

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204370Orig1Orig2s000

**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**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: May 27, 2015

Reviewer(s): Leah Hart, PharmD
Division of Risk Management

Team Leader: Kimberly Lehrfeld, PharmD
Division of Risk Management

Acting Division
Deputy Director: Reema Mehta, PharmD, M. P. H
Division of Risk Management

Drug Name(s): Vraylar® (cariprazine)

Therapeutic Class: Atypical antipsychotic

Dosage and Route: 1.5 mg, 3 mg, 4.5 mg, and 6 mg oral capsules

Application Type/Number: NDA 204-370

Applicant/sponsor: Forest Laboratories

OSE RCM #: 2015-10

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1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) re-evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Vraylar® (cariprazine) oral capsules, NDA 204-370, submitted by Forest Laboratories, Inc. The initial NDA was received November 19, 2012 and received a Complete Response (CR) Letter on November 19, 2013 due to dose related toxicity (including akathisia and other extrapyramidal symptoms (EPS), increased blood pressure, elevations in creatinine phosphokinase, and elevations in transaminases) (b) (4). The Applicant responded to the CR as a NDA Resubmission Class 2 on December 17, 2014. The applicant has proposed (b) (4) 6mg per day for both indications.

DRISK evaluated cariprazine during the first review cycle (DRISK REMS Review, August 16, 2013) and concluded that a REMS was not necessary for the product at that time.

1.1 BACKGROUND

Vraylar is an atypical antipsychotic with two proposed indications: 1) for the treatment of schizophrenia and 2) for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Vraylar is a partial agonist at the dopamine D₂/D₃ receptors and has preferential binding to D₃ receptors. Vraylar also exhibits partial agonism at serotonin 5-hydroxytryptamine (5-HT)_{1A} receptors. Cariprazine has two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which both have pharmacological activity similar to the parent drug.

Schizophrenia is a lifelong, disabling psychiatric disorder affecting approximately 2.4 million American adults age 18 and older. Schizophrenia typically manifests during adolescence or in young adulthood and can be associated with delusions, hallucinations, social withdrawal, and problems with attention and memory. First-line treatment options for schizophrenia are atypical antipsychotics including aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone, lurasidone and paliperidone.

Bipolar mania affects approximately 5.7 million American adults age 18 and older and is associated with significant morbidity and mortality and one of the highest suicide rates among populations with psychiatric illness. This disorder is characterized by dramatic mood swings and behavior that results in significant morbidity and functional impairment. There are several available treatment options for the management of acute mania including atypical antipsychotics, mood stabilizers, anticonvulsants, and neuroleptics, all of which are used as monotherapy or in combination regimens.

1.2 REGULATORY HISTORY

November 19, 2012: Forest Laboratories, Inc. submitted NDA 204-370 for Vraylar. The application was filed on January 18, 2013 and granted a standard review under "the Program" with a user fee goal date of November 19, 2013.

August 16, 2013: DRISK concluded that a REMS was not necessary for cariprazine based on the data available at that time¹.

November 19, 2013: A CR Letter was issued citing dose related toxicity (b) (4).

FDA concluded that the studies demonstrated the efficacy of cariprazine in the treatment of schizophrenia and mania associated with bipolar disorder. However, there were significant dose-related toxicities, including akathisia and other extrapyramidal symptoms (EPS), increased blood pressure, elevations in creatinine phosphokinase, and elevations in transaminases. The Division was concerned about the long half-lives of cariprazine and the active metabolite (DDCAR), along with the significant accumulation of the total active moiety. The Division concluded that (b) (4) toxicities could possibly be mitigated by an alternative dosing regimen, for example, one that would provide a prompt initial response, followed by lower doses which would maintain effective blood levels while reducing the level of toxicity.

April 3, 2014: FDA and the Sponsor met for a Type A meeting to discuss CR. Agreement was reached to resubmit the application with new PK data from studies A002-A11 and RGH-MD-06; additional safety data and analysis to address the safety topics identified in the CR; and the rationale for (b) (4) not exploring an alternative dosing regimen.

December 17, 2014: Forest Laboratories, Inc. submitted NDA 204-370 for Vraylar. The application was considered a complete, class 2 response to the November 19, 2013 action letter. The PDUFA date is June 17, 2015.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSIONS

- Forest Laboratories, Inc. Summary of Clinical efficacy [schizophrenia indication] for Vraylar (cariprazine), received December 17, 2014
- Forest Laboratories, Inc. Summary of Clinical Efficacy [bipolar mania indication] for Vraylar (cariprazine), received December 17, 2014
- Forest Laboratories, Inc. Summary of Clinical Safety for Vraylar (cariprazine), received December 17, 2014
- Forest Laboratories, Inc. Draft Prescribing Information for Vraylar (cariprazine), received December 17, 2014

2.2 OTHER MATERIALS INFORMING REVIEW

- Bunting, J, DRISK REMS Review for Vraylar (cariprazine), dated August 16, 2013

¹ Bunting, J DRISK REMS Review for Vraylar (cariprazine)

- Senior, J, OPE/OSE Memorandum for Vraylar (cariprazine), dated April 2, 2015
- Chambers, W, Ophthalmology Consult for Vraylar (cariprazine), dated August 16, 2013

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The clinical program for cariprazine included 13 Phase 1 studies and 18 Phase 2/3 studies which included approximately 6000 patients. The 13 Phase 1 studies evaluated safety, pharmacodynamics and pharmacokinetic properties of cariprazine in healthy subjects and in patients with schizophrenia. The 7 completed Phase 2/3, double-blinded, placebo-controlled studies form the bases for the primary efficacy and safety assessments.

The Sponsor submitted four additional studies to support the re-submission of the NDA in response to the CR. A summary of these 4 studies is as follows:

A002-A11 is a randomized, open-label, parallel-group, fixed dose, PK, safety and efficacy study of cariprazine in 38 patients (in Japan) with schizophrenia. This study has a 12 week dosing period as well as a 12 week follow-up. The pharmacokinetics of cariprazine and major active metabolites were evaluated during both the treatment period and the washout period.

RGH-MD-06 is a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible- and fixed-dose study to evaluate the efficacy and safety of cariprazine relative to placebo in the prevention of relapse of symptoms in patients with schizophrenia. This study is ongoing and has 5 phases: a screening phase, run-in-phase, stabilization phase, double-blind phase and safety follow-up. The PK data from this study is being used in the current submission to demonstrate the decline in plasma exposure of cariprazine and major active metabolites upon stopping dosing.

RGH-MD-56 is a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed dose study evaluating the safety and efficacy of cariprazine in patients with bipolar depression.

RGH-MD-75 is a multinational, multicenter, randomized, double-blind, placebo-controlled study of cariprazine as adjunctive therapy in Major Depressive Disorder. (b) (4)

The new submission increased the NDA safety database to 2758 total patients and includes 364 cariprazine-treated patients with at least 24 weeks of exposure and 239 patients with at least 48 weeks of exposure.

Indication: Schizophrenia (6 weeks of treatment)

In schizophrenia, dose-related efficacy was demonstrated across the dose range of 1.5 to 9 mg/day in the pivotal studies (b) (4)

The Sponsor has proposed a recommended dose of 1.5 to 6mg/day.

Indication: Bipolar mania (3 weeks of treatment)

The efficacy of cariprazine in adults with manic or mixed episodes associated with bipolar I disorder was demonstrated in 3 pivotal, 3-week, double-blind, placebo-controlled studies (RGH-MD-31, RGH-MD-32, and RGH-MD-33). The primary efficacy endpoint in the bipolar mania trials was the change from baseline to week three of the Young Mania Rating Scale (YMRS). The secondary efficacy endpoint was the change from baseline to week three of the CGI-S. Using MMRM or LOCF, statistically significant and clinically meaningful improvements in the YMRS total score were seen in all three of the bipolar mania pivotal studies. The additional efficacy parameters included the YMRS remission rate and response rate at Week 3; and change from baseline to Week 3 in both Montgomery-Åsberg Depression Rating Scale (MADRS) and PANSS total scores. A significantly higher proportion of patients treated with cariprazine, across the 3 studies, achieved response ($\geq 50\%$ reduction from baseline to Week 3 in YMRS total score) and remission (YMRS total score ≤ 12 at Week 3) compared with placebo treatment.

In any treatments for manic or mixed episodes associated with bipolar I disorder, switching to depression is a concern; therefore, the depressive symptoms were assessed with the MADRS across all 3 studies throughout the trials. The overall decrease in MADRS total scores from baseline to end of treatment, in patients treated with cariprazine, suggests that cariprazine is not associated with switching to depression. Significant improvement in patients' PANSS total scores indicated the efficacy of cariprazine in treating psychotic symptoms associated with bipolar mania.

In bipolar mania, efficacy was demonstrated in the dose range of 3 to 12 mg/day; however, the clinical trials did not show an incremental efficacy benefit for doses above 6 mg/day. The Sponsor has proposed a recommended dose of 3 to 6mg/day.

3.2 SAFETY CONCERNS

The following is a summary of the safety concerns identified in the CR letter.

3.2.1 Akathisia and EPS

Cumulative review from the clinical program suggested a dose-response relationship for akathisia and EPS with the risk being the highest during the first 2-3 weeks of treatment. In the dose range currently under review (1.5-6mg/day) the rate of akathisia was 9.1%-12.5%, compared to 7.2% for aripiprazole and 8.6% for risperidone. Most events were described to be mild or moderate in severity; >97% and >92% of events in Group 1A schizophrenia and Group 2A bipolar mania studies, respectively. These adverse events prompted discontinuation of the study in <1% of schizophrenia patients and <3% of bipolar mania patients. Akathisia was not associated with worsening of psychotic or manic symptoms or suicidality in patients during clinical trials.

3.2.2 Creatinine Phosphokinase and Rhabdomyolysis

Cariprazine treatment was associated with dose-related increases in mean creatine phosphokinase (CPK) levels when clinical study data was examined by modal daily dose. The increased levels were not associated with altered renal function and resolved spontaneously.

Rhabdomyolysis was seen in 2 of the 4540 cariprazine-treated patients (at a rate of 0.04%). This adverse event is included in all product labelling for atypical antipsychotics.

3.2.3 Liver transaminase Elevation

Dose related increases in mean aminotransferase levels were observed with cariprazine treatment. Mean increase in alanine aminotransferase (ALT) levels of ≤ 6 U/L were observed with modal doses up to 6mg/day. The increase with the 9-12mg/day was about 9U/L and placebo was 3.7U/L. In the schizophrenia studies approximately 1-2% of patients across all treatment groups had aminotransferase elevations > 3 x the upper limit of normal (ULN). In the bipolar studies this ranges from 2-4% >3 x the ULN depending on the dose.

Cariprazine was not associated with bilirubin elevations or dose-related mean changes in total bilirubin and there was no evidence of drug-induced serious liver injury.

Dr. Senior was consulted and performed eDISH analysis for newly submitted studies and concluded that the additional data “appears to confirm and support the conclusions reached in the previous consultation (September 2013²), that there do not appear to have been any evidence of serious hepatotoxicity attributable to cariprazine³.”

3.2.4 Blood Pressure Elevation

Dose-related elevations of systolic and diastolic blood pressure were observed with cariprazine therapy. Modal daily doses ≤ 6 mg were less likely to be associated with blood pressure elevations compared to modal doses of 9-12mg/day. Mean changes from baseline with cariprazine doses ≤ 6 mg/day were <2 mmHg and unlikely to be of clinical relevance and similar to those observed in placebo and aripiprazole treatment groups

4 DISCUSSION

Vraylar is an atypical antipsychotic with the proposed indications of treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder. There are several other atypical antipsychotics approved for the proposed indications.

Vraylar, as with other atypical antipsychotics, is associated with neuroleptic malignant syndrome (NMS), tardive dyskinesia, metabolic changes, and potential for cognitive and motor impairment. The safety profile of Vraylar, as demonstrated in the pivotal trials, is consistent with the known safety profile for other currently approved atypical antipsychotics.

² Dr. Senior's 9/2013 memo

³ Dr. Senior's 4/2015memo

There are several dose-related adverse events associated with Vraylar, (b) (4) (b) (4)
[REDACTED]. After a CR the
Sponsor is now proposing to (b) (4) in order to ensure the benefits
outweigh the risk.

Therefore, based on the currently available data, the benefits of Vraylar for the proposed indications outweigh the risks of treatment. Additionally, the safety profile is similar to that of other atypical antipsychotics and can be mitigated through professional labeling.

5 CONCLUSION

In conclusion, risk mitigation measures beyond labeling do not appear warranted for Vraylar. The safety profile for Vraylar for the proposed indication and the proposed dosing schedule is consistent with the known safety profile for other atypical antipsychotics. Of note, other atypical antipsychotics do not have REMS for the proposed indications.

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/s/

LEAH M HART-BANKS
05/27/2015

CYNTHIA L LACIVITA
05/29/2015
Signing on behalf of Reema Mehta

**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 Strategies (REMS) Review

Date: August 16, 2013

Reviewer(s): Jason Bunting, PharmD
Division of Risk Management

Team Leader: Kimberly Lehrfeld, PharmD
Division of Risk Management

Division Director: Claudia Manzo, PharmD
Division of Risk Management

Subject: Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed

Drug Name(s): Vraylar (cariprazine)

Therapeutic Class: Atypical antipsychotic

Dosage and Route: 1.5 mg, 3 mg, 4.5 mg, 6 mg, (b) (4) oral capsules

Application Type/Number: NDA 204-370

Applicant/sponsor: Forest Laboratories, Inc.

OSE RCM #: 2012-2813

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the New Drug Application (NDA) 204-370, for Vraylar (cariprazine) oral capsules, to assess the need for a Risk Evaluation and Mitigation Strategy (REMS).

1.1 BACKGROUND

Vraylar is an atypical antipsychotic with two proposed indications: 1) for the treatment of schizophrenia and 2) for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Vraylar is a partial agonist at the dopamine D₂/D₃ receptors and has preferential binding to D₃ receptors. Vraylar also exhibits partial agonism at serotonin 5-hydroxytryptamine (5-HT)_{1A} receptors.

Schizophrenia is a lifelong, disabling psychiatric disorder affecting approximately 2.4 million American adults age 18 and older. Schizophrenia typically manifests during adolescence or in young adulthood and can be associated with delusions, hallucinations, social withdrawal, and problems with attention and memory. First-line treatment options for schizophrenia are atypical antipsychotics including aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone, lurasidone and paliperidone.

Bipolar mania affects approximately 5.7 million American adults age 18 and older and is associated with significant morbidity and mortality and one of the highest suicide rates among populations with psychiatric illness. This disorder is characterized by dramatic mood swings and behavior that results in significant morbidity and functional impairment. There are several available treatment options for the management of acute mania including atypical antipsychotics, mood stabilizers, anticonvulsants, and neuroleptics, all of which are used as monotherapy or in combination regimens.

The proposed maintenance doses of Vraylar are (b) (4) mg to (b) (4) mg once daily for the treatment of schizophrenia and (b) (4) mg to (b) (4) mg once daily for the treatment of manic or mixed episodes associated with bipolar I disorder. An initial starting dose of 1.5 mg is recommended for both indications.

As with other atypical antipsychotics, a boxed warning for an increased risk of mortality in elderly patients with dementia-related psychosis has been proposed by the Sponsor. The basis for the boxed warning for this class of drugs is an analysis of 17 placebo-controlled trials, mostly in patients taking atypical antipsychotic drugs, which revealed an increased risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Most deaths were cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. There was no REMS proposal submitted with the application.

1.2 REGULATORY HISTORY

- September 19, 2011 - The Division of Psychiatric Products (DPP) held a Type C meeting via teleconference with the Sponsor to discuss the nonclinical and clinical assessment of the potential for retinal toxicity with Vraylar.
- May 24, 2012 - A Type B Pre-NDA meeting was held with the Sponsor to discuss the proposed NDA for Vraylar for the treatment of schizophrenia and manic or

- mixed episodes associated with bipolar I disorder. There was no discussion regarding the necessity of a REMS during the Pre-NDA meeting.
- November 19, 2012 - Forest Laboratories, Inc. submitted NDA 204-370 for Vraylar. The application was filed on January 18, 2013 and granted a standard review under “the Program” with a user fee goal date of November 19, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Forest Laboratories, Inc. Summary of Clinical Efficacy [schizophrenia indication] for Vraylar (cariprazine), received November 19, 2013
- Forest Laboratories, Inc. Summary of Clinical Efficacy [bipolar mania indication] for Vraylar (cariprazine), received November 19, 2013
- Forest Laboratories, Inc. Summary of Clinical Safety for Vraylar (cariprazine), received November 19, 2013
- Forest Laboratories, Inc. Draft Prescribing Information for Vraylar (cariprazine), received November 19, 2013

3 REVIEW FINDINGS FOR VRAYLAR

3.1 OVERVIEW OF CLINICAL PROGRAM

The NDA for Vraylar includes data from 13 Phase 1 studies and 18 Phase 2/3 studies, including six short-term, placebo-controlled studies in patients with schizophrenia or bipolar mania.

There were three pivotal, six-week, randomized, placebo-controlled studies in patients with schizophrenia:

- Study RGH-MD-04 and Study RGH-MD-16 utilized a fixed dose design using Vraylar doses of 1.5 mg, 3 mg, 4.5 mg, and 6 mg per day, and
- Study RGH-MD-05 utilized a fixed-flexible dose design using Vraylar doses of 3 mg to 6 mg per day and 6 mg to 9 mg per day.

The primary efficacy endpoint in the schizophrenia trials was the change from baseline to week six of the Positive and Negative Syndrome Scale (PANSS). The secondary efficacy endpoint was the change from baseline to week six of the Clinical Global Impressions-Severity (CGI-S) score.

There were three pivotal, three-week, randomized, placebo-controlled studies in patients with bipolar mania:

- Study RGH-MD-31 and Study RGH-MD-32 utilized a flexible dose design using Vraylar doses of 3 mg to 12 mg per day, and
- Study RGH-MD-33 utilized a fixed-flexible dose design using Vraylar doses of 3 mg to 6 mg and 6 mg to 12 mg per day.

The primary efficacy endpoint in the bipolar mania trials was the change from baseline to week three of the Young Mania Rating Scale (YMRS). The secondary efficacy endpoint was the change from baseline to week six of the CGI-S.

A total of 2718 patients were treated with Vraylar in schizophrenia and bipolar mania studies, representing 501 patient-years of exposure.

Key Efficacy Findings: Using mixed-effects model for repeated measures (MMRM) or last observation carried forward (LOCF) analyses, statistically significant and clinically meaningful improvements in the PANSS total score were seen in all three of the schizophrenia pivotal studies. The least squares mean differences (LSMD) for Vraylar versus placebo ranged from -6.0 to -10.48 and were consistent with results observed with the active controls (aripiprazole and risperidone).

Using MMRM or LOCF, statistically significant and clinically meaningful improvements in the YMRS total score were seen in all three of the bipolar mania pivotal studies. The LSMD for Vraylar versus placebo ranged from -4.3 to -7.0.

Key Safety Findings: In the schizophrenia studies, the most frequent treatment-emergent adverse events (TEAEs) reported for $\geq 5\%$ of patients in the Vraylar group and with an incidence of at least twice that of placebo were akathisia and extrapyramidal disorder. In the bipolar mania studies, the most frequent TEAEs reported for $\geq 5\%$ of patients in the Vraylar group and with an incidence of at least twice that of placebo were akathisia, extrapyramidal disorder, restlessness, and vomiting.

In the schizophrenia studies, serious adverse events (SAEs) were reported in 5% of Vraylar treated patients and 7% of patients in the placebo group. In the bipolar mania studies, SAEs were reported in 6% of Vraylar treated patients and 5% of patients in the placebo group. In both the schizophrenia and bipolar mania studies, the most common SAEs were associated with worsening of the disorder under study.

Adverse events that led to drop out (ADOs) in the schizophrenia studies was lower in the Vraylar-treated patients (9%) than in the placebo group (12%) with schizophrenia (exacerbation) being the most common cause. In the bipolar mania studies, more patients in the Vraylar-treated group (12%) than in the placebo group (7%) discontinued due to AEs with akathisia being the most common cause.

A total of six deaths were reported during the Vraylar clinical development program in patients who received at least one dose of Vraylar. Three deaths were due to completed suicide, one death due to acute myocardial infarction/ischemic stroke, one death due to cardiac arrest, and one death due to pulmonary embolism. There were no deaths attributed to study drug.

The adverse events observed in Vraylar-treated patients were consistent with the adverse event profiles of other currently approved atypical antipsychotics.

3.2 SAFETY CONCERNS

3.2.1 Ocular Safety

In pooled placebo-controlled trials in both schizophrenia and bipolar mania, Vraylar therapy was associated with a higher incidence of ocular TEAEs relative to placebo,

approximately 4% and 2% respectively. The most common TEAE was blurred vision, followed by dry eye, conjunctivitis, eye irritation, and blepharospasm. Most blurred vision AEs were of short duration and resolved while the patients were still on Vraylar.

During the non-clinical development of Vraylar, other ocular findings were observed prompting the Agency to require the Sponsor to initiate ophthalmology testing in the clinical development program. The non-clinical ocular findings included:

- cataract formation in the 13-week and one-year toxicity studies in dogs,
- melanin binding with an elimination half-life of 28 days in the mass-balance study in pigmented rats, and
- retinal degeneration/atrophy in the two-year rat (albino) carcinogenicity study.

The Division issued an advice letter on March 28, 2011, regarding the concerns about ocular toxicity and among other things requested the Sponsor do the following:

- conduct electroretinogram (ERG) testing in a pigmented species such as a rabbit or dog,
- perform ocular coherent tomography (OCT) testing of the retina on a portion of patients (at least 60) in the 48-week cariprazine study to assess whether there is drug/metabolite deposition in the retina, and
- specify the inclusion of pseudoisochromatic plates which test for Blue-Yellow confusion in the Vraylar clinical trials.

The Sponsor agreed to the above requests by the Agency and presented the results in the NDA.

The ERG study (Study RGH-TX-49) was conducted in dogs and according to the Sponsor, revealed no Vraylar-related retinal effects.

OCT testing was performed on a total of 172 Vraylar-treated patients in the long-term study (Study RGH-MD-11) and approximately 13% had at least one post-baseline abnormal OCT in at least one eye. However, in his clinical review of this application Francis Becker, MD, FACP notes, “...*interpretation of these results is difficult because of inconsistencies in the data collected, lack of adequate baseline ocular evaluation, or lack of adequate follow-up.*” Dr. Becker goes on to describe a case in which a cataract was observed in the right eye during one examination, but was observed in the left eye during a subsequent examination three days later. In another case a cataract was observed during the trial, but was determined to have resolved by the end of the trial, which is highly improbable. Dr. Becker also points out that he observed several cases of abnormal OCT scans including cases of macular edema, macular degeneration, intra-retinal foveal edema, retinal thickening, and thinning of the nerve fiber layer in both eyes. However, in many cases no baseline OCT scan was done making it difficult to determine if these are new findings related to Vraylar treatment.

Color vision testing using pseudoisochromatic plates was performed with ophthalmologic examinations and according to the Sponsor, no change in color discrimination was noted in the majority of patients and most changes in color discrimination were minor.

Overall, the Sponsor concluded:

Ophthalmologic testing in the cariprazine clinical development program revealed no evidence for retinal toxicity or lenticular changes of clinical significance in the clinical studies. Based on these results, no ophthalmologic restrictions or additional ophthalmologic assessments outside of standard medical care are warranted for patients taking cariprazine

The Sponsor's draft labeling for Vraylar discusses ocular changes only in section 13, *Nonclinical Toxicology*; however, the label is still under negotiations with the Sponsor.

At the time of this writing, the ocular data and OCT scans submitted by the Sponsor are under review by the Division of Transplant and Ophthalmology Products (DTOP) to determine if there is a serious risk of ocular toxicity.

4 DISCUSSION

Vraylar is an atypical antipsychotic with the proposed indications of treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder. There are several other atypical antipsychotics approved for the proposed indications.

Vraylar, as with other atypical antipsychotics, is associated with neuroleptic malignant syndrome (NMS), tardive dyskinesia, metabolic changes, and potential for cognitive and motor impairment. The safety profile of Vraylar, as demonstrated in the pivotal trials (Studies RGH-MD-04, RGH-MD-05, RGH-MD-16, RGH-MD-31, RGH-MD-32, and RGH-MD-33), is consistent with the known safety profile for other currently approved atypical antipsychotics.

Regarding the risk for ocular toxicity, the data and observations provided by the Sponsor do not indicate that the non-clinical findings are seen in humans. However, the ocular data and OCT scans submitted by the Sponsor are currently under review by DTOP and their written review is pending at the time of this writing.

Therefore, based on the currently available data, the benefits of Vraylar for the proposed indications outweigh the risks of Vraylar. Additionally, the safety profile of Vraylar is similar to that of other atypical antipsychotic medications. The risks associated with Vraylar, like other atypical antipsychotics, can be mitigated through professional labeling.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond labeling does not appear warranted for Vraylar (cariprazine), however the ocular safety data is still under review by DTOP. The remaining safety profile for Vraylar for the proposed indications is consistent with the known safety profile for other atypical antipsychotics. Furthermore, other atypical antipsychotics do not have REMS for the proposed indications.

DRISK will continue to follow this NDA. Should DPP, in consultation with DTOP, raise further concerns with the risk of ocular toxicity and believe that a REMS may be necessary to mitigate the risk, our recommendation can be re-evaluated.

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/s/

JASON A BUNTING
08/16/2013

CLAUDIA B MANZO
08/16/2013
concur