

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

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

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: July 9, 2015

Reviewer(s): Danny Gonzalez, Pharm.D., M.S.,  
Risk Management Analyst  
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Team Leader: Kim Lehrfeld, Pharm.D., B.C.P.S.  
DRISK

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Drug Name(s): Brexpiprazole

Therapeutic Class: Antidepressant/Antipsychotic

Dosage and Route: 2 mg and 3 mg oral tablets (Major Depressive Disorder)  
2 mg and 4 mg oral tablets (Schizophrenia)

Application Type/Number: NDA 205422

Submission Number: ORIG-1

Applicant/sponsor: Otsuka Pharmaceutical Co., Ltd.

OSE RCM #: 2014-1556  
2014-1750

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## **EXECUTIVE SUMMARY**

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for brexpiprazole's (NDA 205422) major depressive disorder indication. The application was received from Otsuka Pharmaceutical Co., Ltd. on December 15, 2008. The Sponsor did not propose a REMS with the NDA submission.

The proposed indication is for use as (1) an adjunctive therapy to antidepressants for the treatment of major depressive disorder and (2) treatment of schizophrenia.

The evaluation of a need for REMS for the treatment of schizophrenia indication was completed under a separate review; DRISK did not recommend REMS for use in patients with schizophrenia<sup>1</sup>.

The safety concerns of interest described in this review include the risks of seizure and akathisia when used for the treatment of major depressive disorder. Based on currently available safety and efficacy data, DRISK does not recommend that a REMS is needed to ensure the benefits outweigh the risks for brexpiprazole for the treatment of major depressive disorder.

## **1 INTRODUCTION**

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for brexpiprazole, NDA 205422. A 505(b)(1) application for brexpiprazole was received by the Division of Psychiatry Products (DPP) from Otsuka Pharmaceutical Co, Ltd (Otsuka) on July 11, 2014 for adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and as a monotherapy for the treatment of patients with schizophrenia. The Sponsor did not propose a REMS for brexpiprazole.

The evaluation of a need for REMS for the treatment of schizophrenia indication was completed under a separate review; DRISK did not recommend REMS for use in patients with schizophrenia.<sup>1</sup> Therefore, this review will examine the need for additional risk management for the MDD indication.

### **1.1 PRODUCT BACKGROUND**

Brexpiprazole (OPC-34712), was selected for its partial agonistic activity at dopamine D2 receptors and antagonistic activity at serotonin 5-HT<sub>2A</sub> receptors. Brexpiprazole also has high binding affinities and acts as a partial agonist at dopamine D3 and serotonin 5-HT<sub>1A</sub> receptors. Brexpiprazole has modulatory activity at the serotonin-dopamine system that combines partial agonist activity at serotonergic 5-HT<sub>1A</sub> and at dopaminergic D2 receptors with antagonist activities at serotonergic 5-HT<sub>2A</sub> as well as

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<sup>1</sup> Refer to the REMS Review (Gonzalez D. REMS review for brexpiprazole (NDA 205422). March 19, 2015) for rationale on efficacy and safety of brexpiprazole in schizophrenia.

antagonist activity at noradrenergic  $\alpha 1/2$  receptors, and a broad spectrum of binding affinities and actions on several other central monoaminergic receptor subtypes as described further below. The balanced 5-HT<sub>1A</sub>/D<sub>2</sub> receptor partial agonist activity in combination with potent 5-HT<sub>2A</sub> and  $\alpha 1/2$  receptors antagonism of brexpiprazole may correlate with improved antipsychotic and antidepressant efficacy, better impulsivity control, and enhanced cognitive activity. Thus, this profile would be expected to predict good potential clinical outcomes for the treatment of schizophrenia, MDD, and other psychiatric disorders. Compared to aripiprazole, brexpiprazole demonstrates slightly higher D<sub>2</sub> affinity, lower intrinsic activity at D<sub>2</sub> receptors, and higher affinity at the 5-HT<sub>2A</sub> receptor.

## **1.2 DISEASE BACKGROUND**

### **1.2.1 Major Depressive Disorder**

MDD is a debilitating and chronic illness characterized by a broad spectrum of emotional and physical symptoms. It is estimated that MDD affects 7% of the US population, and despite the availability of numerous treatments (e.g., pharmacotherapy, cognitive behavioral psychotherapy, electroconvulsive therapy), achievement of consistent and favorable long-term outcomes remains an unmet medical need. For patients experiencing an initial major depressive episode, the probability of experiencing a second episode in the future can be as high as 85%. In addition, 15% of patients may endure chronic symptoms after the first episode.

Complete remission rates are low (less than 30%) for initial antidepressant monotherapy treatment and partial response is common. Incomplete response to treatment for MDD is associated with increased risk of relapse as well as impaired social and occupational functioning.

If there is an inadequate response to an adequate trial of a first-line antidepressant treatment (ADT), current guidelines recommend switching to another antidepressant (either within or across classes of drugs), adding a second antidepressant, or adjunctive therapy with a non-antidepressant drug. Although switching drugs may be viewed as a conservative option, adjunctive strategies are sometimes favored because of ease of implementation (i.e., no washout or cross titration is required). Adjunctive therapies may also build upon a partial symptomatic response to antidepressant monotherapy.

Practice guidelines emphasize the importance of adequate treatment in individuals at risk of recurrence. Adjunctive treatment with second-generation antipsychotics aripiprazole and quetiapine has been shown to be associated with significant clinical improvements in patients who had not experienced an adequate response to prior antidepressant medications and they have been approved by the Food and Drug Administration for this indication; however, these second-generation antipsychotics are associated with tolerability and/or safety concerns. Somnolence, sedation, akathisia, and weight gain are among the primary reasons for discontinuation of second-generation antipsychotic therapy. In sum, despite the efficacy of second-generation antipsychotics in the treatment

of MDD, the adverse event profile may be unacceptable to some patients, subsequently limiting their use in clinical practice.

### **1.3 REGULATORY HISTORY**

On September 27, 2013, the Agency submitted written responses to the Sponsor's Type C Meeting Request. The general safety topics addressed included the Agency's agreement to pool safety data, proposed definitions of short- and long-term open-label trials, agreement that exposure was sufficient to support the NDA, and agreed on the special safety analyses needed for glucose/lipid metabolism, weight, extra-pyramidal syndrome (EPS), QT prolongation, effect on prolactin, seizures, somnolence, orthostatic hypertension, suicidality, creatine phosphokinase (CPK) elevation and rhabdomyolysis and hypersensitivity reactions.

On February 14, 2014, the Agency issued an Information Request for examining potential risk factors for cases of seizure and other significant adverse events (AEs) and whether these cases were related to brexpiprazole and/or the brexpiprazole metabolite (DM-3411).

On March 12, 2014, the Sponsor submitted a response to the February 2014 Information Request. Otsuka conducted an assessment of seizure and examined whether exposure or accumulation due to drug-drug interactions of brexpiprazole or metabolite DM-3411 are potential risk factors for the observed cases of seizure and other significant adverse events. Based on the data, Otsuka concluded that neither brexpiprazole nor metabolite DM-3411 is a risk factor for seizures and other significant adverse events.

On July 11, 2014, the Sponsor submitted (eCTD Seq. No. 0000) NDA 205422 for review. The submission included a risk management plan which stated that the tolerability profile of brexpiprazole was well characterized and that no risk has been identified that requires a REMS.

On December 30, 2014, the Agency issued a Mid-Cycle Communication. Topics discussed included clinical pharmacology and data supporting the MDD and schizophrenia indications. The Agency reported that only 1 trial showed positive data for the MDD indication and only 1 trial was positive for both the 2 mg and 4 mg doses treating schizophrenia. The Agency did not comment on the need for a REMS in the Midcycle Communication.

On February 3, 2015, the Sponsor submitted responses to the Mid-Cycle Communication. The Sponsor noted that the data for MDD demonstrates that "the drug will have the effect it is claimed to have under the conditions of use in the target patient population as provided in the proposed labeling." The Sponsor submitted a statement describing the efficacy of both the 2 mg and 4 mg daily doses for the schizophrenia indication.

On April 2, 2015, the Late-Cycle Meeting was held with the Sponsor. At this meeting the Agency communicated that the information related to the adjunctive treatment of MDD will need to be removed from the label due to insufficient efficacy data. The Sponsor explained that the pre-specified statistical analysis plan for trial #331-10-227 was too strict and resulted in a negative outcome for the trial. The Sponsor noted that trial # 331-

10-227 can be considered a positive trial based on the retrospective application of new criteria and use of the per protocol population instead of the intent-to-treat population for the primary analysis. This would result in a more appropriate patient population for the trial.

## 2 MATERIALS REVIEWED

The following is a list of materials used to inform our review:

- Otsuka Pharmaceutical Co., Ltd. Summary of Clinical Safety. eCTD Seq. No. 0000. July 11, 2014.
- Otsuka Pharmaceutical Co., Ltd. Proposed Labeling. eCTD Seq. No. 0028. June 2, 2015.
- Farchione T. Clinical Review for brexpiprazole (NDA 205422). July 11, 2015.

## 3 REVIEW OF SAFETY CONCERNS

### 3.1 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

**Table 1. Summary of primary clinical trials - MDD**

<b>Trial #</b>	<b>Trial Description</b>
<b>Major Depressive Disorder Trials</b>	
331-08-211	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 2 Trial - Single-blind placebo (Phase A)+ ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>d</sup> (Phase B)</li> <li>• <u>N</u> = 303 brexpiprazole; 126 placebo</li> <li>• <u>Dose</u>: 0.15 mg fixed; 0.5+/-0.25 mg/day; 1.5 +/-0.5 mg/day placebo</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>e</sup> Total score from end of Phase A to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in CGI-S<sup>c</sup>, Q-LES-Q-SF<sup>f</sup>, and SDS<sup>g</sup> Total score from end of Phase 1 to week 14</li> </ul>
331-09-222	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 2 trial - Single-blind placebo (Phase A)+ ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>d</sup> (Phase B)</li> <li>• <u>N</u> = 185 brexpiprazole; 187 placebo</li> <li>• <u>Dose</u>: 1mg/day to 3 mg/day</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>e</sup> Total score from end of Phase 1 to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in SDS<sup>g</sup> Mean Score from end of Phase 1 to week 14</li> </ul>
331-10-227	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 3 Trial - Single-blind placebo (Phase A) + ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>d</sup> (Phase B)</li> <li>• <u>N</u> = 455 brexpiprazole; 220 placebo</li> <li>• <u>Dose</u>: 1mg/day; 3mg/day</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>e</sup> Total score from end of Phase A to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in SDS<sup>g</sup> Mean Score from end of Phase A to week 14</li> </ul>
331-10-228	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 3 Trial - Single-blind placebo (Phase A) + ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>d</sup> (Phase B)</li> <li>• <u>N</u> = 188 brexpiprazole; 191 placebo</li> </ul>

	<ul style="list-style-type: none"> <li>• <u>Dose</u>: 2 mg/day</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>e</sup> Total score from end of Phase A to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in SDS<sup>g</sup> Mean Score from end of Phase A to week 14</li> </ul>
331-08-212	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Long-term; Phase 2 Trial; Open-label, flexible dose extension</li> <li>• <u>N</u> = 697 brexpiprazole</li> <li>• <u>Dose</u>: 0.25 mg/day to 3 mg/day</li> <li>• <u>Duration</u>: 52 weeks of adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Safety and tolerability</li> </ul>
331-10-238	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Long-term; Phase 3 Trial; Open-label, flexible dose extension</li> <li>• <u>N</u> = 1387 brexpiprazole</li> <li>• <u>Dose</u>: 0.5 mg/day to 3 mg/day</li> <li>• <u>Duration</u>: 26 weeks of adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Safety and tolerability</li> </ul>
<p>PANNS<sup>a</sup> = Positive and Negative Syndrome Scale; PSP<sup>b</sup> = Personal and Social Performance Scale; CGI-S<sup>c</sup> = Clinical Global Impression Scale; ADT<sup>d</sup> = antidepressant therapy; MADRS<sup>e</sup> = Montgomery-Asberg Depression Rating Scale; Q-LES-Q-SF<sup>f</sup> = Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form; SDS<sup>g</sup> = Sheehan Disability Scale</p>	

### 3.2 EFFICACY<sup>2</sup>

The efficacy for brexpiprazole for MDD is supported with data from 6 Phase 2/3 clinical trials (Table 1). Overall, the clinical data provides supportive evidence that brexpiprazole 2 mg/day and 3 mg/day are efficacious as adjunctive therapy in subjects with MDD who had an inadequate response to ADT.

The totality of the data derived from clinical trials was supportive of efficacy for the 2 mg and 3 mg doses. Based on the primary analysis (change in MADRS Total Score) greater improvement was observed for fixed 2 mg/day (p = 0.0001; trial # 331-10-228) and 3 mg/day (p= 0.0327; trial # 331-10-227) doses of adjunctive brexpiprazole than adjunctive placebo. When dosed flexibly (trial # 331-08-211) in a range from 1 to 2 mg/day, adjunctive brexpiprazole was associated with greater improvement than adjunctive placebo (p = 0.0285). The p-values for the efficacy sample did not meet the threshold to validate the findings. However, the efficacy analysis focusing on the target population provided stronger evidence of efficacy in showing a greater magnitude of effect when a per protocol population was used instead of the intention to treat population identified in the original statistical analysis plan.

Based on this data, the recommended starting dose of brexpiprazole as adjunctive treatment for patients with MDD who are currently taking ADT is 0.5 mg/day or 1.0 mg/day. Dose titration up to the recommended target dose of 2.0 mg/day should occur at weekly intervals based on the patient's clinical response and tolerability. A pattern of increased response was observed at higher doses in the clinical development program. The maximum recommended dose is 3 mg/day. In addition, doses below 1 mg/day (based on trial # 331-08-211) did not demonstrate evidence of efficacy.

<sup>2</sup>Refer to the Clinical Review (Farchione T. Clinical Review for brexpiprazole (NDA 205422). July 11, 2015) for rationale on efficacy and safety of brexpiprazole in both schizophrenia and/or major depressive disorder.

Despite the statistical challenges observed in the clinical development program, the clinical reviewer notes that "...the results of trial # 331-10-227 can be viewed as supportive evidence." In addition, the clinical reviewer comments that trial #331-10-228 is a "strongly positive" trial. The reviewer concludes that "with one strongly positive trial and supportive evidence from two additional trials, there is adequate evidence of efficacy to approve this product for the adjunctive treatment of MDD."

### **3.3 SAFETY<sup>2</sup>**

#### **3.3.1 Overall Safety**

The safety database is comprised of all subjects enrolling in clinical trials through January 31, 2014. This includes at least 4,472 subjects, due to ongoing studies, who have been exposed to a dose of brexpiprazole across the Phase 2/3 trials for schizophrenia and MDD. Of these subjects, 1,035 have been exposed for at least 1 year of brexpiprazole treatment within the MDD and schizophrenia clinical trial programs. The details of the safety findings, for MDD, derived from these studies are described below.

#### **3.3.2 Major Depressive Disorder**

The clinical development program for MDD provides data for 1,131 subjects in short-term trials and 2,084 subjects in long-term open-label trials who received adjunctive brexpiprazole. A total of 1,275 subjects were exposed for  $\geq 6$  months and 822 subjects were exposed for  $\geq 1$  year. The most commonly used doses were 2 or 3 mg/day, which were used in 59% of subjects. Overall, the safety profile appears comparable to the safety profile associated with newer generation antipsychotics medications (i.e., aripiprazole).

Common AEs reported in the short-term MDD populations include akathisia and weight gain. The majority of akathisia events emerged by the time steady-state concentration was reached. These cases were reported as mild to moderate in severity and resulted in few discontinuations ( $< 1\%$  in both long- and short-term trials). The incidence of akathisia in the long-term trials were similar to the incidence observed in short-term trials. However, the incidence of akathisia was lower for fixed 2 mg (7.4%) as compared to 3 mg (13.5%). The next most frequently reported AE related to EPS was Parkinsonian syndrome (5.6% for adjunctive brexpiprazole vs. 3% placebo). Weight gain was observed in the short-term trials (1.5 kg for adjunctive brexpiprazole vs. 0.3 kg placebo) and increased in the long-term trials (3.1 kg for adjunctive brexpiprazole for subjects completing 52 weeks of treatment). Weight gain accounted for 3.6% of discontinuations due to AEs. In addition, only 1/26 subjects who had gained at least 15 kg over 52 weeks of treatment had positively met the diagnostic criteria for metabolic syndrome.

Akathisia is of special interest in the MDD study population compared to the schizophrenia population based on clinical trial data and trends in the drug class. A higher incidence of akathisia was reported in the MDD study population as compared with the schizophrenia clinical program despite the difference in maximum doses received for each indication (MDD maximum dose = 3 mg; schizophrenia maximum dose = 4 mg). In the short-term MDD trials, 8.6% of subjects treated with brexpiprazole experienced akathisia (vs. 2.8% in placebo). In the short-term schizophrenia trials, the

incidence of akathisia was 6.2 % (vs. 4.8% in placebo). These trends are similar to those observed for aripiprazole in which the incidence of akathisia is greater in the MDD clinical study population (25% aripiprazole; 4% placebo) than in the schizophrenia clinical study population (8% aripiprazole; 4% placebo).

The incidence of serious adverse events were low in placebo-controlled trials (slightly less for brexpiprazole subjects) and the pattern of SAEs showed events related to underlying depression. Furthermore, 13 cases of death were reported for both the MDD and schizophrenia trials. Investigators reported that brexpiprazole was not directly related to the cause of death in these cases. For the MDD subjects, 2 died in the short-term trials prior to randomization and 5 died in the long-term trials. All of these subjects had confounding medical and psychiatric histories that contributed to an increased risk of mortality.

There were drug class associated safety topics of special interest assessed in the trials. These included tardive dyskinesia, metabolic disturbances, neuroleptic malignant syndrome (NMS), somnolence, hypersensitivity reactions, suicidality, venous thromboembolism (VTE), and seizures. Tardive dyskinesia was rare (reported in 1 subject and resolved upon discontinuation). NMS was not reported. Somnolence was uncommon in controlled trials and the vast majority of cases were mild or moderate in severity. Hypersensitivity reactions were almost all mild or moderate in severity and 1 qualified as a serious AE. This subject received a high dose of brexpiprazole (12 mg). The incidence of suicidality was low and similar between brexpiprazole and placebo groups in the short-term trials. Evaluation of dizziness, orthostasis, syncope, and QT prolongation did not suggest a pattern that was associated with brexpiprazole. In addition, there were 6 cases of VTE in the MDD program. One occurred in a placebo-treated patient and 5 occurred in brexpiprazole subjects in long-term trials. These cases were associated with medical comorbidities including prior history of VTE, dyslipidemia, and hypertension. The 5 long-term subjects continued to receive brexpiprazole and did not have additional VTE incidents. Seizures occurred in 2 subjects in the MDD program. Overall, there were 11 cases of seizure AEs in brexpiprazole clinical trials. Of these cases, 4 occurred in non-brexipiprazole subjects (e.g., placebo, aripiprazole, non-IMP), 2 occurred under blinded conditions, and the vast majority of subjects had predisposing medical factors. The clinical reviewer agreed with the Sponsor that the association of seizures with brexpiprazole were confounded and making a causal link to brexpiprazole impossible to determine. The incidence of AEs of special interest were low and expected for 2nd generation antipsychotic medications. In addition, the clinical reviewer did not believe an advisory committee meeting was necessary for brexpiprazole because there are several previously approved agents in the atypical antipsychotic class of drugs, the evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the design and results of the efficacy trials did not pose particular concerns. In addition, laboratory assessments of special interest (i.e., white blood cell count, neutrophil count, glucose, lipids, and creatine phosphokinase) were also evaluated and showed no clinically meaningful significance. DISCUSSION

The clinical trial program has demonstrated efficacy in the MDD population. The safety profile for brexpiprazole does not present any new, unexpected safety signals compared to other atypical antipsychotic medications currently used to treat MDD. Based on the

described safety and efficacy data, the use of brexpiprazole in the treatment of patients with MDD has a favorable benefit-risk profile which is common and understood by clinicians prescribing drugs in the same class. Thus, no additional risk mitigation strategies are required beyond labeling for MDD.

#### **4 CONCLUSION**

In conclusion, based on the available data, the Office of Surveillance and Epidemiology (OSE), DRISK recommends that brexpiprazole, if approved, does not require REMS to ensure the benefits outweigh the risk for MDD.

#### **5 RECOMMENDATIONS**

The OSE, DRISK does not recommend that brexpiprazole have a REMS program for approval of the MDD indication. Comprehensive labeling discussing the risks associated with brexpiprazole will help to ensure that the benefits outweigh the risks of brexpiprazole for the MDD indication.

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/s/  
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DANNY S GONZALEZ  
07/09/2015

REEMA J MEHTA  
07/09/2015  
I concur.

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

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: March 19, 2015

Reviewer(s): Danny Gonzalez, Pharm.D., M.S.  
Risk Management Analyst  
Division of Risk Management (DRISK)

Team Leader: Kim Lehrfeld, Pharm.D., B.C.P.S.  
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Acting Deputy Director: Reema Mehta, Pharm.D., M.P.H.  
DRISK

Drug Name(s): Brexpiprazole

Therapeutic Class: Antidepressant/Antipsychotic

Dosage and Route: 2 mg and 4 mg oral tablets (Schizophrenia)

Application Type/Number: NDA 205422

Submission Number: ORIG-1

Applicant/sponsor: Otsuka Pharmaceutical Co., Ltd.

OSE RCM #: 2014-1556  
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## **EXECUTIVE SUMMARY**

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for brexpiprazole, NDA 205422, received from Otsuka Pharmaceutical Co., Ltd. on December 15, 2008. The Sponsor did not propose a REMS with the NDA submission.

The proposed indication is for use as (1) an adjunctive therapy to antidepressants for the treatment of major depressive disorder and (2) treatment of schizophrenia.

The safety concern described in this review is the risk of seizure, which was observed during the clinical development program. Based on currently available safety and efficacy data, DRISK does not recommend that a REMS is necessary to ensure the benefits outweigh the risks for brexpiprazole for the treatment of schizophrenia. DRISK defers comment regarding a REMS for the treatment of major depressive disorder due to additional data the Division of Psychiatry Products has requested the Sponsor to provide, which may impact the evaluation of the benefit-risk profile in the MDD population.

## **1 INTRODUCTION**

This review documents the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for brexpiprazole, NDA 205422. A 505 (b) (1) application for brexpiprazole was received by the Division of Psychiatry Products (DPP) from Otsuka Pharmaceutical Co, Ltd (Otsuka) on July 11, 2014 for adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and as a monotherapy for the treatment of patients with schizophrenia. The Sponsor did not propose a REMS for brexpiprazole.

### **1.1 PRODUCT BACKGROUND**

Brexpiprazole (OPC-34712), was selected for its partial agonistic activity at dopamine D2 receptors and antagonistic activity at serotonin 5-HT<sub>2A</sub> receptors. Brexpiprazole also has high binding affinities and acts as a partial agonist at dopamine D3 and serotonin 5-HT<sub>1A</sub> receptors. Brexpiprazole has modulatory activity at the serotonin-dopamine system that combines partial agonist activity at serotonergic 5-HT<sub>1A</sub> and at dopaminergic D2 receptors with antagonist activities at serotonergic 5-HT<sub>2A</sub> as well as antagonist activity at noradrenergic  $\alpha$ <sub>1/2</sub> receptors, and a broad spectrum of binding affinities and actions on several other central monoaminergic receptor subtypes as described further below. The balanced 5-HT<sub>1A</sub>/D2 receptor partial agonist activity in combination with potent 5-HT<sub>2A</sub> and  $\alpha$ <sub>1/2</sub> receptors antagonism of brexpiprazole may correlate with improved antipsychotic and antidepressant efficacy, better impulsivity control, and enhanced cognitive activity. Thus, this profile would be expected to predict good potential clinical outcomes for the treatment of schizophrenia, MDD, and other psychiatric disorders. Compared to aripiprazole, brexpiprazole demonstrates slightly higher D2 affinity, lower intrinsic activity at D2 receptors, and higher affinity at the 5-HT<sub>2A</sub> receptor.

## **1.2 DISEASE BACKGROUND**

### **1.2.1 Schizophrenia**

Schizophrenia is a severely debilitating mental illness that affects approximately 1% of the world population. The illness, typically emerging between the late teens and mid-thirties, is characterized by the presence of positive symptoms (e.g., hallucinations and delusions) as well as negative symptoms (e.g., social withdrawal and lack of emotion, energy, and motivation).

The first antipsychotics developed for the treatment of schizophrenia were dopamine D2 receptor antagonists. These agents were effective against positive symptoms (e.g., hallucinations and delusions), but showed low efficacy for negative symptoms (e.g., social withdrawal and lack of emotion, energy, and motivation) and were also associated with a high incidence of hyperprolactinemia and extrapyramidal symptoms (EPS) (including tardive dyskinesia), and other adverse drug reactions including sedation, seizure, agranulocytosis, and neuroleptic malignant syndrome (NMS). Second-generation antipsychotics, commonly referred to as “atypical antipsychotics,” are antagonists of both D2 and serotonin 5-HT<sub>2</sub> receptors and represent a significant advancement in the treatment of psychotic disorders because they are efficacious and at the same time exhibit a reduced tendency to promote EPS relative to typical antipsychotics, especially tardive dyskinesia. Moreover, treatment with atypical antipsychotics has been shown to be associated with improved safety and tolerability compared to first-generation antipsychotics.

The tolerability of second-generation antipsychotics remains an important cause of medication discontinuation due to adverse drug reactions of somnolence, sedation, akathisia, hyperprolactinemia, and weight gain. Some agents have excess rates of weight gain (e.g., olanzapine and quetiapine), while others have high rates of hyperprolactinemia and associated sexual dysfunction or sedation. Aripiprazole is the first and only D2 partial agonist to be approved by regulatory authorities for treatment of schizophrenia, but it has been associated with activating adverse drug reactions (e.g., akathisia, and insomnia). Aripiprazole is currently not approved with a REMS. Brexpiprazole, if approved, will be the second D2 partial agonist used to treat schizophrenia.

### **1.2.2 Major Depressive Disorder**

Major depressive disorder (MDD) is a debilitating and chronic illness characterized by a broad spectrum of emotional and physical symptoms. It is estimated that MDD affects 7% of the US population, and despite the availability of numerous treatments (e.g., pharmacotherapy, cognitive behavioral psychotherapy, electroconvulsive therapy), achievement of consistent and favorable long-term outcomes remains an unmet medical need. For patients experiencing an initial major depressive episode, the probability of experiencing a second episode in the future can be as high as 85%. In addition, 15% of patients may endure chronic symptoms after the first episode.

Complete remission rates are low (less than 30%) for initial antidepressant monotherapy treatment and partial response is common. Incomplete response to treatment for MDD is associated with increased risk of relapse as well as impaired social and occupational functioning.

If there is an inadequate response to an adequate trial of a first-line antidepressant treatment (ADT), current guidelines recommend switching to another antidepressant (either within or across classes of drugs), adding a second antidepressant, or adjunctive therapy with a non-antidepressant drug. Although switching drugs may be viewed as a conservative option, adjunctive strategies are sometimes favored because of ease of implementation (i.e., no washout or cross titration is required). Adjunctive therapies may also build upon a partial symptomatic response to antidepressant monotherapy.

Practice guidelines emphasize the importance of adequate treatment in individuals at risk of recurrence. Adjunctive treatment with second-generation antipsychotics aripiprazole and quetiapine has been shown to be associated with significant clinical improvements in patients who had not experienced an adequate response to prior antidepressant medications and they have been approved by the FDA for this indication; however, these second-generation antipsychotics are associated with tolerability and/or safety concerns. Somnolence, sedation, akathisia, and weight gain are among the primary reasons for discontinuation of second-generation antipsychotic therapy. In sum, despite the efficacy of second-generation antipsychotics in the treatment of MDD, the adverse event profile may be unacceptable to some patients, subsequently limiting their use in clinical practice.

### **1.3 REGULATORY HISTORY**

On September 27, 2013, the Agency submitted written responses to the Sponsor's Type C Meeting Request. The general safety topics addressed included the Agency's agreement to pool safety data, proposed definitions of short- and long-term open-label trials, agreement that exposure was sufficient to support the NDA, and agreed on the special safety analyses needed for glucose/lipid metabolism, weight, EPS, QT prolongation, effect on prolactin, seizures, somnolence, orthostatic hypertension, suicidality, CPK elevation and rhabdomyolysis and hypersensitivity reactions.

On February 14, 2014, the Agency issued an Information Request for examining potential risk factors for cases of seizure and other significant AEs and whether these cases were related to brexpiprazole and/or the brexpiprazole metabolite (DM-3411).

On March 12, 2014, the Sponsor submitted a response to the February 2014 Information Request. Otsuka conducted an assessment of seizure and examined whether exposure or accumulation due to drug-drug interactions of brexpiprazole or metabolite DM-3411 are potential risk factors for the observed cases of seizure and other significant adverse events. Based on the data, Otsuka concluded that neither brexpiprazole nor metabolite DM-3411 is a risk factor for seizures and other significant adverse events.

On July 11, 2014, the Sponsor submitted (eCTD Seq. No. 0000) NDA 205422 for review. The submission included a risk management plan which stated that the tolerability profile of brexpiprazole was well characterized and that no risk has been identified that requires a REMS.

On December 30, 2014, the Agency issued a Mid-Cycle Communication. Topics discussed included clinical pharmacology and data supporting the MDD and schizophrenia indications. The Agency reported that only 1 trial showed positive data for the MDD indication and only 1 trial was positive for both the 2 mg and 4 mg doses

treating schizophrenia. The Agency did not comment on the need for a REMS in the Midcycle Communication.

On February 3, 2015, the Sponsor submitted responses to the Mid-Cycle Communication. The Sponsor noted that the data for MDD demonstrates that "the drug will have the effect it is claimed to have under the conditions of use in the target patient population as provided in the proposed labeling." The Sponsor submitted a statement describing the efficacy of both the 2 mg and 4 mg daily doses for the schizophrenia indication.

## 2 MATERIALS REVIEWED

The following is a list of materials used to inform our review:

- Otsuka Pharmaceutical Co., Ltd. Summary of Clinical Safety. eCTD Seq. No. 0000. July 11, 2014.
- Otsuka Pharmaceutical Co., Ltd. Proposed Labeling. eCTD Seq. No. 0009. October 14, 2014.

## 3 REVIEW OF SAFETY CONCERNS

### 3.1 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

Table 1 and Table 2 summarize the primary clinical trials used to support the proposed indications.

**Table 1.** Summary of primary clinical trials - Schizophrenia.

<b>Trial #</b>	<b>Trial Description</b>
331-07-203	<ul style="list-style-type: none"> <li>• <u>Trial design:</u> Phase 2 Trial - Double-blind, placebo- and active-controlled</li> <li>• <u>N</u> = 314 brexpiprazole; 95 placebo; 50 aripiprazole</li> <li>• <u>Dose:</u> <ul style="list-style-type: none"> <li>○ Brexpiprazole: 0.25 mg fixed; 1.0 +/- 0.25mg/day; 2.5 +/- 0.5 mg/day; 5.0 +/- 1.0 mg/day</li> <li>○ Aripiprazole: 15 +/- 5.0 mg/day</li> </ul> </li> <li>• <u>Duration:</u> 6 weeks</li> <li>• <u>Primary Endpoint:</u> Change in PANNS<sup>a</sup> Total Score at Week 6</li> <li>• <u>Secondary Endpoint:</u> Change in PANSS positive; PANSS negative, PSP<sup>b</sup>, CGI-S<sup>c</sup> Score at Week 6</li> </ul>
331-10-230	<ul style="list-style-type: none"> <li>• <u>Trial design:</u> Phase 3 Trial - Double-blind, placebo-controlled</li> <li>• <u>N</u> = 490 brexpiprazole; 184 placebo</li> <li>• <u>Dose:</u> 1 mg, 2 mg, and 4 mg/day</li> <li>• <u>Duration:</u> 6 weeks</li> <li>• <u>Primary Endpoint:</u> Change in PANSS<sup>a</sup> total score at Week 6</li> <li>• <u>Secondary Endpoint:</u> Change in PANSS<sup>a</sup> total score at Week 6</li> </ul>
331-10-231	<ul style="list-style-type: none"> <li>• <u>Trial design:</u> Phase 3 Trial - Double-blind, placebo-controlled</li> <li>• <u>N</u> = 452 brexpiprazole; 184 placebo</li> <li>• <u>Dose:</u> 0.25 mg, 2 mg, and 4 mg/day</li> <li>• <u>Duration:</u> 6 weeks</li> <li>• <u>Primary Endpoint:</u> Change in PANSS<sup>a</sup> total score at Week 6</li> <li>• <u>Secondary Endpoint:</u> Change in PANSS<sup>a</sup> total score at Week 6</li> </ul>
331-08-210	<ul style="list-style-type: none"> <li>• <u>Trial design:</u> Phase 2 Trial - Open-label, flexible-dose extension</li> </ul>

	<ul style="list-style-type: none"> <li>• <u>N</u> = 244 brexpiprazole</li> <li>• <u>Dose</u>: 1 mg/day, 2 mg/day, 3 mg/day, 4 mg/day, 5 mg/day, 6 mg/day</li> <li>• <u>Duration</u>: 52 weeks</li> <li>• <u>Primary Endpoint</u>: Safety and tolerability</li> </ul>
331-10-237	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 3 Trial - Open-label, flexible-dose extension</li> <li>• <u>N</u> = 843 brexpiprazole</li> <li>• <u>Dose</u>: 1 mg/day, 2 mg/day, 3 mg/day, 4 mg/day</li> <li>• <u>Duration</u>: 52 weeks</li> <li>• <u>Primary Endpoint</u>: Safety and tolerability</li> </ul>
PANNS <sup>a</sup> = Positive and Negative Syndrome Scale; PSP <sup>b</sup> = Personal and Social Performance Scale; CGI-S <sup>c</sup> = Clinical Global Impression Scale	

**Table 2.** Summary of primary clinical trials - Major Depressive Disorder.

<b>Trial #</b>	<b>Trial Description</b>
331-08-211	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 2 Trial - Single-blind placebo (Phase A)+ ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>a</sup> (Phase B)</li> <li>• <u>N</u> = 303 brexpiprazole; 126 placebo</li> <li>• <u>Dose</u>: 0.15 mg fixed; 0.5+/-0.25 mg/day; 1.5 +/-0.5 mg/day placebo</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>b</sup> Total score from end of Phase A to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in CGI-S<sup>c</sup>, Q-LES-Q-SF<sup>d</sup>, and SDS<sup>e</sup> Total score from end of Phase 1 to week 14</li> </ul>
331-09-222	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 2 trial - Single-blind placebo (Phase A)+ ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>a</sup> (Phase B)</li> <li>• <u>N</u> = 185 brexpiprazole; 187 placebo</li> <li>• <u>Dose</u>: 1mg/day to 3 mg/day</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>b</sup> Total score from end of Phase 1 to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in SDS<sup>e</sup> Mean Score from end of Phase 1 to week 14</li> </ul>
331-10-227	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 3 Trial - Single-blind placebo (Phase A) + ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>a</sup> (Phase B)</li> <li>• <u>N</u> = 455 brexpiprazole; 220 placebo</li> <li>• <u>Dose</u>: 1mg/day; 3mg/day</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>b</sup> Total score from end of Phase A to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in SDS<sup>e</sup> Mean Score from end of Phase A to week 14</li> </ul>
331-10-228	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Phase 3 Trial - Single-blind placebo (Phase A) + ADT/double-blind, brexpiprazole, placebo-controlled + ADT<sup>a</sup> (Phase B)</li> <li>• <u>N</u> = 188 brexpiprazole; 191 placebo</li> <li>• <u>Dose</u>: 2 mg/day</li> <li>• <u>Duration</u>: Phase A = 8 weeks; Phase B = 6 weeks + 6 weeks adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Change in MADRS<sup>b</sup> Total score from end of Phase A to week 14</li> <li>• <u>Secondary Endpoint</u>: Change in SDS<sup>e</sup> Mean Score from end of Phase A to week 14</li> </ul>
331-08-212	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Long-term; Phase 2 Trial; Open-label, flexible dose extension</li> <li>• <u>N</u> = 697 brexpiprazole</li> <li>• <u>Dose</u>: 0.25 mg/day to 3 mg/day</li> </ul>

	<ul style="list-style-type: none"> <li>• <u>Duration</u>: 52 weeks of adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Safety and tolerability</li> </ul>
331-10-238	<ul style="list-style-type: none"> <li>• <u>Trial design</u>: Long-term; Phase 3 Trial; Open-label, flexible dose extension</li> <li>• <u>N</u> = 1387 brexpiprazole</li> <li>• <u>Dose</u>: 0.5 mg/day to 3 mg/day</li> <li>• <u>Duration</u>: 26 weeks of adjunctive therapy</li> <li>• <u>Primary Endpoint</u>: Safety and tolerability</li> </ul>
<small>ADT<sup>a</sup> = antidepressant therapy; MADRS<sup>b</sup> = Montgomery-Asberg Depression Rating Scale; CGI-S<sup>c</sup> = Clinical Global Impression Scale; Q-LES-Q-SF<sup>d</sup> = Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form; SDS<sup>e</sup> = Sheehan Disability Scale</small>	

## 3.2 EFFICACY

### 3.2.1 Schizophrenia

The efficacy of brexpiprazole for schizophrenia is supported with data from 5 Phase 2/3 clinical trials (Table 1). The clinical data provide evidence for efficacy of the 2 mg/day and 4 mg/day doses as monotherapy for subjects with schizophrenia. The clinical reviewers have identified two clinical trials (Trial # 331-10-231 (2 mg and 4 mg) and 331-10-230 (4 mg only)) with enough data to support the schizophrenia indication.

The data collected from clinical trials demonstrates brexpiprazole 2 mg/day and 4 mg/day are efficacious as monotherapy for subjects with schizophrenia. The primary efficacy outcome variable in the clinical trials was the change from baseline to week 6 in PANSS Total Score. The key secondary efficacy endpoint was the change from baseline to week 6 in CGI-S score. Based on the outcomes of the clinical trials, the recommended starting dose for brexpiprazole in the treatment of patients with schizophrenia is 1 mg/day; however, the target dose range is 2 to 4 mg/day. The efficacy of brexpiprazole in the treatment of schizophrenia was established at doses of 4 mg/day (Trial # 331-10-231 & 331-10-230) and 2 mg/day (Trial # 331-10-231). Efficacy on the primary outcome measure, PANSS Total Score, was demonstrated in analyses pooling the 2 mg/day groups from both Phase 3 trials as well the 4 mg/day groups from both Phase 3 trials. However, greater treatment effects in the 4 mg/day groups suggest some patients may benefit from higher doses. The clinical reviewers have identified two clinical trials (Trial # 331-10-231 (2 mg and 4 mg) and 331-10-230 (4 mg only)) with enough data to support the schizophrenia indication. However, only 1 trial (Trial # 331-10-231) demonstrates efficacy for both the 2 mg and 4 mg doses.

### 3.2.2 MDD

The efficacy for brexpiprazole for MDD is supported with data from 6 Phase 2/3 clinical trials (Table 2). However, clinical reviewers have identified only 1 clinical trial (Trial # 331-10-228) with sufficient data to support the MDD indication. Clinical reviewers have requested additional data to support the Sponsor's efficacy claim and do not intend to approve the MDD indication with the data provided in the current NDA submission. This additional data may provide additional efficacy and safety information needed to evaluate the benefit-risk profile in the MDD population. Thus, DRISK defers discussing the MDD indication further in this review.

### 3.3 SAFETY CONCERNS

#### 3.3.1 Overall Safety

The safety database is comprised of all subjects enrolling in clinical trials through January 31, 2014. This includes at least 4,472 subjects who have been exposed to at least 1 dose of brexpiprazole across the Phase 2/3 trials for both schizophrenia and MDD. Of these subjects, 1,035 have been exposed for at least 1 year of brexpiprazole treatment within the MDD and schizophrenia clinical trial programs. The details of the safety findings derived from these studies is described below.

#### 3.3.2 Schizophrenia

The clinical development program for schizophrenia provides data for 1,256 subject in short-term trials and 813 subjects in long-term trials as of January 31, 2014. A total of 425 subjects were exposed for  $\geq 6$  months and 213 subjects were exposed for  $\geq 1$  year. Overall, the safety database does not suggest any new safety signals that have not been previously observed for 2<sup>nd</sup> generation antipsychotic medications.

The rates of discontinuation due to treatment emergent AEs (TEAE) was relatively low in short-term trials (8.1% brexpiprazole; 12.7% placebo). The only adverse event occurring in at least 5% of brexpiprazole subjects and at a greater rate than placebo subjects included akathisia (5.8% brexpiprazole; 4.5% placebo). Almost all the cases of akathisia were mild or moderate. Weight increases were similar for both short- and long-term trials (mean change = 1.1 kg increase) and were not associated with clinically significant metabolic disturbances. Weight gain resulted in 0.6% of all brexpiprazole discontinuations in long-term trials. In addition, serious AEs occurred at rates lower than placebo (2.6% brexpiprazole; 4.3% placebo) and the pattern of serious AEs was related to the underlying psychiatric disorder. There were 13 reported deaths in the entire brexpiprazole program (MDD + schizophrenia trials) but these were not considered related to brexpiprazole. In addition, for the short-term schizophrenia trials, the incidence of TEAEs was 60.6% in all the brexpiprazole subjects and 61.1% in the placebo groups. Most TEAEs in the brexpiprazole groups were mild or moderate in severity. Researchers concluded that the majority of these TEAEs were an exacerbation of psychiatric disorders. No TEAEs met the definition of "common" (i.e.,  $\geq 5\%$  and 2 times the rate of placebo). As previously discussed, the largest and most clinically significant AE observed was for akathisia. In the long-term trials, the incidence of TEAEs was 59.2%. Similar to short-term trials, most TEAEs were mild or moderate in severity and researchers found the majority of severe TEAEs to be related to underlying psychiatric disorders. The most frequently occurring TEAEs are listed in Table 3.

**Table 3.** Schizophrenia - Most frequently occurring ( $\geq 5\%$ ) treatment emergent adverse events

<b>Treatment Emergent Adverse Event</b>	<b>Incidence (%)</b>
Schizophrenia	12.2 %
Insomnia	9.1 %
Weight increased	7.4 %
Akathisia	5.8 %
Headache	5.8 %
Agitation	5.3 %

There were drug class associated safety topics of special interest assessed in the trials. These included tardive dyskinesia, metabolic disturbances, NMS, somnolence, hypersensitivity reactions, suicidality, venous thromboembolism (VTE), and seizures. Tardive dyskinesia and NMS were not reported in the schizophrenia population. The most frequently occurring EPS-related event included akathisia (5.2% on 2mg; 7.1% on 4 mg, and 4.9% on placebo) and parkinsonian symptoms (2.8% on 2mg; 6.0% on 4 mg, and 2.2% on placebo). Somnolence occurred at similar rates in brexpiprazole and placebo. Hypersensitivity reactions were all coded as mild or moderate and none qualified as a serious AE. Suicidality occurred in similar rates in brexpiprazole and placebo. Rates of dizziness, orthostasis, syncope, and QT prolongation did not suggest a pattern associated with brexpiprazole and there were similar rates for the placebo group. VTE was observed in 1 blinded subject in an ongoing schizophrenia trial, but was not considered associated with brexpiprazole due to medical comorbidities including prior history VTE and dyslipidemia. In addition, laboratory assessments of special interest (i.e., white blood cell count, neutrophil count, glucose, lipids, and creatine phosphokinase) were also evaluated and showed no clinically meaningful significance.

According to the Sponsor's response to the March 12, 2014 Information Request, the relationship between seizure and brexpiprazole remains uncertain. One subject on blinded trial medications had a seizure. The Sponsor considered this possibly related due to temporal association and lack of risk factors. Overall, the occurrence of seizures and seizure-related AEs was similar in the brexpiprazole group (n=6) and the non-brexpiprazole group (n= 2 placebo + 1 aripiprazole + 2 prior to randomization + 2 at > 1 week after discontinuing brexpiprazole). In addition, the majority of the subjects experiencing seizures had predisposing medical risk factors. There is a low rate of events of special interest with brexpiprazole use and, if present, were expected for 2<sup>nd</sup> generation antipsychotic medications. The Agency's clinical review of this topic is ongoing.

#### **4 DISCUSSION**

Overall, the clinical trial program has demonstrated efficacy in the schizophrenia population. There are limited data for the MDD population and the indication is not recommended for approval during this cycle by DPP. The safety profile for brexpiprazole

does not present any new, unexpected safety signals compared to other atypical antipsychotic medications currently used to treat schizophrenia. Based on the described safety and efficacy data, the use of brexpiprazole in the treatment of patients with schizophrenia has a favorable benefit-risk profile which is common and understood by clinicians prescribing drugs in the same class. Thus, no additional risk mitigation strategies are required beyond labeling.

## **5 CONCLUSION**

In conclusion, based on the available data, the Office of Surveillance and Epidemiology (OSE), DRISK recommends that brexpiprazole, if approved, does not require a REMS to ensure the benefits outweigh the risk for the treatment of schizophrenia. DRISK defers comment regarding a REMS for the treatment of MDD due to additional data DPP has requested the Sponsor to provide, which may impact the evaluation of the benefit-risk profile in the MDD population.

## **6 RECOMMENDATIONS**

The OSE, DRISK does not recommend that brexpiprazole have a REMS program for approval when used to treat schizophrenia. Comprehensive labeling discussing the risks associated with brexpiprazole will ensure that the benefits outweigh the risks of brexpiprazole.

Should DPP determine that the proposed indication for MDD could be considered for approval, a consult should be provided to DRISK.

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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.**  
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/s/  
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DANNY S GONZALEZ  
03/19/2015

REEMA J MEHTA  
03/19/2015  
I concur.