CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205422Orig1s000
205422Orig2s000

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/BLA #	**NDA 205422/Orig-1** (adjunctive MDD) **& NDA 205422/Orig-2** (Schizophrenia)
Product Name:	RESULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

PMR/PMC Description: **PMC 2929**-1 - Deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing brexpiprazole in the relevant pediatric population.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission **(331-10-233)**:	03/2014(Submitted)
	Study/Trial Completion:	05/2016
	Final Report Submission:	11/2016
	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

Schizophrenia is much more common in adult population. Therefore, the pharmacokinetics, efficacy and safety of Brexpiprazole 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."

Reference ID: 3790553

The goal of this pediatric pharmacokinetic study is to characterize pharmacokinetic features of Brexpiprazole 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.

Pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing brexpiprazole in the relevant pediatric population.

Reference ID: 3790553

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

Reference ID: 3790553

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)

Reference ID: 3790553

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/BLA #	**NDA 205422/Orig-1** (adjunctive MDD) **& NDA 205422/Orig-2** (Schizophrenia)
Product Name:	RESULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
PMR/PMC Description:	**PMC 2929**-2 - Deferred pediatric study under PREA for the treatment of schizophrenia in children aged 13 to 17 years. Conduct a Phase 3, Efficacy: multicenter, randomized, double-blind, trial with two phases: Phase 1 placebo- and active-controlled, short-term (6 weeks) study; Phase 2 – active-controlled long-term extension (26 weeks) study. Goal of both phases is to obtain data on the efficacy and safety of brexpiprazole in the relevant pediatric population.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission **(331-10-234)**:	06/2016
	Study/Trial Completion:	12/2020
	Final Report Submission:	06/2021
	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

   Schizophrenia is much more common in adult population. Therefore, the efficacy and safety of Brexpiprazole 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."

Reference ID: 3790553

The goal of both phases of this pediatric study is to obtain data on the efficacy and safety of Brexpiprazole for the treatment of schizophrenia in children ages 13 to 17 years.

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 schizophrenia in pediatric patients aged 13 to 17 is required under PREA to obtain data on efficacy and safety of brexpiprazole in children ages 13 to 17 years.

Reference ID: 3790553

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 efficacy and safety 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?
☒ 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

Reference ID: 3790553

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)

Reference ID: 3790553

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/BLA #	**NDA 205422/Orig-1** (adjunctive MDD) **& NDA 205422/Orig-2** (Schizophrenia)
Product Name:	RESULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
PMR/PMC Description:	**PMC 2929**-3 - Deferred pediatric study under PREA for the treatment of schizophrenia in adolescents aged 13 to17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (2 years) study to obtain data on the safety of brexpiprazole in the relevant pediatric population.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission **(331-10-236)**:	06/2016
	Study/Trial Completion:	12/2022
	Final Report Submission:	06/2023
	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

Schizophrenia is much more common in adult population. Therefore, the efficacy and safety of Brexpiprazole 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."

Reference ID: 3790553

The goal of this pediatric study is to obtain long-term safety data on the use of Brexpiprazole for the treatment of schizophrenia in children ages 13 to 17 years.

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 schizophrenia in pediatric adolescent patients aged 13 to 17 is required under PREA to obtain long-term safety data on the use of brexpiprazole in children ages 13 to 17 years.

Reference ID: 3790553

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)
Long-term pediatric safety study

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

Reference ID: 3790553

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)

Reference ID: 3790553

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/BLA #: **NDA 205422/Orig-1** (adjunctive MDD) **& NDA 205422/Orig-2** (Schizophrenia)

Product Name: RESULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

PMR/PMC Description: **PMC 2928**-1 - A placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients who require adjunctive treatment of major depressive disorder.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	03/2016
Study/Trial Completion:	12/2021
Final Report Submission:	06/2022
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

A maintenance study is not required prior to approving new drugs for the adjunctive treatment of major depressive disorder (MDD). Typically, this is a postmarketing commitment.

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."

Reference ID: 3790553

This study has been requested to be conducted as a PMC to assess long-term efficacy. This PMC request is not based on safety concerns.

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.

This study must be a relapse prevention study with a randomized withdrawal design in the adult population who requires adjunctive treatment for MDD.

Note: The Sponsor agrees to this postmarketing commitment (PMC) and would like to discuss with FDA an appropriate design, the draft protocol, and timelines. They p propose to submit a meeting request post-approval to further discuss the details of the PMC.

Reference ID: 3790553

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

Reference ID: 3790553

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.*

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(signature line for BLAs)

Reference ID: 3790553

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/BLA # **NDA 205422/Orig-1** (adjunctive MDD) **& NDA 205422/Orig-2** (Schizophrenia)
Product Name: RESULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

PMR/PMC Description: **PMC 2929-4** - A placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients with schizophrenia.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	09/2012(Submitted)
	Study/Trial Completion:	02/2015(Completed)
	Final Report Submission:	10/2015
	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

   A maintenance study is not required prior to approving new drugs for the treatment of schizophrenia. Typically, this is a postmarketing commitment.

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."

Reference ID: 3790553

This study has been requested to be conducted as a PMC to assess long-term efficacy. This PMC request is not based on safety concerns.

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.

This study must be relapse prevention study with a randomized withdrawal design in the adult population with a diagnosis of schizophrenia.

Reference ID: 3790553

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

Reference ID: 3790553

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)

Reference ID: 3790553

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/s/

KOFI B ANSAH
07/10/2015

MARC B STONE
07/10/2015

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

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

Memorandum

Date: June 26, 2015

To: Kofi Ansah, Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 205422
OPDP labeling comments for Rexulti (brexpiprazole) tablets, for oral use
Labeling Review

OPDP has reviewed the proposed package insert (PI) and carton/container labeling for Rexulti (brexpiprazole) tablets, for oral use (Rexulti) that was submitted for consult on August 18, 2014. Comments on the proposed PI are based on the version sent via email from Kofi Ansah (RPM) on June 11, 2015 entitled "SCPI (06-11-15)_MASTER draft-LABEL_Brexipi (v.06-02-15).docx and the draft carton/container labeling submitted June 15, 2015.

Comments regarding the PI are provided on the marked version below.

We have no comments on the draft carton/container labeling

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
06/26/2015

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 23, 2015
To:	Mitchell Mathis, M.D. Acting Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Melissa Hulett, MSBA, MSN, FNP-BC, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Susannah O'Donnell, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	REXULTI (brexpiprazole)
Dosage Form and Route:	tablet
Application Type/Number:	NDA 205422
Applicant:	Otsuka Pharmaceutical Development & Commercialization, Inc.

1 INTRODUCTION

On July 11, 2014, Otsuka Pharmaceutical Development & Commercialization, Inc submitted for the Agency's review an original New Drug Application (NDA) for REXULTI (brexpiprazole) tablets as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and as a monotherapy for the treatment of patients with schizophrenia.

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 August 8, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Otsuka Pharmaceutical Development & Commercialization, Inc.

2 MATERIAL REVIEWED

- Draft REXULTI (brexpiprazole) MG received on July 11, 2014, and received by DMPP on June 11, 2015.
- Draft REXULTI (brexpiprazole) received on July 11, 2014, and received by OPDP on June 11, 2015.
- Draft REXULTI (brexpiprazole) tablets Prescribing Information (PI) received on July 11, 2014, revised by the Review Division throughout the review cycle, and received by DMPP June 11, 2015.
- Draft REXULTI (brexpiprazole) tablets Prescribing Information (PI) received on July 11, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on June 11, 2015.
- Approved ABILIFY (aripiprazole) comparator labeling dated December 12, 2014.

3 REVIEW METHODS

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 Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG is consistent with the approved comparator labeling where applicable.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

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/

SHARON W WILLIAMS
06/23/2015

SUSANNAH O'DONNELL
06/23/2015

MELISSA I HULETT
06/23/2015

LASHAWN M GRIFFITHS
06/23/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 22, 2015
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 205422
Product Name and Strength:	Rexulti (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
Submission Date:	June 15, 2015
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd.
OSE RCM #:	2014-1688
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised Rexulti container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.[1]

2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations.

[1] Holmes L. Labels and Labeling Review for Rexulti (NDA 205422). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Mar 19. 16 p. OSE RCM No.: 2014-1688.

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Reference ID: 3782729

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/s/

LORETTA HOLMES
06/22/2015

DANIELLE M HARRIS
06/22/2015

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 29, 2015

TO: Kofi Ansah, Regulatory Project Manager
Tiffany Farchione, M.D., Clinical Reviewer/Deputy Director
Division of Psychiatry Products (DPP)

FROM: Jenn Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.,
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205422

APPLICANT: Otsuka Pharmaceutical Company, Ltd.

DRUG: Brexpiprazole

NME: Yes

REVIEW: Standard Review

INDICATION: Adjunctive therapy for Major Depressive Disorder (MDD) and monotherapy for schizophrenia

CONSULTATION REQUEST DATE: September 19, 2014

CLINICAL INSPECTION SUMMARY DATE: May 11, 2015
DIVISION ACTION GOAL DATE: July 10, 2015
PDUFA DATE: July 11, 2015

I. BACKGROUND

The sponsor Otsuka Pharmaceutical Company, Ltd., conducted 2 well-controlled clinical trials (Study 331-10-227 and Study 331-10-228) in support of approval of brexpiprazole for the adjunctive therapy of major depressive disorder (MDD) and 2 well-controlled clinical trials (Study 331-10-230 and Study 331-10-231) in support of approval of brexpiprazole for the treatment of schizophrenia. A brief description of the protocols selected for audit, is provided in the following section.

Study 331-10-227 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm, short-term efficacy study that compared 2 fixed doses of brexpiprazole (1 mg/day and 3 mg/day) to placebo as adjunctive therapy in the treatment of adult MDD patients aged 18 and 65 years who had incomplete responses to anti-depressant therapy. The primary study objective was to evaluate the additional treatment effect of brexpiprazole to anti-depressant therapy and the safety.

Briefly, the study design was as follows: all eligible subjects at the baseline visit entered an 8-week monotherapy anti-depressant therapy (ADT) phase (Phase A). At the end of Phase A (Week 8 visit), nonresponders to ADT were randomized 1:1:1 into 3 groups: brexpiprazole 1 mg/day + ADT; brexpiprazole 3 mg/day + ADT; and placebo + ADT for a 6-week double blind treatment phase (Phase B). Those who responded to ADT continued their ADT treatment regime for another 6 weeks.

The study primary efficacy measurement was the change from baseline (end of Phase A [Week 8]) to the end of Phase B (Week 14) in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score.

According to the sponsor, 93.6% of subjects completed the study. However, neither adjunctive 3 mg/day brexpiprazole ($p = 0.0327$) nor adjunctive 1 mg/day ($p = 0.0925$) met the prespecified criteria for statistical significance.

Study 331-10-228 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-arm, short-term efficacy study that compared 1 fixed dose of brexpiprazole (2 mg/day) to placebo as adjunctive therapy in the treatment of adult MDD patients aged 18 and 65 years who had incomplete responses to anti-depressant therapy. The study design was the same with 331-10-227 except the study dose of brexpiprazole was 2 mg/day.

Study results showed that adjunctive brexpiprazole 2 mg/day was superior to placebo +ADT for the primary endpoint of mean change from baseline to endpoint in MADRS Total Score

Study 331-10-230 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 4-arm, short-term efficacy study that compared 3 fixed-dose of brexpiprazole (4, 2, and 1

mg/day) to placebo in the treatment of adult patients aged 18 and 65 years with acute schizophrenia.

The primary study objective was to compare the efficacy of each of three fixed doses of brexpiprazole with placebo in the treatment of acute schizophrenia in adults.

Subjects who met eligibility criteria were enrolled into a 6-week double-blind treatment phase and randomized in a 3:3:2:3 ratio to receive either brexpiprazole 4 mg/day, brexpiprazole 2 mg/day, brexpiprazole 1 mg/day, or placebo, respectively.

The study primary efficacy measurement was change from baseline to endpoint (Week 6) in Positive and Negative Syndrome Scale (PANSS) Total Score.

The study results showed that among 3 fixed brexpiprazole doses (4, 2, and 1 mg/day), only 4 mg/day was superior to placebo in the primary efficacy endpoint, change in PANSS Total Score from baseline to endpoint (Week 6) (LS mean difference = −6.47, p = 0.0022).

Study 331-10-231 was a phase 3, multicenter, randomized, double-blind, placebo-controlled 4-arm, short term efficacy study that compared 3 fixed-dose brexpiprazole (4, 2, and 0.25 mg/day) to placebo in the treatment of adult patients aged 18 and 65 years with acute schizophrenia.

The study design was similar to that of Study 331-10-230 except study doses and randomization ratio was different: eligible subjects were enrolled into a 6-week, double-blind treatment phase and randomized in a 2:2:1:2 ratio to receive either, brexpiprazole 4 mg/day, brexpiprazole 2 mg/day, brexpiprazole 0.25 mg/day, or placebo. The study primary efficacy measurement was the same: the change from baseline to endpoint (Week 6) in PANSS Total Score.

The study results showed that both brexpiprazole 4 mg/day and 2 mg/day were superior to placebo in the primary efficacy endpoint, change in PANSS Total Score from baseline to endpoint (Week 6) ($p < 0.01$ and $p < 0.0001$, respectively).

Division of Psychiatry Products (DPP) requested inspection of four clinical investigator sites because data generated from these sites were considered essential to support the new drug application (NDA) approval. These sites were selected for inspection primarily due to their large enrollment of subjects.

The Office of Scientific Investigations (OSI) made a decision to inspect the sponsor, Otsuka, because brexpiprazole is a new molecular entity (NME) and the sponsor inspection was considered essential to ensure that there were no data integrity concerns with the data submitted for this application.

II. RESULTS (by Site):

Name of Clinical Investigator (CI) Location	Protocol Study Site Number of Subjects Enrolled (n)	Inspection Dates	Classification *
Beal Essink, M.D. Oregon Center for Clinical Investigations, Inc. 2232 NW Pettygrove Street Portland, OR 97210	331-10-227 Site #206 N = 15	10/27/2014 to 11/06/2014	VAI
Alexander E. Horwitz, M.D. Oregon Center for Clinical Investigations, Inc. 702 Church St. NE Salem, OR 97301	331-10-228 Site #215 N = 38	10/27/2014 to 11/14/2014	VAI
Scott Segal, M.D. Segal Institute for Clinical Research 1065 Northeast 125th Street Suite 300 North Miami, Florida 33161	331-10-230 Site #507 N = 31	12/03/2014 12/04/2014 12/05/2014 12/08/2014 12/18/2014 12/22/2014	NAI
David Walling, Ph.D. Collaborative Neuroscience Network, LLC 12772 Valley View Street Suite 3 Garden Grove, CA 92845	331-10-231 Site #525 N = 41	01/20/2015 to 01/23/2015	NAI
Sponsor: Name and Location Otsuka Pharmaceutical Company, Ltd. 2440 Research Boulevard, Rockville, MD 20850	331-10-227 Site #206 N = 15 331-10-228 Site #215 N = 38 331-10-230 Site #507 N = 31 331-10-231 Site #525 N = 41	11/12/2014 to 11/19/2014	NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Deviation(s) from regulations. Data acceptable
OAI = Significant deviations from regulations. Data unreliable
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Beal Essink, M.D.**
2232 NW Pettygrove Street, Portland, OR 97210

   a. **What was inspected**: At this site, 63 subjects were screened, 51 subjects entered Phase A+ of the study, 15 subjects were randomized into Phase B of the study, and a total of 38 subjects completed either Phase A+ or Phase B of the study. A complete review of all case histories for 15 subjects who were randomized into the double-blind Phase B of the study, and the informed consent forms, adverse events (AEs), and concomitant medications for all other subjects.

   b. **General observations/commentary:** Significant regulatory violations were noted, and Form FDA 483 was issued citing two inspectional observations. Specifically, the inspection of Dr. Essink's site revealed the following findings:

(b) (4)

CGI-I: Clinical Global Impression-improvement
HMD: Hamilton Depression Scale
IDS-SR: Inventory of Depressive Symptomatology (Self Report)
HAM-A: Hamilton Anxiety Rating Scale

(b) (4)

Dr. Essink adequately responded to the inspection findings in a letter dated November 13, 2014, and states that he has implemented new policies to prevent the recurrence of the inspection findings.

c. **Assessment of data integrity**: The above observations are isolated findings and are unlikely to impact data integrity. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Alexander E. Horwitz, M.D.**
702 Church St. NE, Salem, OR 97301

a. **What was inspected**: At this site, 89 subjects were screened, 22 subjects entered Phase A+ of the study, 38 subjects were randomized into Phase B of the study, and a total of 55 subjects completed either Phase A+ or Phase B of the study. An audit of all screened subjects' records for the protocol was conducted.

b. **General observations/commentary:** A Form FDA 483 was issued citing two inspectional observations. Specifically, the inspection of Dr. Horwitz's site revealed the following findings:

(b) (4)

(b) (4)

Dr. Horwitz adequately responded to the inspection findings in a letter dated December 2, 2014, and states that he plans to implement corrective actions to prevent the recurrence of the inspection findings.

c. **Assessment of data integrity:** Although regulatory violations were noted above, it is unlikely based on the nature of the violations that they significantly affect overall reliability of safety and efficacy data from the site. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. **Scott Segal, M.D.**
1065 Northeast 125th Street, Suite 300, North Miami, Florida 33161

a. **What was inspected:**
This site was previously inspected in January, 2013 (IND 101871) in response to a complaint (Complaint # 3742). Specifically, the complainant alleged that Dr. Segal enrolled a subject with a diagnosis of bipolar disorder in a schizophrenia study.

The inspection found that Subject #S0014 was enrolled and randomized in the schizophrenia study (Protocol # 331-10-230). Post enrollment verification of the site's database, during the course of the inspection, disclosed this subject had previously participated in a bipolar study (Protocol # RGH-MD-36).

The field classified the inspection as VAI for failure to conduct Protocol 331- 10-230 in accordance with the investigational plan because Dr. Segal did not verify Subject #S0014's prior participation in the previous bipolar disorder trial (Protocol #RGH-MD-36).

However, the final headquarters classification was NAI due to the fact that the protocol did not exclude subjects with a prior diagnosis of bipolar disorder, and Dr. Segal responded to the inspection finding in a letter dated February14, 2013, specifically providing supportive evidence to confirm the subject's diagnosis of schizophrenia.

At this site, 57 subjects were screened, 31 subjects enrolled, and 17 subjects

completed the study. This inspection reviewed all data listings, and covered subjects since the inspection in January 2013 (2 subjects' ICF and 7 subjects' complete source).

b. **General observations/commentary:** The data listing of all 57 subjects were reviewed and verified at the clinical site. There was no evidence of under-reporting of AEs. Primary efficacy endpoint data were verifiable. No significant regulatory violations were noted and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. **David Walling, Ph.D.**
12772 Valley View Street Suite 3, Garden Grove, CA 92845

a. **What was inspected:** At this site, 71 subjects were screened, 41 were enrolled, and 33 completed the study. A complete review of 18 subject records including all 12 subjects in the brexpiprazole 2 mg dose group; the PANSS Total Scores for all 41 enrolled subjects; and an audit of other subject records were conducted. The inspection also covered regulatory files such as the FDA 1572, informed consent forms for all 71 screened subjects, and IRB.

b. **General observations/commentary:** The data listing of all subjects reviewed were verified at the clinical site. The primary efficacy endpoint (PANSS Total Scores) and the key secondary efficacy endpoint (CGI-S) data were verifiable. There was no evidence of under-reporting of AEs. No significant regulatory violations were noted and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5. **Otsuka Pharmaceutical Company, Ltd.**
2440 Research Boulevard, Rockville, MD, 20850

a. **What was inspected**: The oversight plan, the monitoring reports and correspondence, regulatory documents, work instructions (WI), and Transfers of Regulatory Obligations (TOROs) were reviewed.

In addition, the study records for Site #206 (Protocol 331-10-227) and Site #215 (Protocol 331-10-228), Site #507 (Protocol 331-10-230), and Sites #525 and 541 (Protocol 331-10-231) were reviewed. The records reviewed included monitoring reports and correspondence, completed Form FDA 1572s, Institutional Review Board (IRB) approvals, financial disclosure forms,

approved informed consent forms, standard operation procedures (SOP), serious adverse event (SAE) reporting, drug accountability, and training records.

b. **General observations/commentary:** No significant regulatory violations were noted and no Form FDA 483 was issued. The sponsor generally maintained adequate oversight of the clinical trial. The monitoring of the investigator sites was adequate. There was no evidence of under-reporting of AEs.

c. **Assessment of data integrity:** The sponsor monitoring of sites appeared to be reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator sites and the sponsor were inspected in support of NDA #205422.

For Drs. Essink and Horwitz's sites, regulatory violations were noted but these violations were unlikely to impact data integrity. For the inspection of Drs. Segal and Walling's sites and the sponsor, no violations were noted.

Based on results of these inspections, data submitted by the Applicant in support of the requested indication are considered reliable.

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D. F.A.A.P.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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/s/

JENN W SELLERS
04/30/2015

SUSAN D THOMPSON
04/30/2015

KASSA AYALEW
04/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 19, 2015
Requesting Office or Division:	Division of Psychiatry Products
Application Type and Number:	NDA 204522
Product Name and Strength:	Rexulti (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otsuka Pharmaceutical Company, Ltd.
Submission Date:	July 11, 2014 and February 27, 2015
OSE RCM #:	2014-1688
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS

Reference ID: 3718385

1 REASON FOR REVIEW

The Division of Psychiatry Products asked the Division of Medication Error Prevention and Analysis (DMEPA) to review the proposed labels and labeling for Rexulti (brexpiprazole) Tablets (NDA 204522) to determine if they are at risk for confusion that can result in medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling noted the following areas of needed improvement:

- The layout and or size of product identifying information on the container labels, (b) (4) and carton labeling is not optimal and should be revised for improved readability and clarity.

- In the Prescribing Information, there is an inconsistency between the administration information contained in the Highlights of Prescribing Information and Full Prescribing Information Section 2 with that contained in Full Prescribing Information Section 17. The discrepancy should be reconciled for consistency between all three sections.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the labels and labeling where product information needs to be relocated, resized, or clarified in order to help ensure the safe use of the product. We provide

recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing and Full Prescribing Information, Sections 2 and 17

There is an inconsistency between the administration information contained in Highlights of Prescribing and Full Prescribing Information Sections 2 and 17. Section 17 states that (b) (4) This information is not provided in Highlights or Section 2. We recommend reconciling this discrepancy in the insert labeling.

4.2 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICALS COMPANY

We recommend the following is implemented prior to approval of this NDA:

A. All Container Labels and Carton Labeling

1. Revise the dosage form "tablets" to the same font and font size as the active ingredient to ensure compliance with 21 CFR 201.10(g)(2).

2. The statement of strength lacks prominence due to its small size. Additionally, the colored background area in the upper right triangle used to differentiate the strengths is too small in size, resulting in inadequate strength differentiation within the product line. Increase the font size of the statement of strength. Consider relocating the statement of strength to the lower right corner triangle and applying the colored background to that area, or use other means, in order to facilitate an increase in the font size and a larger colored background area.

3. The (b) (4) colors used to differentiate the 0.5 mg and 1 mg strengths are similar and do not provide sufficient differentiation between the two strengths. We recommend the use of a different color for one of the strengths (one that is not similar to those used to differentiate the other strengths). Additionally, the (b) (4) background used to provide differentiation for the 4 mg strength overlaps with the large (b) (4) main background on the principal display panel and thus does not provide sufficient differentiation. Consider using a colored background (one that is not similar to those used to differentiate the other strengths) for the 4 mg strength in order to improve its differentiation.

4. The 1 mg statement of strength (b) (4) lacks sufficient contrast against the "yellow" background. Increase the contrast by using a dark font color (e.g., black) or by using other means.

5. The three middle digits of the NDC number are sequential from a lower to higher number starting with the lowest tablet strength (e.g., XXXXX-035-XX and XXXXX-036-XX). Similarity in product code numbers has led to selecting and dispensing of the wrong strength. To help minimize product selection errors, we recommend that you increase the prominence of the three middle digits by increasing their size in comparison to the remaining digits or put them in bold type (e.g., XXXXX-035-XX or XXXXX-**036**-XX).[1]

6. The statement [redacted] (b) (4) is redundant and contributes to clutter on the principal display panel. Consider deleting the statement since there is already a statement on the side panel that conveys the same information.

7. The Medication Guide (MG) statement, as currently presented, does not state how the MG is provided as required per 21 CFR 208.24 (d). We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton. Place on the principal display panel in a prominent and conspicuous manner:

    a. "Dispense the enclosed Medication Guide to each patient" or

    b. "Dispense the accompanying Medication Guide to each patient"

[redacted] (b) (4)

See Comments A.1, A.3, A.4 and A.5, above.

[1] See the FDA guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* available at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm349009.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rexulti that Otsuka Pharmaceutical Company submitted on October 14, 2014.

Table 2. Relevant Product Information for Rexulti

Initial Approval Date	N/A
Active Ingredient	Brexpiprazole
Indication	Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) Treatment of schizophrenia
Route of Administration	Oral
Dosage Form	Tablets
Strengths	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
Dose and Frequency	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, or 4 mg orally once daily
How Supplied	

Tablet Strength	Pack Size
0.25 mg	Bottle of 30 (b) (4)
0.5 mg	Bottle of 30 (b) (4)
1 mg	Bottle of 30 (b) (4)
2 mg	Bottle of 30 (b) (4)
3 mg	Bottle of 30 (b) (4)
4 mg	Bottle of 30 (b) (4)

Storage	Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Container Closure	(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Rexulti labels and labeling submitted by Otsuka Pharmaceutical Company on February 27, 2015.

- Container labels
- Carton labeling (Retail (b) (4)
- (b) (4)
- Prescribing Information (no image)

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

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

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/s/

LORETTA HOLMES
03/19/2015

IRENE Z CHAN
03/19/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: March 10, 2015

From: Carrie Ceresa, Pharm D, MPH
Clinical Analyst, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Tamara Johnson, M.D., M.S., Acting Team Leader
Division of Pediatric and Maternal Health
Office of New Drugs

Hari Cheryl Sachs, M.D., Team Leader
Division of Pediatric and Maternal Health
Office of New Drugs

Lynne Yao, M.D., Acting Director
Division of Pediatric and Maternal Health
Office of New Drugs

To: Division of Psychiatry Products (DPP)

Drug: Rexulti (brexpiprazole /OPC-34712)

NDA: 205422

Subject: DPMH Labeling Recommendations and PeRC Preparation Assistance

Applicant: Otsuka Pharmaceutical Company, Ltd

Materials Reviewed:

- July 11, 2014, Original NME NDA 205422 submission

- April 24, 2014, DARRTS, Agreed upon initial Pediatric Study Plan (iPSP) for Schizophrenia and MDD.
- August 22, 2014, amended iPSP for Schizophrenia submitted by the Applicant.

Consult Question: "DPP is requesting this consultation with PMHS [now DPMH] to solicit your input on all relevant sections of the label, e.g., Section 8 - use in specific populations (pregnancy, labor and delivery, nursing mothers, pediatric use), highlights, patient counseling, and med guide."

INTRODUCTION

On July 11, 2014, Otsuka submitted original New Drug Application NDA 205422 for Brexpiprazole (OPC-34712) tablets as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and as monotherapy for the treatment of patients with schizophrenia. The proprietary name Rexulti was conditionally accepted by the FDA on November 24, 2014.

DPP consulted DPMH to review and update the Pregnancy, Lactation and Pediatrics information in the brexpiprazole labeling and to assist with the preparation of the PeRC paper work. This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Pediatrics subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Product Background

Brexpiprazole is an atypical antipsychotic with a similar molecular structure to aripiprazole. Brexpiprazole is a serotonergic-noradrenergic-dopamineric acting product that binds with high affinity to serotonin, dopamine and noradrenergic receptors. The exact mechanism of action is unknown; however, brexpiprazole has shown to be a partial agonist at serotonin 1A and $D_{2/3}$ receptors and strongly antagonistic at 5-HT_{2A}, $\acute{\alpha}_{1B}$ - and $\acute{\alpha}_{2C}$ - adrenergic receptors.[1]

Schizophrenia

Signs of schizophrenia normally manifest in the teen years or early adulthood. Some signs and behaviors include but are not limited to hearing voices, seeing things that do not exist, bizarre thoughts, moodiness, confusion, paranoia and withdrawal. Schizophrenia is a condition that typically requires chronic treatment.[2] The following atypical antipsychotics are currently FDA approved for schizophrenia:

[1] Maeda, K., Lerdrup, L., Sugino, H., Akazawa, H., Amada, N., McQuade, R., et al. (2014). Brexpiprazole II: Antipsychotic-Like and Procognitive Effects of a Novel Serotonin-Dopamine Activity Modulator. The Journal of Pharmacology and Experimental Therapeutics, 350:605-614. http://dx.doi.org/10.1124/jpet.114.213819

[2] American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5. Washington, D.C: American Psychiatric Association.

Reference ID: 3713376

Drug Name	Approval	Comments
*Aripiprazole	Adults and adolescents 13 – 17 years	Also approved for Tourette's disorder (6 to 17years)
Asenapine	Adults only	Final report for pediatric studies submitted Sept 2014
Clozapine	Adults only	PREA requirements waived
Iloperidone	Adults only	Pediatric PREA PMR (ongoing)
Lurasidone	Adults only	Pediatric PREA PMR (ongoing)
*Olanzapine	Adults and adolescents 13 – 17 years	
*Quetiapine	Adults and adolescents 13 – 17 years	
*Risperidone	Adults and adolescents 13 – 17 years	
Paliperidone	Adults and adolescents 12 – 17 years	
Ziprasidone	Adults only	Pediatric PREA PMR (ongoing)

*Also available as a long acting injectable antipsychotics approved for adults only

Symptoms of schizophrenia in women usually manifest in adulthood during the reproductive years. Pregnancy and schizophrenia is associated with many obstetrical adverse outcomes such as prematurity, low birth weights, small for gestational age (SGA), stillbirth, death and low APGAR score.[3] It is not clear if these adverse outcomes are due to the illness itself or that many females with schizophrenia often have poor prenatal habits such as lack of prenatal care, poor eating habits, smoking and often illegal drug use. Therefore, discontinuing medication use during pregnancy in women with schizophrenia can be detrimental to the woman and the fetus.

Schizophrenia in children is very rare but can manifest as early as the age of 5.[4] Schizophrenia in children is hard to diagnose and recognize but usually begins with unusual behavior and thought patterns.[5] Symptoms in children and adolescents can be different from those seen in adults with schizophrenia. A child's behavior can also change overtime as the symptoms worsen and the child becomes more withdrawn.

[3] Robinson, G. (2012). Treatment of Schizophrenia in Pregnancy and Postpartum. *J Popul Ther Clin Pharmcol*, 19(3):e380-e386.
[4] Rogge, T., Zieve, D., Ogilvie, I. Editorial Team. Schizophrenia. U.S. National Library of Medicine. National Institutes of Health. http://www.nlm.nih.gov/medlineplus/ency/article/000928.htm Web 30 Dec 2014.
[5] American Academy of Child and Adolescent Psychiatry. Facts for Families, Schizophrenia in Children No. 49. November 2012.

Reference ID: 3713376

Major Depressive Disorder (MDD)

MDD is a type of depressive disorder that includes severe symptoms of depression which interfere with life such as the inability to sleep, work and eat. Episodes can occur in as few as once in a lifetime but most individuals experience more than one episode. Depressive disorders are disorders of the brain that are a combination of genetic, environmental and biological elements. The most common treatments include medication and psychotherapy.[6] Aripiprazole is the only atypical antipsychotic currently FDA approved for MDD and only in adults. Other drug products used to treat MDD include selective-serotonin reuptake inhibitors (SSRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and norepinephrine-serotonin reuptake inhibitors (SNRIs). The following SSRI's are FDA approved in pediatric patients: escitalopram (12 – 17 years) and fluoxetine (8 - ≤18 years).

Depression often begins in the reproductive years in women between 20 and 30 years of age. Approximately, one in four women deal with depression in their lifetime.[7] Estimated rates of pregnant women experience depression are 18.4% and 7.3% for major depressive disorder.[8] Depression during pregnancy is linked to poor prenatal care and an increase use of alcohol, cigarettes and illegal drugs. Likewise, untreated depression has also been linked to adverse fetal outcomes such as preeclampsia, miscarriage, short for gestational length, preterm birth, small for gestational age and low APGAR scores.[8]

The occurrence rates of MDD in children are approximately between 0.5 and 2.5% and in pre-adolescents from 2.5 to 8%.[9] In adolescents, rates of depression increase from ages 13 to 18.[10] Major Depressive Disorder in adolescents is associated with long-term morbidities, impaired social functioning, substance abuse and suicide risk.[11]

DISCUSSION

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[12] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of

[6] What is Depression? National Institute of Mental Health. National Institutes of Health. http://www nimh nih.gov/health/topics/depression/index.shtml Web 31 December 2014.
[7] Kahn, D., Moline, M., Ross, R., Cohen, L., Altshuler, L. Major Depression During Conception and Pregnancy: A Guide for Patients and Families. www.womensmentalhealth.org. Web 31 December 2014.
[8] Epstein, R., Moore, K., Bobo, W. (2014). Treatment of nonpsychotic major depression during pregnancy: patient safety and challenges. *Drug, Healthcare, and Patient Safety*, 6:109-129.
[9] Choe CJ, Emslie GJ, Mayes TL. (2012). Depression. *Child Adolesc Psychiatric Clin N Am*, 21:807-829.
[10] Avenevoli, S., Swendsen, J., He, J., Burstein, M., Merikangas, K. (2015). Major Depression in the National Comorbidity Survey-Adolescent Supplement: Prevalence, Correlates, and Treatment. *J Am Acad Child Adolesc Psychiatry*, 54(1):37-44.
[11] US Preventive Services Task Force. (2009). Screening and Treatment for Major Depressive Disorder in Children and Adolescents: US Preventative Services Task Force Recommendation Statement. *Pediatrics*, 123(4): 1223-1228.
[12] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

Reference ID: 3713376

reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[13] format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will officially take effect on June 30, 2015. In the meantime, conversion to the PLLR format is voluntary. The recommendations in this review are consistent with the PLLR format.

Pregnancy

A search of published literature was performed and no data was found with the use of brexpiprazole in pregnant women. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits given brexpiprazole during organogenesis at doses 73 times and 146 times the maximum recommended human dose. Decreased body weight, ossification and incidences of visceral and skeletal variations were observed in rabbit fetuses at 150 mg/kg/day, a dose where maternal toxicity was present. ,

Lactation

The Drugs and Lactation Database (LactMed)[14] was searched for available lactation data with the use of brexpiprazole, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

In animal reproduction studies, brexpiprazole was excreted in the milk of lactating rats.

Pediatrics

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products granted pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Safety and effectiveness have not been established with brexpiprazole in pediatric patients. The Applicant has submitted an Agreed initial Pediatric Study Plans (iPSP) for Schizophrenia and MDD and this Agreed iPSP constitutes the applications pediatric plan.[15] DPP agrees with the Applicants iPSP.

[13] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[14] United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
[15] April 24, 2014. DARRTS. Advice/Information Request Letters. iPSP.

Reference ID: 3713376

The Applicant has requested a partial waiver for brexpiprazole for the treatment of schizophrenia in pediatric patients ages 12 years and younger. The criteria for the waiver being that "necessary studies are highly impracticable "the disease or condition does not occur in patients in this age group or number of patients in this subgroup is small."[16] The Applicant has requested a deferral for pediatric patients ages 13 to 17 years for the schizophrenia indication to be delayed until there is sufficient efficacy and safety in adult patients with schizophrenia which has led to an approval of brexpiprazole in adults.

The Applicant has requested a full waiver for MDD in all pediatric age groups

- Pediatric patients 0-6 years: "the disease or condition does not occur in patients in this age group or number of patients in this subgroup is small."[16]
- Children 7-11 years and Adolescents 12-17 years: "The drug (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients."[17]

The initial Pediatric Study Plans for schizophrenia and MDD were reviewed by the PeRC on April 23, 2014 and March 5, 2014, respectively, and agreed upon.[18]

Of note, the Applicant submitted an amended iPSP for the schizophrenia indication on August 22, 2014. This amendment includes a change to the study population for their Phase 2 PK/PD, safety study in patients ages 13 to 17 years (Study 331-10-233). See underlined change below:

- To assess the safety, tolerability and pharmacokinetics of oral brexpiprazole in adolescent subjects with schizophrenia <u>or other related psychiatric disorders</u>.

Both Pediatric Study Plans are scheduled to be reviewed by the PeRC in the Spring of 2015.

CONCLUSION

The Pregnancy and Lactation of labeling were structured to be consistent with the PLLR. DPMH refers to the NDA action for final labeling.

DPMH LABELING RECOMMENDATIONS

Pregnancy and Nursing Mothers Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Reformat subsection per the Pregnancy and Lactation Labeling Rule (PLLR) *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
- Add contact information for the National Pregnancy Registry for Atypical Antipsychotics.

[16] Section 505B(a)(4)(B)(i) of the Pediatric Research Equity Act.
[17] Section 505B(a)(4)(A)(iii) of the Pediatric Research Equity Act
[18] May 6, 2014. DARRTS. PeRC Minutes. G. Greeley.

Reference ID: 3713376

(b) (4)

[redacted]

Pediatric Labeling

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- Provide the appropriate regulatory statement from 21 CFR 201.57(c)(9)(iv) regarding indications and age groups in which safety and effectiveness have not been established.

DPMH Labeling Excerpts

HIGHLIGHTS

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Rexulti during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Adequate and well-controlled studies have not been conducted with Rexulti in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like Rexulti, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. In animal reproduction studies, no teratogenicity was observed with oral administration of brexpiprazole to pregnant rats and rabbits during organogenesis at doses up 73 and 146 times, respectively, of maximum recommended human dose (MRHD) of 4 mg/day

(b) (4)

(b) (4)

[redacted]

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonateswhose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without

specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Brexpiprazole was not teratogenic and did not cause adverse developmental effects (b) (4)

(b) (4)

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production. Brexpiprazole is (b) (4) in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Rexulti and any potential adverse effects on the breastfed infant from Rexulti or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness (b) (4) have not been established.

17 Patient Counseling Information

Pregnancy

Advise patients that third trimester use of Rexulti may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients (b) (4) [*see Use in Specific Populations (**Error! Reference source not found.**)*].

(b) (4)

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Rexulti during pregnancy *[see Use in Specific Populations (8.1)]*.

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/s/

CARRIE M CERESA
03/10/2015

TAMARA N JOHNSON
03/10/2015

HARI C SACHS
03/10/2015
I agree with these recommendations.

LYNNE P YAO
03/11/2015

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 # 205422 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: OPC-34712 Established/Proper Name: Brexpiprazole Dosage Form: TABLETS Strengths: 0.25, 0.5, 1, 2, 3, and 4 mg		
Applicant: Otsuka Pharmaceutical Company, Ltd. Agent for Applicant (if applicable):		
Date of Application: July 11, 2014 Date of Receipt: July 11, 2014 Date clock started after UN:		
PDUFA Goal Date: July 11, 2015	Action Goal Date (if different): **July 10, 2015**	
Filing Date: September 9, 2014	Date of Filing Meeting: August 25, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only): NCE		
Proposed indication(s)/Proposed change(s): (i) Adjunctive treatment of Major Depressive Disorder & (ii) Treatment of Schizophrenia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

Reference ID: 3632303

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): IND 101871 & IND 103958

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☒		Contact DR to change goal due date from 5/11/15 to 7/11/15
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	☒	☐		
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)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

Reference ID: 3632303

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☐	
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)].**	☐	☐	☐	
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)]?** ***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***	☐	☐	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Reference ID: 3632303

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications
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.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* 8/14/14 <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☒	☐	But CSS consulted as of 8/14/14

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Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*	☒	☐		PeRC notified and PeRC meeting scheduled for 5/13/15
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☒	☐	☐	Full Waiver requested for MDD and granted 3/7/14
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? ***If no, request in 74-day letter***	☒	☐	☐	Partial Waiver & Deferral requested for Schizophrenia and granted 4/24/14
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)? ***If no, request in 74-day letter***	☐	☒	☐	Requested in 74-day Letter
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	TN request under review by DMEPA
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

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	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	PI in PLR format
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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If no, request in 74-day letter.				
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) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	PMHS Consult (8/19/14)
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9/25/13 CMC Pre-NDA & 5/12/14 Pre-NDA ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 08/25/14

BLA/NDA/Supp #: NDA 205422

PROPRIETARY NAME: OPC-34712

ESTABLISHED/PROPER NAME: Brexpiprazole

DOSAGE FORM/STRENGTH: Tablets 0.25, 0.5, 1, 2, 3, and 4 mg

APPLICANT: Otsuka Pharmaceutical Development & Commercialization, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (i) Adjunctive treatment of Major Depressive Disorder & (ii) Treatment of Schizophrenia

BACKGROUND: OTSUKA submitted this new original NME NDA for Brexpiprazole (OPC-34712); proposing two indications: Adjunctive treatment of MDD and treatment of Schizophrenia. This is a split NDA that will be reviewed under the program according to the provisions in PDUFA V.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kofi Ansah, Pharm.D.	Y
	CPMS/TL:	Paul David/ Renmeet Grewal, Pharm.D.	N
Cross-Discipline Team Leader (CDTL)	Tiffany Farchione, M.D.		Y
Clinical	Reviewer:	Tiffany Farchione, M.D.	Y
	TL:		
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial*	Reviewer:		

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products)			
	TL:		

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Clinical Pharmacology	Reviewer:	Huixia Zhang, Ph.D.	Y
	TL:	Hao Zhu, Ph.D.	Y
Biostatistics	Reviewer:	George Kordzakhia, Ph.D. & Xiang Ling, Ph.D.	Y
	TL:	Peiling Yang, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Violetta Klimek, Ph.D.	Y
	TL:	Linda Fossom, Ph.D.	N
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman, Ph.D.	Y
	TL:	Karl Lin, Ph.D.	Y
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wendy Wilson, Ph.D. & Thomas Wong, Ph.D.	Y
	TL:	David Claffey, Ph.D.	N
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe, Ph.D.	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes, Pharm.D.	Y
	TL:	Irene Chan, Pharm.D.	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:	John Lee, M.D.	N
	TL:	Janice Pohlman, M.D.	N
Controlled Substance Staff (CSS)	Reviewer:	Martin Rusinowitz & Katherine Bonson	N
	TL:	Silvia Calderon	N
Other reviewers	Minerva Hughes, Ph.D. (Biopharmaceutics Reviewer)		Y
Other attendees	Dr. Robert Temple, M.D.		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

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• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: This drug is not the first in its class & 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
• Abuse Liability/Potential **Comments**: CSS consulted	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Categorical Exclusion claimed	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Reviewer provided comments for 74-day Letter	☐ Not Applicable ☒ YES ☐ NO

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Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	Quality/Stability Data
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

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• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis Unger, M.D. (Director of ODE-I)

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 12/9/14

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

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☐	If priority review: • 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)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	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]
☒	Other Biopharmaceutics comments provided by reviewer for 74-day letter.

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

/s/

KOFI B ANSAH
09/23/2014

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205422/Original-1 and NDA 205422/Original-2

Application Type: New NDA

Name of Drug/Dosage Form: OPC-34712 (brexpiprazole) Tablet 0.25, 0.5, 1, 2, 3, and 4 mg

Applicant: Otsuka Pharmaceutical Development & Commercialization, Inc.

Receipt Date: July 11, 2014

Goal Date: July 11, 2015

1. Regulatory History and Applicant's Main Proposals

OTSUKA submitted this new original NME NDA for Brexpiprazole (OPC-34712); proposing two indications: Adjunctive treatment of MDD and treatment of Schizophrenia. This is a split NDA that will be reviewed under the program according to the provisions in PDUFA V.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (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. 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 by 10/16/14 (i.e., within 3 weeks of receiving the 74-day Letter). The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

Selected Requirements of Prescribing Information

HIGHLIGHTS GENERAL FORMAT

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

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *HL is more than 1/2 page -- Request a waiver if you haven't already.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be 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: *Wanrnings and Precautions (replace "/" with "and")*

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW 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 and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Selected Requirements of Prescribing Information

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC 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 in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. 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 in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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 in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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
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:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. 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

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW 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 and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are 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 practice."

Comment:

N/A 40. When postmarketing adverse reaction data are 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 Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

Reference ID: 3632304

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

/s/

KOFI B ANSAH
09/23/2014