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RESEARCH**

APPLICATION NUMBER:

204447Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 204447
Product Name: Brintellix (vortioxetine)

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Submitted
		<u>11/18/2011</u>
	Study/Trial Completion:	<u>07/30/2014</u>
	Final Report Submission:	<u>02/28/2015</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Major Depressive Disorder is much more common in adult population. Therefore, the pharmacokinetics, efficacy and safety of vortioxetine in adults need to be established before we request pediatric studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this pediatric pharmacokinetic study is to characterize pharmacokinetic features of vortioxetine in pediatric patients. This information will be used to identify appropriate doses in efficacy and safety studies in relevant pediatric patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pediatric study is required under PREA to obtain data on the pharmacokinetic, safety and tolerability of vortioxetine in pediatric patients 7 to 17 years of age. This study can be an open-label study in pediatric patients with adequate sample size to determine relevant pharmacokinetic parameters.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA # 204447
Product Name: Brintellix (vortioxetine)

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

PMR Schedule Milestones:	Final Protocol Submission:	<u>08/31/2015</u>
	Study/Trial Completion:	<u>10/31/2018</u>
	Final Report Submission:	<u>04/30/2019</u>

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Major Depressive Disorder is much more common in adult population. Therefore, the efficacy and safety of vortioxetine in adults need to be established first before we request pediatric studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this pediatric study is to explore the efficacy and safety of vortioxetine for treatment of MDD in children ages 7 to 11 years. The original NDA for adult MDD is under review.

Vortioxetine is a serotonergic drug. The most common adverse events are nausea, constipation and vomiting in adults. No significant new safety signal was identified compared to other SSRIs/SNRIs.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred pediatric study for the treatment of Major Depressive Disorder is required under PREA to obtain data on the safety and efficacy of vortioxetine in children ages 7 to 11 years. The study must be a randomized, double-blind, placebo- and active-controlled fixed-dose study.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Pediatric safety and efficacy studies
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? Yes, it meets PMR requirement
- Are the objectives clear from the description of the PMR/PMC? Yes.
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes.

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 204447
Product Name: Brintellix (vortioxetine)

PMR Description: Deferred pediatric study under PREA for the treatment of major depressive disorder in adolescents aged 12 to 17 years. Conduct a study to obtain data on the efficacy and safety of vortioxetine in the relevant pediatric population. This must be a placebo-controlled and active-controlled (fluoxetine) study. This study must be a fixed-dose study.

PMR Schedule Milestones:	Final Protocol Submission:	<u>08/31/2015</u>
	Study/Trial Completion:	<u>10/31/2018</u>
	Final Report Submission:	<u>04/30/2019</u>

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Major Depressive Disorder is much more common in the adult population. Therefore, the efficacy and safety of vortioxetine in adults need to be established first before we request pediatric studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this pediatric study is to explore the efficacy and safety of vortioxetine for treatment of MDD in adolescents ages 12 to 17 years. The original NDA for adult MDD is under review.

Vortioxetine is a serotonergic drug. The most common adverse events are nausea, constipation, and vomiting in adults. No significant new safety signal was identified compared to other SSRIs/SNRIs.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A deferred pediatric study for the treatment of Major Depressive Disorder is required under PREA to obtain data on the safety and efficacy of vortioxetine in adolescents ages 12 to 17 years. The study must be a randomized, double-blind, placebo- and active-controlled fixed-dose study.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Pediatric safety and efficacy studies
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
Yes, the study meets the criteria for a PMR under PREA.
- Are the objectives clear from the description of the PMR/PMC? Yes.
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes.
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA # 204447
Product Name: Brintellix (vortioxetine)

PMR/PMC Description: In-vivo pharmacokinetic trial in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/31/2014
Trial Completion: 09/30/2015
Final Report Submission: 05/31/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The depression patient population with severe hepatic impairment is relatively small. However, increased vortioxetine exposure is anticipated in patients with severe hepatic impairment. It is still important to optimize dose in this population. Since data from patients with only mild or moderate liver impairment was presented in the NDA submission, it would be appropriate to collect data on subject with severe liver impairment post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Vortioxetine is extensively metabolized through liver. Therefore, an increase in vortioxetine exposure is anticipated in depressed patients with severe hepatic impairment. The requested study is to quantify exposure increase in patients with severe hepatic impairment. The information obtained from the study is essential to guide dose adjustment and to avoid adverse events in this patient population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be conducted in subjects with severe hepatic impairment mainly based upon the Child Pugh Score.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

Study pharmacokinetics in subjects with severe hepatic impairment.

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 204447
Product Name: Brintellix (vortioxetine)

PMR/PMC Description: In-vitro determination of vortioxetine and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/31/2014
Study Completion: 05/31/2015
Final Report Submission: 08/31/2015
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The main objective of the study is to optimize dose in patients receiving comedications, if there is significant interaction.. The patient population receiving drugs as substrates of major transporters and vortioxetine concomitantly is anticipated to be relatively small. However, the current FDA guidance states that, “Because there have been clinically significant interactions demonstrated for critical drugs that are known substrates for P-gp (e.g., digoxin), BCRP (e.g., rosuvastatin), OATP1B1/OATP1B3 (e.g., statin drugs), OAT1/OAT3 (e.g., methotrexate, tenofovir) and OCT2 (e.g., metformin), evaluation of investigational drugs as inhibitors for these transporters should be conducted.” A P-gp study was conducted by the firm in the NDA but studies with the other potential transporters was not conducted.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The studies will initially be conducted using in vitro methodology. If positive results related to transporter inhibition are obtained based upon the decision tree in the drug drug interaction guidance then in vivo studies may be needed.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
In-vitro study
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 204447
Product Name: Brintellix (vortioxetine)

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

PMC Schedule Milestones:	Final Protocol Submission:	<u>10/31/2014</u>
	Study/Trial Completion:	<u>04/30/2019</u>
	Final Report Submission:	<u>04/30/2020</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check type and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A maintenance study is not required prior to approving new drugs for the treatment of MDD. Additionally, the sponsor has conducted a non-US maintenance study that covers doses of 5 to 10 mg/day. The study was positive and was used to support approval of the NDA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This study has been requested to be conducted as a PMC for the following reasons:
1) to further characterize the dose-response relationship of vortioxetine in the US
2) to find out if high dose (20 mg/day) vortioxetine is necessary for maintenance treatment

This PMC request is not based on safety concerns.

3. If the study/clinical trial is a **PMR**, check the applicable regulation. N/A

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study must be relapse prevention study with a randomized withdrawal design in the adult population with a diagnosis of MDD. The study must also be a placebo-controlled, fixed dose study covering the dose range of 5 to 20 mg/day.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Additional data in the efficacy of the maintenance treatment in US MDD patients.

- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMCs? Yes
- Are the objectives clear from the description of the PMC? Yes
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

TERRY HARRISON
09/30/2013

VICTOR CRENTSIL
09/30/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	BRINTELLIX (vortioxetine) tablets for oral administration
Applicant	Takeda Pharmaceuticals USA, Incorporated
Application/Supplement Number	NDA 204447
Type of Application	Original
Indication(s)	Treatment of major depressive disorder
Established Pharmacologic Class ¹	There is no official EPC for this product.
Office/Division	ODEI/DPP
Division Project Manager	Hiren Patel
Date FDA Received Application	October 2, 2012
Goal Date	October 2, 2013
Date PI Received by SEALD	September 27, 2013
SEALD Review Date	September 27, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: Insert 1/2 inch margin at top of HL page.

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: DPP to grant waiver of 1/2 page HL limit in approval letter.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: Under *Contraindications* heading, second bulleted item, correct cross reference to "4".

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *Initial U.S. Approval date is missing; insert bolded 4-digit year of approval.*

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- NO** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment: Center BW heading in HL.

- NO** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment: Center statement and change text to *italics*.

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- N/A** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *This drug does not belong to an established pharmacologic class.*

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

YES

Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: Remove "FDA-approved" from statement; see third bulleted example above.

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

Selected Requirements of Prescribing Information

- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

Selected Requirements of Prescribing Information

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Insert Medication Guide at the end of the PI.*

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: *Subsection 2.4, correct cross reference to include section, not subsection, heading and italicize, i.e., “[see Warnings and Precautions (5.2)]”. Subsection 7.2, correct cross references to 7.4 to read, “[see Drug Interactions (7.4)]”.*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- NO** 42. All text is **bolded**.

Comment: *Bold all text in BW in FPI.*

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“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 trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Remove italics from reference; use non-italicized text.*

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/s/

DEBRA C BEITZELL
09/27/2013

LAURIE B BURKE
09/27/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: September 25, 2013
Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis
Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis
Drug Name and Strengths: Brintellix (vortioxetine) Tablets
5 mg, 10 mg, 15 mg, and 20 mg
Application Type/Number: NDA 204447
Applicant: Takeda Pharmaceuticals USA, Inc.
OSE RCM #: 2012-3005

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1 INTRODUCTION

This review evaluates the revised container labels and carton labeling for Brintellix (vortioxetine) Tablets, NDA 204447, submitted by the Applicant on September 23, 2013 (Appendices A, B, and C) for areas of vulnerability that could lead to medication errors.

The revised labels and labeling reflect a slight change to the trademark statement. The statement was revised from [REDACTED] (b) (4) to read: *“Brintellix is a trademark of H. Lundbeck A/S and is used under license by Takeda Pharmaceuticals America, Inc.”*

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the following Brintellix labels and labeling:

- Labels and labeling submitted on October 2, 2012: Comments were provided in OSE Review 2012-3005 Brintellix Label, Labeling, and Packaging Review, dated May 15, 2013.
- Labels and labeling submitted on June 28, 2013: Comments were provided via an email sent to the Applicant on August 2, 2013.
- Labels and labeling submitted on August 12, 2013: Recommendations were provided in OSE Memorandum 2012-3005, Brintellix Label and Labeling Memorandum, dated August 19, 2013.

2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the revised container labels and carton labeling submitted on September 23, 2013. We compared the revised labels and labeling against the labels and labeling previously submitted on June 28, 2013 and August 12, 2013 to assess whether the change to the trademark statement introduced any new areas of concern from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the revised container labels and carton labeling determined the revision to the trademark statement does not introduce any new areas of concern, thus, we find the revision acceptable. Therefore, we have no further recommendations at this time.

If you have further questions or need clarifications, please contact Louis Flowers, OSE Project Manager, at 301-796-3158.

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/s/

LORETTA HOLMES
09/25/2013

IRENE Z CHAN
09/26/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: August 19, 2013
Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis
Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis
Drug Name and Strengths: Brintellix (Vortioxetine) Tablets
5 mg, 10 mg, 15 mg, and 20 mg
Application Type/Number: NDA 204447
Applicant: Takeda Pharmaceuticals USA, Inc.
OSE RCM #: 2012-3005

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1 INTRODUCTION

This memorandum evaluates the revised professional sample container labels and carton labeling for Brintellix (Vortioxetine) Tablets, submitted by the Applicant on August 12, 2013 (see Appendices A and B) in response to recommendations provided via email on August 2, 2013 (see Appendix C). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the following Brintellix labels and labeling:

- Labels and labeling submitted on October 2, 2012: Recommendations were provided in OSE Review 2012-3005 Brintellix Label, Labeling, and Packaging Review, dated May 15, 2013.
- Labels and labeling submitted on June 28, 2013: Recommendations were provided via an email sent to the Applicant on August 2, 2013.

2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the revised professional sample container labels and carton labeling submitted on August 12, 2013. We compared the revised labels against our recommendations, sent via email on August 2, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the revised professional sample container labels and carton labeling determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations at this time.

If you have further questions or need clarifications, please contact Louis Flowers, OSE Project Manager, at 301-796-3158.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LORETTA HOLMES
08/19/2013

IRENE Z CHAN
08/19/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: August 15, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne P. Yao, MD
Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Psychiatry Products (DPP)

Drug: Brintellix (vortioxetine) NDA 204447

Subject: Proposed labeling for vortioxetine, a new molecular entity (NME) submitted for NDA approval

Applicant: Takeda Pharmaceuticals USA, Inc. (Takeda)

Materials Reviewed: Vortioxetine product labeling and available literature regarding pregnancy and lactation

Consult Question: DPP requested PMHS-MHT input on all relevant section of labeling, e.g., use in specific populations, highlights, patient counseling and medication guide.

INTRODUCTION

On October 1, 2012, Takeda Pharmaceuticals USA, Inc. (Takeda) submitted a New Drug Application (NDA) for Brintellix (vortioxetine) Tablets. Vortioxetine is a New Molecular Entity (NME) with a proposed indication for treatment of major depressive disorder (MDD).

Vortioxetine is a serotonin reuptake inhibitor with additional serotonin receptor activity. It is an inhibitor of the 5-hydroxytryptamine transporter (5-HTT), a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, and 5-HT_{1A} receptor agonist. The drug is thought to enhance serotonergic activity in the central nervous system (CNS), by selective inhibition of serotonin reuptake, however, the mechanism of antidepressant effect is not fully understood.^{1,2} Other currently approved products in the selective serotonin reuptake inhibitor (SSRI) class of drugs for treatment of MDD include: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, vilazodone.¹

On March 5, 2013, the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DPP to provide input regarding relevant sections of labeling (use in specific populations, highlights, patient counseling, and medication guide). This review includes PMHS-MHT comments and recommendations for vortioxetine labeling.

BACKGROUND

Vortioxetine and Pregnancy

Vortioxetine is an NME with limited human pregnancy data available. A summary of pregnancy data are described in the Integrated Summary of Safety (ISS)³ submitted by the applicant and are summarized below. During the clinical development program, all reported pregnancies were captured in the applicant's safety data base and followed to resolution. There were two sponsors for studies, Takeda and Lundbeck. In Takeda sponsored studies, pregnancy was only reported as an adverse event if there were maternal complications or adverse infant outcomes. In Lundbeck sponsored studies, pregnancy was reported as an adverse event (AE), and became a serious adverse event (SAE) if pregnancy outcomes were other than live birth of a healthy infant. All spontaneous and elective abortions were reported as adverse events. Narrative descriptions for each AE/SAE provided information regarding the pregnancy exposure; however, no information was documented on counseling provided to study subjects after pregnancy exposure.

There were 52 pregnancies reported among enrolled subjects, with 34 pregnancies occurring in the vortioxetine exposed group. Of the 34 exposed subjects, 10 pregnancies resulted in live birth, with no congenital malformations or other defects reported by the applicant. Of the 52 total pregnancies, 13 resulted in elective abortions (25%), with 10 of the 13 exposed to vortioxetine. These exposures occurred at 6 to 10 weeks gestation according to available information.

¹ NDA 204447 Brintellix (vortioxetine) Clinical Review, June 5, 2013.

² NDA 204447 Brintellix (vortioxetine) Pharmacology/Toxicology NDA Review and Evaluation, June 4, 2013.

³ NDA 204447 Brintellix (vortioxetine) Integrated Summary of Safety, submitted October 1, 2012.

Spontaneous or missed abortions occurred in 25% of subjects (13/52), with nine of those subjects exposed to vortioxetine. Table 5.i in the ISS describes when spontaneous abortion occurred (range 6-17 weeks gestation) and other spontaneous abortion risk factors in these nine subjects; three with prior abortions, five that were obese (per body mass index), one with unspecified infertility issue and one who received an aborticide from her general practitioner. A causal relationship between spontaneous abortion and exposure to vortioxetine could not be established due to these confounding factors. In addition, four pregnancies were reported in the female partners of male study subjects who were taking vortioxetine. One resulted in spontaneous abortion, one was lost to follow-up and two resulted in live births with no congenital anomalies or other fetal defects reported by the applicant.

In animal developmental reproductive studies, vortioxetine caused decreased fetal body weight and delayed ossification when given to rats and rabbits during the period of organogenesis at doses above 30 and 10 mg/kg (15 and 10 times the maximum recommended human dose (MRHD)) of 20 mg on a mg/m² basis, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. Decreased fetal body weight and delayed ossification occurred in rabbits when given vortioxetine during the period of organogenesis at oral doses between 2 and 30 mg/kg (2 and 29 times the MRHD). There were no teratogenic effects in rats at doses up to 77 times the MRHD of vortioxetine given during organogenesis.^{2,4}

Reviewer Note:

The animal data above are described based on preliminary discussions between the vortioxetine non-clinical review team and PMHS-MHT. Discussions regarding the most appropriate description of animal developmental reproductive study data are ongoing and may be revised to reflect the outcome of pending further discussions. PMHS-MHT labeling recommendations regarding the animal data section of pregnancy labeling reflect data as described above and are also subject to change pending further discussion.

Vortioxetine and Lactation

It is not known if vortioxetine is present in human milk. A search of the LactMed database revealed human lactation data for the following approved selective serotonin reuptake inhibitors (SSRIs): citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine. The available data indicate that most SSRIs are present in human breast milk at levels that are low compared to the maternal serum levels at therapeutic doses. Therefore, the estimated infant dose through breast milk will be lower than the mother's dose, with varying amounts of active drug and/or drug metabolites of most SSRIs detected in the serum of breastfed infants. In all cases, where drug or drug metabolites were detected in infant serum, there were no adverse effects on infant development reported. Adverse events were reported in some cases as "occasional mild side effects", colic, drowsiness and fussiness, without clear association regarding the role of breast milk.⁵

⁴ NDA 204447 Brintellix (vortioxetine) proposed Full Prescribing Information, submitted October 1, 2012.

⁵ Website: Drugs and Lactation Database (LactMed) <http://toxnet.nlm.nih.gov> accessed on July 17, 2013.

REVIEW OF SUBMITTED MATERIALS

Applicant Proposed Vortioxetine Labeling

The PMHS-MHT reviewed the applicant's proposed vortioxetine labeling, submitted October 1, 2012 and has participated in labeling/team meetings during the review period. Discussions regarding labeling are ongoing; therefore, PMHS-MHT recommendations regarding labeling are subject to amendment, pending the outcome of discussions. A summary of current PMHS-MHT labeling recommendations appear immediately following Discussion and Conclusions with labeling excerpts provided in **Appendix A**.

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

MHT Summary of Labeling Comments and Recommendations

Highlights of Prescribing Information

Pregnancy and Nursing Mothers language under "Use in Specific Populations" was revised to display preferred labeling language based on current labeling regulations.

8 Use in Specific Populations

8.1 Pregnancy

The Pregnancy section was restructured to align with current labeling recommendations and to provide an organized presentation of data. Class labeling language under the sub-heading "Non-teratogenic Effects", containing information regarding the potential for neonatal withdrawal syndrome was retained and now appears under the sub-heading "Clinical Considerations". Additional SSRI class labeling language regarding the potential for persistent pulmonary hypertension of the newborn (PPHN) and the risk/benefit of treating depression during pregnancy were added in subsequent paragraphs under "Clinical Considerations".

8.3 Nursing Mothers

The Nursing Mothers section was revised to state the appropriate regulatory language, and to replace the term (b) (4) with the term “present”.

Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

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/s/

TAMMIE B BRENT HOWARD
08/15/2013

JEANINE A BEST
08/15/2013

LYNNE P YAO
08/19/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 12, 2013

TO: Thomas Laughren, M.D.
Director, Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Sam H. Haidar, Ph.D., R.Ph
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-447 Vortioxetine (Lu AA21004) tablet, 5, 10, 15 and 20 mg from Takeda Pharmaceuticals USA, Inc.

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected clinical and analytical portions of the following studies:

Clinical:

123: "A Phase 1, Open-Label, Randomized, Single Dose, 3-Period Crossover Study to Evaluate the Bioavailability of Lu AA21004 Formulation 4 Relative to Formulation 3 and to Assess the Effect of Food on Pharmacokinetics of Formulation 4 in Healthy Subjects"

The inspection of the clinical portion of the study was conducted by **Joseph R. Lambert (ORA)** at **Celerion, Inc. 621 Rose Street, Lincoln, NE**. Following the inspection (February 5-7, 2013), no major issues were identified and no Form FDA-483 was issued.

Analytical:

- 106:** "A Phase 1, Open-Label, Randomized, Single-Dose, 3-Period Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Formulation 3 of Lu AA21004 and to Determine the Relative Bioavailability of Formulation 3 to Formulation 1 of Lu AA21004 in Healthy Adult Subjects (n=24)"
- 103:** "Effect of multiple doses of fluconazole or ketoconazole on the PK of AA21004 (n=36)"
- 102:** "Effect of multiple doses of LuAA21004 on the steady-state PK and PD of ethinyl estradiol and levonorgestrel (n=28)"
- 11826A:** "Effect of multiple doses of AA21004 on the PK of omeprazole (n=18)"
- 101:** "An Open-Label, Multiple-Dose Study in Healthy Adults to Assess the Drug Interaction Potential of Lu AA21004 Using Indiana Cocktail (n=24)"

The inspection of the analytical portions was conducted by **Sripal R. Mada, Ph.D. (OSI) and Sam H. Haidar, Ph.D. (OSI)** (b) (4)

(b) (4)
The above analytical studies were conducted (b) (4)
(b) (4)
(b) (4) and after this site closed, the records were transferred (b) (4).

Following the inspection (b) (4), Form FDA-483 was issued (**Attachment 1**). The firm's response was received on June 7, 2013 (**Attachment 2**).

The Form FDA-483 observations, (b) (4) response to Form FDA-483 and DBGLPC's evaluation follow:

1. **Failure to document and report wash samples inserted in chromatographic runs after high concentration calibrator samples. The wash samples were intended to prevent carryover interferences in later chromatograms. This occurred in Studies #101, #102, #103, #106 and #11826A during analysis of Lu AA21004, Lu AA34443 and Lu AA39835.**

In their response to the Form FDA-483, (b) (4) acknowledged this observation and said the investigation was carried out during 2009 to 2010 in collaboration with MHRA (Medicines and Healthcare products Agency). Subsequently, MHRA provided information about the investigation to the FDA in 2011. Takeda also informed the FDA of the misconduct and impacted studies submitted to the FDA. Currently, (b) (4) GLP Quality System has no relation to that used (b) (4) at the time of study conduct, and no bioanalytical personnel were relocated (b) (4) after the (b) (4) (b) (4)

In the opinion of these reviewers, (b) (4) analyst failed to document and report wash samples inserted in chromatographic runs after high calibrators in impacted runs. The wash samples were intended to minimize carryover interferences in subsequent chromatograms. This practice limits the ability to properly evaluate carryover interference for impacted runs. The sponsor did submit an evaluation of possible carryover effect on impacted studies using "worst case scenarios". Evaluation of source records at the site and recalculation of possible carryover effect appear to support the sponsor's conclusion of little impact on the results of all impacted studies. We recommend, however, that the OCP reviewer should evaluate the impact of carryover on the study data generated in Studies #101, #102, #103, #106 and #11826A during analysis of Lu AA21004, Lu AA34443 and Lu AA39835, and determine the significance if any.

2. (a) Failure to retain Analyst[®] software version 1.2 audit trails (both electronic and paper documents) and chromatograms with result tables (electronic documents) for Study #101. The failure to retain audit trails and electronic result tables resulted in failure to confirm the submitted data.
(b) Runs #2, #3, #6 and #13 in study #101 were re-injected; however, the firm failed to document reasons for the re-injections, and failed to retain the original source documents.

In their response to Form FDA-483, (b) (4) acknowledged the observation and said that the absence of the electronic data for Study #101 was communicated to FDA prior to the inspection. (b) (4) stated that electronic data were archived on CDs, and during their investigation of the misconduct, the CDs were apparently misplaced and subsequently lost. Additionally, no printouts of the electronic data were available. Also for Study 101, there were cases of sample re-injections. (b) (4) could not

explain the reasons for the re-injections, as these were not documented on the sample analysis forms at the time of study.

In the opinion of these reviewers, (b) (4) failed to retain Analyst audit trails in both electronic and paper documents. Also, the chromatograms with result tables in electronic documents were missing for Study #101. The failure to retain both audit trails and result tables resulted in failure to confirm the submitted data.

- 3. Chromatograms were inconsistently re-integrated in Studies #101, #102, #103, #106 and #11826A during analysis of Lu AA21004, Lu AA34443 and Lu AA39835. Specifically, failure to apply the changed integration parameters from individual samples in runs #SA006, SA007 to SA009, SA012 for study #101, runs #SA001, SA003 to SA007, SA010 to SA012, SA014 for study #102, runs #SA001, SA005 to SA007, SA009 to SA028, SA030 to SA032, SA034 to SA036, SA048 for study #103, runs SA001 to SA019, SA021 to SA026, SA028 to SA036, SA038 to SA054 for study #106, and in validation runs to all the samples in those batches.**

In their response to Form FDA-483, (b) (4) said SOP (SOP - MP-07.006) allowed changes in the integration parameters for single chromatograms within a batch if the automatic integration was not appropriate. In addition, (b) (4) said current (b) (4) SOP for integration is fully in compliance with FDA's expectation and guidelines.

In the opinion of these reviewers, OCP reviewer should evaluate the impact of re-integrations in the respective runs listed above on the study outcome.

In addition, DBGLPC investigated and addressed the following questions from OCP:

- Potential carryover was masked by the staff under investigation by inserting wash samples between the high calibrator or QC sample and the carryover assessment in blank injections. The wash samples were electronically removed and not reported.**

Please see Form FDA-384, item 1 above.

- Batches that were automatically stopped because of software or hardware failure were identified. These batches were subsequently restarted from the point of failure.

During the inspection, the impact of run stoppage was evaluated and it was determined that this item had no effect on data accuracy.

- Individual unknown samples were re-injected at the end of an analytical batch without having been bracketed by calibrators or QC samples and the results were subsequently inserted into the previously acquired batch.

In the opinion of these reviewers, this item had no effect on data accuracy.

- Individual calibrators were re-injected when internal standard response indicated that auto sampler misinjection had occurred and the results were electronically inserted into the original batch data file.

Please see Form FDA-483, item 2 above.

- A high sample index number at the beginning of a batch indicated previous acquisition of that batch within the data folder. Where this deficiency was indicated by the audit trail, the batch has been identified to be annotated as a proposed reinjection.

During the inspection, the impact of sample index number was evaluated and it was determined that this item had no effect on data accuracy.

- Poor or unacceptable integrations particularly for calibrator and QC samples and Manual integration of incorrect peak. Removal of integrations for pre-dose sample blanks and carryover blanks.

Please see Form FDA-483, item 3 above.

Conclusions:

Following the evaluation of the inspectional findings and (b) (4) response, the DBGLPC reviewers recommend the following:

- The OCP reviewer should evaluate the impact of carryover on the study data generated in Studies #101, #102, #103, #106 and #11826A during analysis of Lu AA21004, Lu AA34443 and Lu AA39835 for few observed runs >20% as set by (b) (4), based on the data provided by the sponsor (see **Form FDA-483, item 1**).
- (b) (4) failed to retain Analyst audit trails in both electronic and paper documents. Also, the chromatograms with result tables in electronic documents were missing for Study #101. This resulted in failure to confirm the integrity of submitted data. Thus, data integrity is not assured for Study #101 (see **Form FDA-483, item 2**).
- The OCP reviewer should evaluate the impact of re-integrations in runs #SA006, SA007 to SA009, SA012 for study #101, runs #SA001, SA003 to SA007, SA010 to SA012, SA014 for study #102, runs #SA001, SA005 to SA007, SA009 to SA028, SA030 to SA032, SA034 to SA036, SA048 for study #103, runs SA001 to SA019, SA021 to SA026, SA028 to SA036, SA038 to SA054 for study #106, on the study outcome (see **Form FDA-483, item 3**).

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Sam H. Haidar, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

NAI - Celerion, Inc., Lincoln, NE
FEI: 1915582

VAI - (b) (4)

FEI: (b) (4)

Page 7 - NDA 204-447 Vortioxetine (Lu AA21004) tablet, 5, 10, 15
and 20 mg

cc:

OSI/Moreno

OSI/DBGLPC/Taylor/Dejernett

OSI/DBGLPC/BB/Haidar/Mada

OND/ODE1/DPP/Patel/Laughren

OCP/DCP1/Jackson/Zhu

ORA/ (b) (4) /Lambert

Draft: SRM 07/08/2013

Edit: SHH 07/09/2013; WHT 07/11/2013

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FACTS: 1491186

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

ATTACHMENT: 1

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SRIPAL R MADA
07/12/2013

SAM H HAIDAR
07/12/2013

WILLIAM H TAYLOR
07/12/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 9, 2013

To: Hiren Patel, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA #204447**
Brintellix (vortioxetine) Tablets

OPDP has reviewed the draft product labeling (PI) for Brintellix (vortioxetine) Tablets as requested in the consult from DPP dated October 26, 2012.

OPDP's comments on the draft PI for Brintellix are based on the version provided by email from Hiren Patel on June 21, 2013, and are provided directly on the draft PI below.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

SUSANNAH O'DONNELL
07/09/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 28, 2013

To: Mitchell Mathis, M.D.
Acting Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name: BRINTELLIX (vortioxetine)

Dosage Form and Route: tablets

Application
Type/Number: NDA 204447

Applicant: Takeda Pharmaceuticals America, Inc.

1 INTRODUCTION

On October 2, 2012, Takeda Pharmaceuticals America, Inc. submitted for the Agency's review an original New Drug Application (NDA) for BRINTELLIX (vortioxetine) Tablets. BRINTELLIX is indicated for the treatment of Major Depressive Disorder (MDD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on October 26, 2012 and October 26, 2012, respectively, for DMPP and OPDP to review the Applicant's proposed review the Applicant's proposed Medication Guide (MG) for BRINTELLIX (vortioxetine) Tablets.

2 MATERIAL REVIEWED

- Draft BRINTELLIX (vortioextine) Tablets MG received on October 2, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on June 21, 2013
- Draft BRINTELLIX (vortioextine) Tablets MG received on October 2, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 21, 2013
- Draft BRINTELLIX (vortioextine) Tablets Prescribing Information (PI) received on October 2, 2012, revised by the Review Division throughout the review cycle, and received by DMPP June 21, 2013
- Draft BRINTELLIX (vortioextine) Tablets Prescribing Information (PI) received on October 2, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 21, 2013
- PRISTIQ (desvenlafaxine) Extended-Release Tablets comparator labeling approved February 14, 2013

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
06/28/2013

SUSANNAH O'DONNELL
06/28/2013

MELISSA I HULETT
06/28/2013

LASHAWN M GRIFFITHS
06/28/2013



NDA 204447

LABELING PMR/PMC DISCUSSION COMMENTS

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

Dear Ms. Sambor:

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

We also refer to our December 6, 2012, letter in which we notified you of our target date of June 14, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On January 24, 2013, we received your January 24, 2013 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

Additionally, we are recommending the following postmarketing requirements/commitments:

Clinical Pharmacology

1. An in vivo study in subjects with severe hepatic impairment compared to healthy subjects using the 5 mg dose.
2. In vitro determination of vortioxetine and its major metabolites as potential inhibitors of major transporters as recommended by the drug-drug interaction guidance.

Clinical

3. Pediatric studies: as a PREA requirement you will need to conduct two multi-center, double-blind, placebo-controlled pediatric studies in children and adolescents (7 to 17 years old) in the treatment of major depressive disorder. At least one of these studies must be a fixed-dose study.
4. A relapse prevention study in the US: since only Lu AA21004 20 mg/day demonstrated efficacy in the US and the relapse prevention study (11985A) was a non-US study, you will need to conduct a relapse prevention study to further characterize the dose response relationship of Lu AA21004 in the United States. This

study should be a fixed dose study and the dose choice should cover the approved dose range.

If you have any questions, email me, at (301) 796-2087.

Sincerely,

{See appended electronic signature page}

LCDR Hiren D. Patel, Pharm.D., M.S., RAC
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

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/s/

HIREN PATEL
06/14/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: May 24, 2013

TO: Hiren Patel, Pharm.D., Regulatory Project Manager
Jenn Sellers, M.D., Medical Officer
Jing Zhang, M.D., Clinical Team Leader
Division of Psychiatry Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D., Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204-447

APPLICANT: Takeda Pharmaceuticals USA, Inc.

DRUG: Vortioxetine (Lu AA21004, no trade name)

NME: Yes

INDICATION: Treatment of major depressive disorder

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: November 16, 2012

INSPECTION SUMMARY GOAL DATE: May 24, 2013

REGULATORY ACTION GOAL DATE: October 2, 2013

PDUFA DUE DATE: October 2, 2013

I. BACKGROUND

Major depressive disorder (**MDD**) affects 5% of the adult population in the United States (**US**) at any given time, and poses a lifetime risk of 15% worldwide. Available pharmacologic agents for managing MDD include tricyclic antidepressants (**TCA**), selective serotonin reuptake inhibitors (**SSRI**), and serotonin-norepinephrine reuptake inhibitors (**SNRI**). TCAs are effective but often have unacceptable histaminic or cholinergic adverse effects. SSRIs and SNRIs have fewer adverse effects than do TCAs, and SNRIs appear more effective than are TCAs and SSRIs. However, with currently available agents (including SNRIs), pharmacologic monotherapy remains either ineffective or inadequate in up to two-thirds of patients with MDD.

Vortioxetine (Lu AA21004) is a new agent, structurally different from all currently known psychotropic agents, with antidepressant, anxiolytic, and analgesic effects. Vortioxetine directly modulates serotonin receptors and inhibits serotonin reuptake. In the rat brain, Lu AA21004 has been shown to increase extracellular levels of serotonin, noradrenalin, dopamine, histamine, and acetylcholine. Antidepressant and anxiolytic effects in humans have been shown in many clinical studies. Under the current NDA, the sponsor seeks marketing approval for vortioxetine for the treatment of MDD. The pivotal studies described below have been selected for good clinical practice (**GCP**) inspections.

Study Lu AA21004-305

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed-Dose Study Comparing the Efficacy and Safety of 3 Doses of Lu AA21004 in Acute Treatment of Adults with Major Depressive Disorder

In this randomized, double-blind, placebo-controlled study, 556 subjects with MDD were enrolled at 48 sites in Europe, Asia, Australia, and South Africa. The primary objective was to evaluate the efficacy of 3 fixed doses of vortioxetine (1, 5, and 10 mg, once daily) versus placebo after 8 weeks of treatment in subjects with MDD. All psychiatric diagnoses were to meet the diagnostic criteria defined in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*.

The 14-week study consisted of screening (up to 10 days), double-blind treatment (8 weeks), and safety follow-up phone call (4 weeks after study completion or withdrawal). Subjects completing the core treatment period had the option to continue treatment in an open-label, extension study (Study Lu AA21004-301). The study was completed over 12 months, from August 2008 to August 2009.

Subject Selection

- Men or women (age 18-75 years) with primary diagnosis of MDD per DSM-IV-TR criteria
- Current major depressive episode (**MDE**) of at least 3 months per DSM-IV-TR criteria
- Confirmation of MDD and current MDE with Mini International Neuropsychiatric Interview (**MINI**).
- Montgomery Asberg Depression Rating Scale (**MADRS**) total score ≥ 26
- Exclusion of subjects with psychiatric comorbidities and disorders other than MDD

Treatment Groups

- Randomization in equal ratio to daily oral vortioxetine 1 mg, 5 mg, 10 mg, or placebo
- Subject evaluation weekly for the first two weeks of treatment, then every two weeks until end of treatment

Major Endpoints

- Primary: Mean change (from baseline) in the 24-item Hamilton Depression Scale (**HAM-D24**) total score after 8 weeks of treatment
- Major secondary: Mean change in the Sheehan Disability Score (**SDS**) total score at Week 8

- Safety: Adverse events (**AE**), clinical laboratory tests, vital signs and body weight, physical examination findings, and electrocardiograms (**ECG**)

Major Results

Relative to placebo, subjects given vortioxetine 10 mg had improved MDD symptoms as defined for the primary endpoint ($p < 0.001$). All dose levels were well tolerated. The incidence of nausea was greater for vortioxetine than for placebo.

Study Lu AA21004-315

A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Duloxetine-Referenced, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses (15 and 20 mg) of Lu AA21004 in Acute Treatment of Adults with Major Depressive Disorder

In this randomized, double-blind, placebo-controlled study, 614 subjects with MDD were enrolled at 58 US sites. The primary objective was to evaluate the efficacy of vortioxetine 15 and 20 mg once daily compared with placebo using MADRS after 8 weeks of treatment. All psychiatric diagnoses were to meet the diagnostic criteria defined in DSM-IV-TR. The 13-week study consisted of screening (1 week), double-blind treatment (8 weeks), single-blind treatment discontinuation (2 weeks), and safety follow-up (phone call 4 weeks after study completion or withdrawal). Subjects completing core treatment had the option to continue in the open-label extension study (Study Lu AA21004-314). The study was completed over 21 months, from June 2010 to March 2012.

Subject Selection

- Men or women (age 18 to 75 years) with primary diagnosis of MDD per DSM-IV-TR criteria
- MDE of at least 3 months per DSM-IV-TR criteria
- Confirmation of MDD and MDE using Structured Clinical Interview for DSM Disorders (**SCID**)
- MADRS total score ≥ 26 and a Clinical Global Impression-Severity of Illness (**CGI-S**) score ≥ 4

Treatment and Evaluation

- Randomization in equal ratio to four arms (daily oral vortioxetine 15 or 20 mg, duloxetine 60 mg, or placebo) stratified by baseline sexual function (normal or abnormal) per Arizona Sexual Experiences Scale (**ASEX**) score.
- For the first week of treatment (titration period), subjects received reduced doses of the study medication, vortioxetine 10 mg or duloxetine 30 mg. Subjects were evaluated weekly for 2 weeks, then every other week until end of treatment.
- At treatment completion, subjects entered a 2-week single-blind taper period to assess the potential for discontinuation symptoms using the Discontinuation-Emergent Signs and Symptoms (**DESS**) scale. During taper Week 1, subjects on either vortioxetine or placebo received placebo only, and subjects on duloxetine 60 mg received duloxetine 30 mg. All subjects received placebo during taper Week 2.

Major Endpoints

- Primary Efficacy: Mean change from baseline in the MADRS total score after 8 weeks of treatment
- Major Secondary Efficacy:
 - MADRS response at Week 8, defined as $\geq 50\%$ decrease from baseline in MADRS total score
 - Mean Clinical Global Impression Scale-Improvement (**CGI-I**) score at Week 8
- Safety Endpoints:
 - AEs, clinical laboratory tests, physical examination (including vital signs and body weight), ECG, and Columbia-Suicide Severity Rating Scale (**C-SSRS**)

- Number of subjects developing sexual dysfunction and change from baseline in ASEX total score; DESS scores and AEs at one and two weeks after treatment discontinuation

Major Results

- Vortioxetine 20 mg was superior to placebo in mean change from baseline in MADRS total score at Week 8 ($p = 0.02$). Vortioxetine 15 mg was not significantly different from placebo. Duloxetine separated from placebo at Week 8, validating the study. The secondary efficacy endpoints did not separate from placebo (nominal $p < 0.05$) at either vortioxetine dose.
- Compared with the placebo group, more subjects in the vortioxetine 20 mg group were considered responders as defined by MADRS total score or CGI-I. The proportions of subjects in remission as defined by MADRS total score or CGI-S were generally similar across treatment groups.
- Vortioxetine was safe and well tolerated. There were no clinically relevant abnormalities noted in vital signs, ECG values, or laboratory values. Abrupt discontinuation of treatment resulted in no significant differences in DESS total scores compared to placebo. The ASEX analysis showed no difference in the rates of treatment-emergent sexual dysfunction between vortioxetine and placebo groups.

Study Lu AA21004-316

A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses (10 and 20 mg) of Lu AA21004 in Acute Treatment of Adults with Major Depressive Disorder

In this randomized, double-blind, placebo-controlled study, 462 subjects with MDD were enrolled at 37 US sites. The primary objective of this study was to evaluate the efficacy of vortioxetine 10 and 20 mg once daily compared with placebo as assessed using MADRS after 8 weeks of treatment in subjects with MDD. All psychiatric diagnoses were to meet the diagnostic criteria defined in DSM-IV-TR. The 13-week study consisted of screening (1 week), double-blind treatment (8 weeks), single-blind treatment discontinuation (2 weeks), and safety follow-up phone call (4 weeks after study completion or withdrawal). Subjects completing the core treatment period had the option to continue treatment in an open-label, extension study (Study Lu AA21004-314). The study was completed over 18 months, from July 2010 to January 2012.

Subject Selection

- Men or women (age 18 to 75 years) with primary diagnosis of MDD per DSM-IV-TR criteria
- Current MDE of at least 3 months per DSM-IV-TR criteria
- Confirmation of MDD and MDE using SCID
- MADRS total score ≥ 26 and CGI-S total score ≥ 4

Treatment and Evaluation

- Randomization in equal ratio to three arms (daily oral vortioxetine 10 or 20 mg, or placebo) stratified by baseline sexual function (normal or abnormal) per ASEX score.
- For the first week of treatment (titration period), subjects received reduced doses of the study medication, vortioxetine 10 mg. Subjects were evaluated weekly for 2 weeks, then every other week until end of treatment.
- Subjects completing treatment entered a two-week single-blind taper period to assess potential discontinuation symptoms using DESS scale and by monitoring AEs.

Major Endpoints

- Primary Efficacy: Mean change from baseline in the MADRS total score after 8 weeks of treatment

- Major Secondary Efficacy:
 - MADRS response at Week 8, defined as $\geq 50\%$ decrease from baseline in MADRS total score
 - Mean CGI-I score at Week 8
- Pharmacokinetic: Individual exposure parameters of vortioxetine and its metabolites, including:
 - Area under the plasma concentration-time curve (**AUC**)
 - Average concentration at steady state (**C-avg**)
 - Maximum observed plasma concentration (**C-max**)
- Safety Endpoints:
 - AEs, clinical laboratory tests, vital signs and body weight, physical examination findings, and ECGs
 - Number of subjects developing sexual dysfunction anytime during the study, change from baseline in ASEX total score at each week assessed, and DESS scores and AEs at one and two weeks after treatment discontinuation

Major Results

- Vortioxetine 20 mg was superior to placebo in mean change from baseline in MADRS total score at Week 8 ($p < 0.05$). Vortioxetine 10 mg was not significantly different from placebo. The secondary efficacy endpoint CGI-I separated from placebo (nominal $p < 0.05$) for vortioxetine 20 mg.
- Vortioxetine was safe and well tolerated; no new safety signals were observed. Abrupt discontinuation of treatment resulted in no significant differences in DESS total scores compared to placebo. The ASEX analysis showed no difference in the rates of treatment-emergent sexual dysfunction between vortioxetine and placebo groups.

Study 11985A

A Double-blind, Randomised, Placebo-controlled, Multi-centre, Relapse-prevention Study with Two Doses of Lu AA21004 in Patients with Major Depressive Disorder

In this randomized, double-blind, placebo-controlled, relapse-prevention study, 639 subjects with MDD were enrolled at 66 international study sites (1-7 per country): Australia, Austria, Belgium, Canada, Finland, France, Germany, India, Korea, Norway, Poland, South Africa, Sweden, Taiwan, Thailand, Turkey, and United Kingdom. The primary objective of this study was to evaluate the efficacy of vortioxetine 5 and 10 mg in preventing relapse of MDE. All psychiatric diagnoses were to meet the diagnostic criteria defined in DSM-IV-TR. The study consisted of two consecutive periods: 12 weeks of open-label treatment was followed by 24-64 weeks of double-blind, fixed-dose, placebo-controlled treatment. The study was completed over 21 months, from December 2007 to September 2009.

Subject Selection

- In-patients or out-patients, age 18 to 75 years, with primary diagnosis of MDE per DSM-IV-TR
- At least one previous MDE, and current MDE of at least 4 weeks per DSM-IV-TR
- MADRS total score ≥ 26 at screening and at baseline

Treatment and Evaluation

- The initial dose of open-label treatment was 5 mg (daily, oral). If clinically indicated, the dose was increased to 10 mg or decreased back to 5 mg during Weeks 2-8. The dose was fixed at Week 8.
- Subjects in remission (MADRS total score < 10) at Weeks 10 and 12 of open-label treatment were randomized in equal ratio to double-blind treatment, to either vortioxetine at the fixed dose at Week 8 of open-label treatment or placebo. Non-remitters at Weeks 10 or 12 were withdrawn from the study.

- Throughout double-blind treatment, the subjects were evaluated for relapse, defined as a MADRS total score > 22 or an insufficient clinical response (per investigator judgment). Subjects in relapse were withdrawn from the study.
- Efficacy and safety data were collected every two weeks during open-label treatment, and at Weeks 1, 2, 4, and thereafter every four weeks during double-blind treatment. A safety follow-up contact was scheduled for four weeks after completion of (or withdrawal from) the study.

Major Endpoints

- Primary Efficacy: Time to relapse within 24 weeks of double-blind treatment, based on:
 - MADRS total score \geq 22, or
 - Unsatisfactory treatment effect (lack of efficacy) as judged by the investigator
- Major Secondary Efficacy: MADRS total scores (double-blind Weeks 1, 2, 4, and every 4 weeks)
- Safety: AEs, laboratory tests, vital signs and body weight, physical examination, and ECGs

Major Results

Vortioxetine 5 or 10 mg significantly reduced the risk of relapse (twice lower relative to placebo). Antidepressant effect during 12 weeks of open-label treatment was maintained during double-blind treatment. Long-term treatment appeared to be well tolerated. The incidence of reported AEs at discontinuation was low and appeared to be comparable between vortioxetine and placebo.

II. INSPECTIONS

For this NDA for a new molecular entity (NME), four studies were audited at six sites: five clinical study sites (shown below) and the sponsor site (Takeda Pharmaceuticals USA). The clinical investigator (CI) sites were selected for inspection based on: (1) relatively large subject enrollment, (2) significant efficacy contribution, (3) potential SAE underreporting, and (4) no prior or recent (< 2 years) FDA inspection.

	Inspected Entity	Studies, Sites, Subjects	Inspection Outcome
1	Donald Garcia, Jr., M.D. Austin, TX	Lu AA21004-315 Site 5009, 24 subjects	January 7 - 11, 2013 NAI
2	John M. Joyce, M.D. Jacksonville, FL	Lu AA21004-315 Site 5013, 28 subjects	December 17 -19, 2012 NAI
3	Lorena Wallhausser, M.D. Cincinnati, OH	Lu AA21004-316 Site 6010, 30 subjects	December 5 - 20, 2012 NAI
4	Bettina Bergtholdt, M.D. Berlin, Germany	Lu AA21004-305 Site 88, 32 subjects	February 11 - 15, 2013 Pending (preliminary NAI)
5	Leo Ruelens, M.D. Tielt, Belgium	11985A Site BE003, 20 subjects	February 2 - 8, 2013 VAI
6	Takeda Pharmaceuticals USA Deerfield, IL	Lu AA21004-305, Lu AA21004-315 Lu AA21004-316, and 11985A	January 9 - 28, 2013 NAI

NAI = no action indicated (no significant GCP deviations); VAI = voluntary action indicated (significant GCP deviations); OAI = official action indicated (serious GCP deviations and/or data unreliable)

Pending: Preliminary classification is based on information on Form FDA 483 and preliminary communication with the field investigator. The final establishment inspection report has not been received from the field office and OSI's complete review of the EIR remains pending as of this clinical inspection summary.

1. Donald Garcia, Jr., M.D.

a. What was inspected:

- Compliance with the study protocol, good clinical practice (**GCP**) regulations, and standard operating procedures (**SOPs**)
- Data verification: subject eligibility, informed consent, subject randomization, major efficacy endpoints (MADRS and CGI-S), adverse events, protocol deviations, subject discontinuations, and concomitant medications
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records.
- At this site, for Study Lu AA21004-315: 40 subjects were screened, 24 were enrolled (~4% of total study enrollment), and 17 completed the study through the core double-blinded treatment period. Of the 17 subjects completing core treatment, 12 opted to continue treatment and were enrolled in the open-label extension Study Lu AA21004-314.
- Subject case records were reviewed for 21 of the 24 enrolled subjects, including complete review for 19 subjects.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued.
 - IRB oversight and study monitoring appeared to be adequate.
 - All subjects signed the informed consent document.
 - Drug accountability was well documented.
 - Source records appeared factual, complete, and matched corresponding CRFs.
 - Endpoint data matched among source records, CRFs, and NDA data listings.
- One minor deficiency was verbally discussed (not cited on Form FDA 483, inspector discretion). Three blood samples for pharmacokinetic (**PK**) evaluation (Subjects 5009510, 5009512, and 5009513) were stored at 1 - 4 °C for two weeks (not stored frozen \leq -20 °C).

c. Assessment of data integrity:

Efficacy and safety data from this study site appear reliable as reported in the NDA. PK data from Subjects 5009510, 5009512, and 5009513 may not be reliable (improper PK sample storage).

2. John M. Joyce, M.D.

a. What was inspected:

- Compliance with the study protocol, GCP regulations, and SOPs
- Data verification: subject eligibility, informed consent, subject randomization, major efficacy endpoints (MADRS and CGI-S), adverse events, protocol deviations, subject discontinuations, and concomitant medications
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records.
- At this site, for Study Lu AA21004-315: 53 subjects were screened, 28 were enrolled (~5% of total study enrollment), and 23 completed the study through the core double-blinded treatment period.
- Subject case records were reviewed for all enrolled subjects, including complete review for 17 subjects.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued.
 - IRB oversight and study monitoring appeared to be adequate.
 - All subjects signed the informed consent document.
 - Drug accountability was well documented.
 - Source records appeared factual, complete, and matched corresponding CRFs.
 - Endpoint data matched among source records, CRFs, and NDA data listings.
- Verbal discussions (not cited on Form FDA 483, inspector discretion):
 - Disqualification of a temporary rater (special qualification approval) after continued evaluation of performance in rating MADRS, HAM-D24, and C-SSRS
 - Pregnancy in one subject leading to immediate subject safety evaluation (including unblinding of treatment assignment) and discontinuation of the subject from study
 - Use of the prohibited medication clonazepam (anxiolytic) in one subject in managing an AE of anxiety attack in the emergency room
 - Unused study medication not recovered from a subject lost to follow up; late informed consent (second follow up consent) in one subject; late reporting of protocol deviations; and deficiencies reported as protocol violations

c. Assessment of data integrity: The verbal discussion items included many observations about the site's handling of study events (not deficiencies) that indicate due diligence in adhering to GCP. Data from this study site appear reliable as reported in the NDA.

3. Lorena Wallhausser, M.D.

a. What was inspected:

- Regulatory compliance with the study protocol, GCP regulations, and applicable SOPs, and verification of NDA data, to include: subject eligibility, informed consent, subject randomization, major efficacy endpoints (MADRS and CGI-S), adverse events, protocol deviations, subject discontinuations, and concomitant medications
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records.
- Study Lu AA21004-316: 42 subjects were screened, 30 were enrolled (~6% of total study enrollment), and all 30 enrolled subjects completed the study through the core double-blinded treatment period. Subject case records were reviewed for all 30 enrolled subjects.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued.
 - IRB oversight and study monitoring appeared to be adequate.
 - All subjects signed the informed consent document.
 - Source records appeared factual, complete, and matched corresponding CRFs.
 - Endpoint data matched among source records, CRFs, and NDA data listings.
- Drug accountability appeared to be adequate. However, test article disposition was tracked (well documented) at the level of the blister pack (each containing 10 capsules), and not for the individual capsules. This minor isolated deficiency in drug accountability was verbally discussed and not cited on Form FDA 483 (inspector discretion).

c. Assessment of data integrity: Data from this study site appear reliable as reported in the NDA.

4. Bettina Bergtholdt, M.D.

a. What was inspected:

- Regulatory compliance with the study protocol, GCP regulations, and applicable SOPs, and verification of NDA data, to include: subject eligibility, informed consent, subject randomization, major efficacy endpoints (MADRS and CGI-S), adverse events, protocol deviations, subject discontinuations, and concomitant medications
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records.
- Study Lu AA21004-305: 41 subjects were screened, 32 were enrolled (~6% of total study enrollment), and 31 enrolled subjects completed the study through the core double-blinded treatment period. Subject case records were completely reviewed for 11 enrolled subjects and reviewed in detail for the 21 remaining enrolled subjects, to include informed consent, MADRS and CGI-S endpoints, serious adverse events, and subject disposition.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued.
 - IRB oversight and study monitoring appeared to be adequate.
 - All subjects signed the informed consent document.
 - Source records were complete and matched corresponding CRFs.
 - Endpoint data matched among source records, CRFs, and NDA data listings.
 - Drug accountability appeared to be adequate.
- The following minor, apparently isolated deficiency observations were discussed verbally and not cited on Form FDA 483 (inspector discretion).
 - Subject 526: AE data discrepancies between source documents and CRFs

Adverse Event	Source Documentation	CRF Data
Dizziness	intermittent, medication changed	continuous, no action taken
Depressed consciousness	intermittent and mild, poss bly related to study treatment	continuous and moderate, not related to study treatment

- Subject 503: Subject-administered SDS assessments were not performed (no documented explanation); presumably, the assessments could not be performed because the subject refused to complete the self-administered questionnaires.

c. Assessment of data integrity: Data from this study site appear reliable as reported in the NDA.

Note: The final inspection report has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator.

5. Leo Ruelens, M.D.

a. What was inspected:

- Regulatory compliance with the study protocol, GCP regulations, and applicable SOPs, and verification of NDA data, to include: subject eligibility, informed consent, subject randomization, major efficacy endpoints (MADRS and CGI-S), adverse events, protocol deviations, subject discontinuations, and concomitant medications

- Record review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records.
 - Study 11985A: 33 subjects were screened, 20 were enrolled (~3% of total study enrollment), and 10 enrolled subjects completed the study. Subject case records were reviewed for all 20 enrolled subjects.
- b. General observations and comments:
- A Form FDA 483 was issued for the following deficiencies:
 - Miscalculations on the drug inventory log: For five subjects (Subjects 1064, 1219, 1264, 1378, and 1571), the numbers of capsules returned were inaccurate by ~ 10% (math errors). The amount of the study medication taken appeared to be accurate.
 - Improper source record correction: For at least 8 subjects, errors on the drug inventory log (> 7 subjects) or on the MINI assessment form (one subject, Subject 1117) were corrected by obliterating the original, without the correction date, and/or without the corrector's initials.
 - The cited deficiencies appeared to be isolated instances of minor significance. No significant deficiencies were observed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data matched among source records, CRFs, and NDA data listings.
- c. Assessment of data integrity: Data from this study site appear reliable as reported in the NDA.

6. Takeda Pharmaceuticals USA, Inc. (Sponsor)

- a. What was inspected:
- Compliance with GCP regulations and adequacy of financial disclosure, informed consent procedures, and IRB oversight
 - Adequacy of and adherence to SOPs for oversight of clinical study sites and contract research organizations (**CROs**), handling of protocol deviations, AE reporting, data management, and drug accountability, including the review of the following documents:
 - *Study Planning*
 - *Site Initiation*
 - *Interim Monitoring*
 - *Study Closure Reports*
 - *Interactive Voice and Web Response System*
 - *Monitoring Plan*
 - *Oversight of Outsourced Clinical Study Management and Clinical Site Monitoring*
 - *Management of Protocol Deviations*
 - *Clinical Study Protocol Deviations*
 - *Serious Adverse Event Reporting and Handling in an eCRF*
 - *Clinical Trial Material Accountability*
 - *Handling of Serious Non-Compliance and Serious Breaches*
 - *Scientific Misconduct*
- b. General observations:
- A Form FDA 483 was not issued. The sponsor's records indicated adequate control over the various aspects of the audited studies. There was no evidence of unblinding or biased data

collection. The reported protocol deviations were accurately reported in the NDA listings. Drug accountability records were adequate.

- The following two deficiency observations were verbally discussed and not cited on Form FDA 483 (inspector discretion):
 - In Study Lu AA21004-305, eight shipments of the study medication to three study sites in June 2009 (Sites 0019, 0088, and 0089) were delayed when the computer software for tracking product shipment (*Drug Expiry Warning*) failed without appropriate manual tracking and override. The adverse impact of the delayed shipment appeared to be limited to delayed Visit 6 (delayed dispensing of future study medication supply) for three subjects at Site 088 (Subjects 534, 537, and 541). The existing supply of the study medication was not depleted and the dosing schedule was not interrupted.
 - The sponsor did not have a mechanism in place for preventing the enrollment of a subject in more than one study within a pre-specified timeframe.
 - Site BE002 in Study 11985A (Denis Voleke; Waregem, Belgium) was terminated after the sponsor's audit in March 2009 revealed that: (1) at least four of 12 enrolled subjects were not eligible due to not meeting the subject selection criteria for psychiatric diagnoses, (2) five subjects were given one or more prohibited study medications, and (3) many CRF data were not supported by source records. In the NDA, the sponsor reported the study results with and without the data from this terminated site, apparently to show that this single non-compliant study site had no significant impact on the overall study outcome.
- c. Assessment of data integrity: The verbal observations (not cited on Form FDA 483) appear to be isolated deficiencies that had no impact on the audited studies, but nonetheless potentially important for future studies. The inspectional observations otherwise indicate adequate sponsor oversight of the audited clinical studies. The study data reported in the NDA appear reliable.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

The sponsor (Takeda Pharmaceuticals USA, Inc.) seeks marketing approval for vortioxetine (Brintellix[®]) for the treatment of MDD. Vortioxetine is a new agent structurally different from all currently available psychotropic agents touted to have anxiolytic and analgesic effects, in addition to antidepressant effects. Four pivotal studies were identified for GCP audit at 6 sites: 5 clinical study sites and the sponsor site. The clinical study sites were selected for inspection primarily based on large subject enrollment.

At all 6 inspections, no significant deficiencies were observed (Form FDA 483 not issued at 5 of 6 sites), and the clinical efficacy and safety data from all inspected sites appear reliable as reported in the NDA. The major observations for each inspected site were:

- Site 5009, Study Lu AA21004-315 (Donald Garcia, 4% of total study enrollment): Three blood samples for pharmacokinetic (**PK**) evaluation (Subjects 5009510, 5009512, and 5009513) were stored at 1 - 4 °C for two weeks (not stored frozen \leq -20 °C). The PK data from Subjects 5009510, 5009512, and 5009513 may not be reliable due to improper sample storage.
- Site 5013, Study Lu AA21004-315 (John Joyce, 5% of total study enrollment): (1) use of clonazepam (prohibited medication) in one subject in the emergency room in treating an anxiety attack, (2) unused study medication not recovered from one subject lost to follow up, (3) late informed consent in one subject, and (4) late reporting of protocol deviations.
- Site 6010, Study Lu AA21004-316 (Lorena Wallhausser, 6% of total study enrollment): Test article disposition was tracked at the level of the blister pack and not for the individual capsules.

- Site 88, Study Lu AA21004-305 (Bettina Bergtholdt, 6% of total study enrollment): (1) for Subject 526, a few AE data discrepancies between source documents and CRFs, and (2) Subject 503 apparently refused to self-administer SDS assessments (no documentation of subject refusal).
- Takeda Pharmaceuticals USA, Inc. (Sponsor): No significant deficiencies were observed. The sponsor's records indicated adequate control over the various aspects of the audited studies.
- Site BE003, Study 11985A (Leo Ruelens, 3% of total study enrollment): A Form FDA 483 was issued at this site for: (1) miscalculations on the drug inventory log for five subjects; and (2) improper practice in correcting errors on source documents.

In brief, deficiencies were observed at all six sites inspected, including the five NAI sites. All deficiency observations (whether or not cited on Form FDA 483) appear to be minor, isolated, and unlikely to affect study outcome. All audited study data appear reliable as reported in the NDA. The inspectional observations are nonetheless summarized to facilitate the on-going NDA review, should they prove significant as the review progresses.

Note: For Site 88 in Study Lu AA21004-305 (Bettina Bergtholdt, Germany), the final EIR has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division if the final classification changes from the pending classification, or if additional observations of clinical or regulatory significance are discovered after completing the EIR review.

{See appended electronic signature page}

John Lee, M.D.

Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.

Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

JONG HOON LEE
05/21/2013

SUSAN D THOMPSON
05/22/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: May 15, 2013
Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis
Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis
Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis
Drug Name and Strengths: Brintellix (Vortioxetine) Tablets
5 mg, 10 mg, 15 mg, and 20 mg
Application Type/Number: NDA 204447
Applicant: Takeda Pharmaceuticals USA, Inc.
OSE RCM #: 2012-3005

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1 INTRODUCTION

This review evaluates the proposed labels and labeling for Brintellix (Vortioxetine), NDA 204447, for areas of vulnerability that can lead to medication errors. Vortioxetine is a new molecular entity (NME).

1.1 PRODUCT INFORMATION

The following product information is provided in the October 2, 2012 original submission:

- Active Ingredient: Vortioxetine
- Indication of Use: Treatment of Major Depressive Disorder (MDD)
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 5 mg, 10 mg, 15 mg, and 20 mg
- Dose and Frequency: The recommended starting dose for is 10 mg administered orally once daily without regard to meals. (b) (4)
Depending upon individual patient response at a 10 mg dose, the patient may benefit from dose modification down to 5 mg or up to a maximum of 20 mg once daily.
- How Supplied: 30, 90, and 500-count bottles; professional sample cartons containing four 7-count bottles; and professional sample cartons containing four 7-count blister cards.
- Storage: Store at 25°C (77°F); excursions permitted to 15° C to 30°C (59° F to 86°F). (b) (4)
- Container and Closure System: The 7-count professional sample bottles and the 30 and 90-count commercial bottles have (b) (4); the 500-count bottle does not have a CRC.

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Retail Container Labels submitted on October 2, 2012 (Appendix A)
- Professional Sample 7-count Bottle Labels submitted on October 12, 2012 (Appendix B)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Professional Sample Carton Labeling for the 7-count bottles submitted on December 12, 2012 (Appendix C)
- Professional Sample Carton Labeling for the 7-count Blister Cards submitted on October 12, 2012 (Appendix D)
- Professional Sample Blister Card submitted on October 12, 2012 (Appendix E)
- Insert Labeling submitted on October 12, 2012 (no image)
- Actual samples of the professional sample packaging

3 MEDICATION ERROR RISK ASSESSMENT

Our risk assessment of the Brintellix labels and labeling determined that there is adequate strength differentiation within the product line. Additionally, we note the Applicant submitted labels and labeling for professional sample cartons containing four 7-count bottles and professional sample cartons containing four 7-count blister cards. According to the Applicant, two professional sample packaging configurations were submitted in the NDA to allow for options once the drug is approved. The intent will be to only utilize one of these packaging configurations. The Applicant envisions the 7-count bottles will be the chosen packaging configuration to be used for professional samples. We provide comments for both configurations. We also note the Applicant has placed an asterisk after the strength to highlight the equivalence statement on the side panel. Our understanding of the CDER MAPP 5021.1 “Naming of Drug Products Containing Salt Drug Substances” is that an asterisk is no longer necessary. Our risk assessment of the proposed labels and labeling identified the following areas of concern:

Proprietary Name Presentation:

- The graphic above the letter “i” is distracting and interferes with the readability of the proprietary name.

Retail Container Label (500-count)

- The child-resistant statement is too prominent on the 500-count retail container label.

Retail Container Labels and Professional Sample Bottle Labels

- The statement of strength lacks prominence on the retail container labels and professional sample bottle labels.

Professional Sample Blister Cards

- The Brintellix website address is too prominent on the inside right panel and is duplicative information.
- The professional sample blister card lacks an “XX mg per tablet” statement.
- The directions for tablet removal lack clarity.
- The directions for tablet removal lack prominence.
- The net quantity statement is not optimally worded for clarity.

Professional Samples: Blister Cards, Sample Bottles and their Respective Carton Labeling

- The sample blister cards have the same NDC number as their respective cartons. Similarly, the sample bottles have the same NDC number as their respective cartons.

Professional Sample Carton Labeling for the 7-count Bottles

- The Brintellix website address is too prominent.

Insert Labeling

- There are instances where the numerical dose is not followed by its unit of measure each time it is mentioned in the Dosage and Administration sections of the insert labeling.
- The *Dosage of Administration* section of Full Prescribing Information states the [REDACTED] (b) (4) However, per response from the Applicant regarding our inquiry about the rationale for including this information; the Applicant stated the formulation of the product does not necessitate inclusion of the statement. The rationale was based on general concern around patients not taking the medication as prescribed.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes the proposed labels and labeling can be improved to increase the readability and prominence of important information in order to promote the safe use of the product and prevent medication errors.

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to approval of this NDA:

A. Insert Labeling

1. Dash marks (hyphens) are used in the *Dosage and Administration* section of the insert labeling. Dashes can be misinterpreted as periods or overlooked. Consider replacing dashes with the word “to”.
2. There are instances where the numerical dose is not followed by its unit of measure each time it is mentioned in the Dosage and Administration sections of the insert labeling (e.g., 5 and 10 mg/day and 5-10 mg/day). Ensure the numerical dose is followed by its appropriate unit of measure each time it is mentioned (e.g., 5 mg and 10 mg/day or 5 mg to 10 mg/day).
3. The *Dosage of Administration* section of Full Prescribing Information states [REDACTED] (b) (4) However, per response from the Applicant regarding our inquiry about the rationale for including this information, the Applicant stated the formulation of the product does not necessitate inclusion of the statement. The rationale was based on general concern around patients not taking the medication as prescribed. Therefore, we recommend removing this statement since it is typically reserved

for product formulations (e.g., extended-release) [REDACTED] (b) (4)
[REDACTED] have an impact on the pharmacokinetics and/or absorption
of the product or there is some other safety concern [REDACTED] (b) (4)
[REDACTED].

4.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. General Comment for all Labels and Labeling

The graphic above the letter “i” is distracting and interferes with the readability of the name. Remove the graphic or, alternatively, consider relocating it away from the proprietary name, established name, and strength.

B. Retail Container Label (500-count)

The “child-resistant” statement is located in the center of the principal display panel of the 500-count retail container labels and is too prominent in this location. Exchange the locations of the “child-resistant” statement and the Medication Guide (MG) statement. Additionally, debold the font of the “child-resistant” statement and revise the text to appear in title case.

C. Retail Container Labels and Professional Sample Bottle Labels

The statement of strength lacks prominence on the retail container labels and professional sample bottle labels because there does not appear to be sufficient color contrast between the statement of strength and the white background. Increase the size of the statement of strength, increase the point weight of the text, or darken the hue to ensure there is sufficient contrast between the statement of strength and background color.

D. Professional Sample Blister Card

1. The directions for tablet removal lack clarity. Revise the directions to read “To remove tablet, push the tablet through the foil backing from this side” or use similar verbiage.
2. The directions for tablet removal lacks prominence on the inside right panel. Move the “To remove tablet...” statement to where the Brintellix website address is currently located. The Brintellix website address should be removed since it is duplicative information that is already listed on the inside left panel. Additionally, relocate the “Store in original container” statement to the bottom of the inside right panel.
3. Revise the statement of strength to read “XX mg per tablet” on all panels.
4. The net quantity statement, [REDACTED] (b) (4) is not optimally worded for clarity. Revise the statement to read “Contains 7 tablets”.

E. Professional Samples: Blister Cards, Sample Bottles and their Respective Carton Labeling

1. We note the NDC identification codes on the blister carton labeling and blister cards are identical. This is inappropriate because four blister cards are packaged in each carton. Therefore, revise the NDC identification code for the carton labeling.
2. We note the NDC identification codes on the sample bottle carton labeling and sample bottles are identical. This is inappropriate because four sample bottles are packaged in each carton. Therefore, revise the NDC identification code for the carton labeling.

F. Professional Sample Carton Labeling for the 7-count Bottles

The Brintellix website address is too prominent. On the top flap of the carton for the 7-count bottle, exchange the locations of the website address and the MG statement. Additionally, decrease the font size of the website address. Consider relocating the website address to a side or back panel.

If you have further questions or need clarifications, please contact Sandra Rimmel, Project Manager, at 301-796-2445.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LORETTA HOLMES
05/15/2013

IRENE Z CHAN
05/16/2013

SCOTT M DALLAS
05/16/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 22, 2013

TO:  igations Branch

Chief, Medical Products & Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **High Priority User Fee NDA Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 204-447

DRUG: Vortioxetine (Lu AA21004) tablet, 5, 10, 15,
and 20 mg

SPONSOR: Takeda Pharmaceuticals USA, Inc.
One Takeda Parkway
Deerfield, IL 60015

SPONSOR'S CONTACT: Joanna Sambor, MS
Associate Director, Regulatory Affairs
(TEL) 224-554-2948
(FAX) 224-554-7870

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioavailability studies. Following identification of the investigator, please contact the Division of Bioequivalence and GLP Compliance (DBGLPC) point of contact (POC) for background materials. **A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise.** Please contact DBGLPC upon receipt of this assignment to arrange the analytical site inspection. Because of the PDUFA review due date, these inspections should be completed by 6/15/2013.

Please note that these inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001 and not conducted under CP 7348.811 for Good Clinical Practices (GCP).

After the completion of the inspections, please send a scanned copy of the completed sections A & B to Sam Haidar and the POC listed at the end of this memo.

Study Number: Lu AA21004_123
Study Title: A Phase 1, Open-Label, Randomized, Single Dose, 3-Period Crossover Study to Evaluate the Bioavailability of Lu AA21004 Formulation 4 Relative to Formulation 3 and to Assess the Effect of Food on Pharmacokinetics of Formulation 4 in Healthy Subjects

Clinical Site: Celerion, Inc.
621 Rose Street
Lincoln, NE 68502

Study Period: 09/09/2010 to 11/16/2010

Investigator: Scott Rasmussen, MD
(Tel) 402-476-2811
(Fax) 402-939-0428

Study Description: This study was a randomized, open-label, single-center, single-dose, 3-way crossover study in healthy adult subjects to compare bioavailability of the to-be-marketed formulation with that of the clinical formulation.

Study Objectives:

- To compare the bioavailability of the Formulation 4 tablet relative to the Formulation 3 tablet following a single oral dose of Lu AA21004 20 mg in healthy adult subjects.
- To evaluate the effect of food on the pharmacokinetics of Lu AA21004 following a single oral dose of Formulation 4 20-mg tablet in healthy adult subjects.

Please audit the reports of all 23 subjects who completed the study (Lu AA21004_123) and the one subject who did not complete the study. The subject records in the NDA submission should be compared to the original documents at the firm.

SECTION A

RESERVE SAMPLES: Because this is a bioequivalence study, the site conducting the study is responsible for randomly selecting and retaining reserve samples from each shipment of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for blinded studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>). Please refer to CDER's Guidance for Industry, Handling and Retention of BA and BE Testing Samples (May 2004), that clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.
- Please get written assurance from the Investigator (CI) or the responsible person at the investigator's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit.
- If the reserve samples were stored at an alternate site, please verify and collect an affidavit to confirm that the alternative site is independent from the sponsor, packager and manufacturer. In the event that reserve samples were not retained or are not adequate, please notify the Center reviewer/POC immediately.
- Samples of the Formulation 3 and 4 should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Dr. Benjamin (Nick) Westenberger
(Phone: 314-539-3869)
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002

St. Louis, MO 63101

SECTION B

Data Audit Checklist:

- Evidence of under-reporting of AEs identified? _____
- Evidence of inaccuracy in data capture? _____
- Presence of 100% of signed and dated informed consent forms obtained according to regulations:_____
- Number of subjects screened at the site:_____
- Number of subjects enrolled at the site:_____
- Number of subjects completing the study:_____
- Number of subject records reviewed during the inspection:_____
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol:_____
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:_____
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents and case report forms for dosing, whether the **randomization schedule was followed for dosing of subjects**, etc.)

- Other Comments:

The following is information for five studies that require analytical inspections.

Study Number: 106
Study Title: A Phase 1, Open-Label, Randomized, Single-Dose, 3-Period Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Formulation 3 of Lu AA21004 and to Determine the Relative Bioavailability of Formulation 3 to Formulation 1 of Lu AA21004 in Healthy Adult Subjects (n=24)

Study Number: 103

Study Title: Effect of multiple doses of fluconazole or ketoconazole on the PK of AA21004 (n=36)

Study Number: 102
Study Title: Effect of multiple doses of LuAA21004 on the steady-state PK and PD of ethinyl estradiol and levonorgestrel (n=28)

Study Number: 11826A
Study Title: Effect of multiple doses of AA21004 on the PK of omeprazole (n=18)

Study Number: 101
Study Title: An Open-Label, Multiple-Dose Study in Healthy Adults to Assess the Drug Interaction Potential of Lu AA21004 Using Indiana Cocktail (n=24)

Analytical Data Audi

(b) (4)

Please note that bioanalysis of the above five studies were conducted (b) (4)
After the site in (b) (4)

(b) (4)

(b) (4)

Analytical Method: LC/MS/MS
Extraction Method: Solid Phase Extraction method
Analytes Assayed: Lu AA21004, Lu AA34443 and Lu AA39835

Please confirm the following during the inspection:

- Examine all pertinent items related to the analytical methods used for the measurement of Lu AA21004 and its metabolites, Lu AA34443 and Lu AA39835, in human plasma or urine.
- Compare the analytical data provided by the sponsor in the NDA submissions with the original documents at the site.
- Determine if the validated analytical method was employed for the subject sample analysis.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Determine if the subject samples were analyzed within the validated stability period.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze/thaw cycles sufficiently covered stability of reanalyzed subject samples.
- Examine correspondence files between the analytical sites and the sponsor for their content.

Additionally, the following specific items should be addressed during the inspection:

- The studies 106, 103, 102, 11826A and 101 are studies whose information will be important for the labeling. Based on the wide array of possible compliance issues, the investigation should concentrate on the following:
 - Verify for studies 106, 103, 102 that for carryover tests, the highest observed carryover in the study was used to assess each analytical batch and that the worst case carryover was identified and used for all corrections.
 - Verify that there was no carryover for the following studies and batches:

Study	Batch	Analyte
Study 101	SA003 and SA012	Lu AA21004, Lu AA39835
Study 11826A	SA026	Lu AA21004, Lu AA34443

The following is a list of problems that special attention should be paid to:

- Potential carryover was masked by the staff under investigation by inserting wash samples between the high

standard samples or quality control samples (QCSs) and the carryover assessment blank injections.

- The wash samples were electronically removed and not reported.
- Batches that were automatically stopped because of software or hardware failure were identified. These batches were subsequently restarted from the point of failure.
- Individual unknown samples were re-injected at the end of an analytical batch without having been bracketed by calibration standards or QCSs and the results were subsequently inserted into the previously acquired batch.
- Individual calibration standards were re-injected when internal standard response indicated that auto sampler mis-injection had occurred and the results were electronically inserted into the original batch data file.
- A high sample index number at the beginning of a batch indicated previous acquisition of that batch within the data folder. Where this deficiency was indicated by the audit trail, the batch has been identified to be annotated as a proposed reinjection.
- Samples not bracketed by QCs or calibration standards.
- Poor or unacceptable integrations particularly for standards and QCs.
- Manual integration of incorrect peak
- Removal of integrations for pre-dose sample blanks and carryover blanks

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study-specific instructions may be identified by DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records on site.

Please fax/email a copy of Form FDA-483 if issued, as soon as possible. **If at close-out of the inspection, it appears that the violations warrant an OAI classification, please notify the DBGLPC POC as soon as possible.** At completion of the inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Sam Haidar (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov) and DBGLPC POC as below.

Page 8 - BIMO Assignment, NDA 204-447; Vortioxetine (Lu AA21004)
tablet, 5, 10, 15, and 20 mg

DBGLCP POC for Domestic inspections: Young Moon Choi, Ph.D.
young.choi@fda.hhs.gov
Tel: (301) 796-1516
FAX: (301)-847-8748

DBGLPC POC for Foreign Inspections: Arindam Dasgupta, Ph.D.
arindam.dasgupta@fda.hhs.gov
Tel: (301)-796-3326
FAX: (301)-847-8748

cc:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Skelly/Mada/Dasgupta/Cho/Choi/Dejernett/CF
ORAHQ/OMPTO/DMPTI/BIMO/Arline/Turner/Alexis/Braswell/Johnson/Colo
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ORA/KAN-DO/Bromley (DIB)/Lopicka (BIMO)

OCP/DCP1/Jackson/Zhu

ODE/DPP/Patel

Draft: YMC 11/14/2012

Edit: SRM 11/29/2012; JC 1/22/2013; SHH 12/5/2012, 01/29/2013;

OSI: BE6389; O:\BE\assigns\bio204476.doc

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Laboratory Practice Compliance/Electronic Archive/BEB/

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/s/

YOUNG M CHOI
01/29/2013

SAM H HAIDAR
01/30/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 204447

Application Type: New NDA

Name of Drug: vortioxetine tablets

Applicant: Takeda Pharmaceuticals USA, Inc.

Submission Date: October 2, 2012

Receipt Date: October 2, 2012

1.0 Regulatory History and Applicant's Main Proposals

This NME NDA was received on October 2, 2012 and therefore will be reviewed under The Program. Takeda has developed vortioxetine for the treatment of Major Depressive Disorder. The signatory authority for this NDA is Dr. Temple and a standard review determination has been made. The PDUFA date is October 2, 2013.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format within three weeks from the date of the letter. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Subsection title 9.2 should read “Abuse” and a new subsection with the title “Dependence” should be created under subsection 9.3.

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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 trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

HIREN PATEL
12/05/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204447 BLA#	NDA Supplement #: BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: vortioxetine Dosage Form: tablets Strengths: 5 mg, 10mg, 15mg, and 20 mg		
Applicant: Takeda Pharmaceuticals USA, Inc. Agent for Applicant (if applicable):		
Date of Application: 10/2/12 Date of Receipt: 10/2/12 Date clock started after UN:		
PDUFA Goal Date: 10/2/13	Action Goal Date (if different):	
Filing Date: 11/13/12	Date of Filing Meeting: 11/13/12	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Major Depressive Disorder		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 76307 and 112581				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?	X			
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 	X			
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?		X		Takeda initially submitted a list of clinical sites only for pivotal (phase 2/3) studies and therefore was requested to submit information for all clinical sites. Takeda complied with the request and submitted the additional information on 11/8/12.
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21	X			

CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>			X	

<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
--	--	--	--	--

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>		X		The sponsor's deferral request per FDCA Section 505B(a)(3), includes a reason for requesting deferral of pediatric studies in children and adolescents ages 7-17. However, evidence, in the form of a statement, that the studies are being conducted or will be conducted with due

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

				diligence and at the earliest possible time is not included. Takeda has complied with the certification required under FDCA Section 505B(a)(4).
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?			X	

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		X		The Medication Guide was consulted to the Patient Labeling Team.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			Consults: 1) New Drug Microbiology Staff (10/26/12) 2) OSI – Division of GCP Compliance Branch(11/16/12) 3) OSI – Division of BE and GLP Compliance (10/31/12) 4) Patient Labeling Team (10/26/12)
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): February 13, 2008	X			

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): June 22, 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): 1/17/07	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 13, 2012

NDA #: 204447

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: vortioxetine

DOSAGE FORM/STRENGTH: 5 mg, 10mg, 15mg, and 20 mg

APPLICANT: Takeda Pharmaceuticals USA, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Major Depressive Disorder

BACKGROUND: This NME NDA was received on October 2, 2012 and therefore will be reviewed under The Program. The signatory authority for this NDA is Dr. Temple and a standard review determination has been made. The PDUFA date is October 2, 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Hiren Patel	Y
	CPMS/TL:	Paul David/Renmeet Grewal	N
Cross-Discipline Team Leader (CDTL)	Jing Zhang		Y
Clinical	Reviewer:	Jenn Sellers	Y
	TL:	Jing Zhang	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Andre Jackson	N
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	George Kordzakhia	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Linda Fossom	Y
	TL:	Antonia Dow	Y
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wendy Wilson	Y
	TL:	Chhagan Tele	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	John Metcalfe	N
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Derek Smith	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	N
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Reema Mehta	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	John Lee – Division of GCP	N
	TL:	Susan Leibenhaut - Division of GCP Sam Haider – Division of BE and GLP Compliance	N
Patient Labeling Team	Reviewer:	Robin Duer	N
	TL:	Melissa Hulett	N
Office of Prescription Drug Promotion	Jessica Cleck Derenick		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIostatistics</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Robert Temple	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): February 26, 2012	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input checked="" type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

HIREN PATEL
11/29/2012