer & Team Leader: Antonia Dow (reviewer) and Ikram Elayan (TL) Clinical Pharmacology reviewer & Team Leader: Di Zhu (reviewer) and Hao Zhu (TL) Other: • Stats – Semhar Ogbagaber (reviewer), Peiling Yang (TL) • OPDP – Christine Bradshaw (reviewer)	
PRINTED NAME or SIGNATURE OF REQUESTOR: Jasmeet (Mona) Kalsi	METHOD OF DELIVERY (Please check) ☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 10/14/2014

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/s/

JASMEET K KALSI
07/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204447/S-009

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

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

Dear Ms. Sambor:

Please refer to your supplemental New Drug Application (sNDA) dated May 10, 2016, received May 10, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Trintellix (vortioxetine) 5 mg, 10 mg, 15 mg, and 20 mg tablets.

We also refer to your amendment dated June 22, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 10, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 14, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. For study 202, please provide the instructions that were given to the investigator for rating the Clinical Global Impression of Improvement Scale (GCI-I) and the Clinical Global Impression of Severity Scale (CGI-S).

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Mona Kalsi, Regulatory Project Manager, at (240) 402-8977.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
07/07/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Jasmeet (Mona) Kalsi, PharmD, RPM, Division of Psychiatry Products (DPP)/240-402-8977

Graciela Gonzalez, MD, Clinical Reviewer, MO, DPP

Jasmine Gatti, MD, Clinical Reviewer TL, MO, DPP

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
06/08/16		**204447/S-009**	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Trintellix (vortioxetine)	**Standard**		**January 23, 2016**

NAME OF FIRM:
Takeda Pharmaceuticals

PDUFA Date: **March 10, 2017**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission:
EDR: \\Cdsesub1\evsprod\NDA204447\0116

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
DPP is requesting OPDP to review the proposed changes to section 14 and comment as necessary. We also request your attendance to the meetings listed below:
Mid-Cycle Meeting: **October 4, 2016**
Labeling Planning Meeting: **October 18, 2016**
Labeling Meetings:

- **1: October 31, 2016**
- **2: November 14, 2016**
- **3: November 30, 2016**

Wrap-Up Meeting: **February 1, 2017**

SIGNATURE OF REQUESTER

Jasmeet Kalsi, PharmD	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

JASMEET K KALSI
06/08/2016

MITCHELL V Mathis
06/08/2016

Kalsi, Jasmeet (Mona)

From: Kalsi, Jasmeet (Mona)
Sent: Tuesday, June 07, 2016 12:52 PM
To: Sambor, Joanna
Cc: David, Paul A; Hardeman, Steven D; Patel, Hiren; Kiedrow, Keith; Kalsi, Jasmeet (Mona)
Subject: sNDA 204447/s-009 Information Request
Attachments: PLLR Guidance.pdf; sNDA 204447/s-009 Information Request

Categories: Applicant/Sponsor

Dear Joanna,

This is in reference to the subject efficacy supplement submitted on May 10, 2016. The review team has requested the following information to be submitted to the application:

- Please submit your PI in PLLR format (guidance attached).

Also, please note to have this IR and the one sent on June 1, 2016 formally submitted to the application by **June 23, 2016**.
Please let me know if you have any questions.

Thanks,
Mona

Kindest Regards,
Jasmeet (Mona) Kalsi, PharmD
Regulatory Health Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov

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/s/

JASMEET K KALSI
06/07/2016

Kalsi, Jasmeet (Mona)

From: Kalsi, Jasmeet (Mona)
Sent: Wednesday, June 01, 2016 9:06 AM
To: Sambor, Joanna
Cc: David, Paul A; Hardeman, Steven D; Patel, Hiren; Kiedrow, Keith; Kalsi, Jasmeet (Mona)
Subject: sNDA 204447/s-009 Information Request

Categories: Applicant/Sponsor

Dear Joanna,

This is in reference to the subject efficacy supplement submitted on May 10, 2016. The review team has requested the following information to be submitted to the application:

- Please provide an environmental assessment or claim of categorical exclusion.

Please submit this by June 15, 2016 as a formal submission to the application.

Thank you,
Mona

Kindest Regards,
Jasmeet (Mona) Kalsi, PharmD
Regulatory Health Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov

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/s/

JASMEET K KALSI
06/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204447/S-009

ACKNOWLEDGMENT
PRIOR APPROVAL SUPPLEMENT

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

Dear Ms. Sambor:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 204447

SUPPLEMENT NUMBER: 009

PRODUCT NAME: Trintellix (vortioxetine) 5 mg, 10 mg, 15 mg, and 20 mg tablets.

DATE OF SUBMISSION: May 10, 2016

DATE OF RECEIPT: May 10, 2016

This supplemental application proposes the following change: to add text in the Clinical Studies section of the US package insert (USPI) regarding vortioxetine's effect on the Clinical Global Impression-Improvement (CGI-I) scale.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 9, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be March 10, 2017.

If you have not already done so, promptly submit the 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 204447/S-009** submitted on May 10, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (240) 402-8977.

Sincerely,

{See appended electronic signature page}

Jasmeet (Mona) Kalsi, PharmD
Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

JASMEET K KALSI
05/20/2016