

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204370Orig1Orig2s000**

**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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

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PMR/PMC Description: 2947 –1  
A 3-month cariprazine toxicity study in the juvenile rat starting at the appropriate age that corresponds to children age of 10 years. A dose range finding/toxicokinetic (TK) study should be conducted prior to a definitive toxicity/TK study. TK assessment should include cariprazine and the metabolites DCAR and DDCAR.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2016</u>
	Study/Trial Completion:	<u>09/2017</u>
	Final Report Submission:	<u>03/2018</u>

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

This juvenile animal study is needed to support a pediatric drug development program. The Division granted a deferral for clinical studies of cariprazine required under the Pediatric Research Equity Act (PREA) in pediatric patients until the safety and efficacy has been demonstrated in adults. These pediatric studies will be conducted post-NDA approval. Therefore, the juvenile animal study was not required pre-approval and is appropriate for a PMR because it must be completed prior to post-approval initiation of pediatric clinical studies in children 10 to 12 years of age.

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

The goal of the definitive toxicity study in the juvenile rat is to assess general toxicity parameters (with full histopathology), prolactin, creatinine kinase, cholesterol and triglycerides levels, ophthalmology, growth (including bone length and density) and neurobehavioral development assessments, along with post-dose reproductive performance.

These parameters should be assessed in the juvenile animals because organ systems identified as undergoing considerable growth and development in children of age 10 and older include the nervous, reproductive and skeletal systems. Moreover, cariprazine increased prolactin level in nonclinical studies; prolactin can affect growth and other parameters. In addition, cariprazine administration caused decreases in cholesterol and triglycerides, and produced cataracts and retinal changes in adult animals.

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 3-month cariprazine toxicity study in the juvenile rat starting at the appropriate age that corresponds to children age of 10 years.

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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

PMR/PMC Description: 2947-2  
A 6-month study in the juvenile dog starting at the appropriate age that corresponds to children age of 10 years.  
A dose range finding/TK study should be conducted prior to a definitive toxicity/TK study. TK assessment should include cariprazine and the metabolites DCAR and DDCAR.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2016</u>
	Study/Trial Completion:	<u>10/2017</u>
	Final Report Submission:	<u>03/2018</u>

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

This juvenile animal study is needed to support a pediatric drug development program. The Division granted a deferral for clinical studies of cariprazine required under the Pediatric Research Equity Act (PREA) in pediatric patients until the safety and efficacy has been demonstrated in adults. These pediatric studies will be conducted post-NDA approval. Therefore, the juvenile animal study was not required pre-approval and is appropriate for a PMR because it must be completed prior to post-approval initiation of pediatric clinical studies in children 10 to 12 years of age.

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

The goal of the definitive toxicity study in the juvenile dog is to assess general toxicity parameters (with full histopathology), prolactin, creatinine kinase, cholesterol and triglycerides levels, ophthalmology, and growth (including bone length and density).

The reason for a second juvenile animal species, in this case the dog, is that the dog is the most sensitive species for the cariprazine toxicity and the metabolism of cariprazine in the dog is similar to that in humans, with high levels of the active metabolite DDCAR; the rat produces minimal amount of DDCAR. Moreover, chronic active inflammation of the lungs, cataracts, and vesiculation/vacuolation and hypertrophy/hyperplasia of adrenals were observed in the adult dogs.

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 6-month cariprazine toxicity study in the juvenile dog starting at the appropriate age that corresponds to children age of 10 years.

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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

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PMR/PMC Description: 2947-3  
Deferred pediatric study under PREA (ages 10 to 17 years) with a diagnosis of schizophrenia or bipolar disorder to obtain pharmacokinetic, safety, and tolerability data to inform the selection of doses in efficacy and safety studies in pediatric schizophrenia and bipolar disorder.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2016</u>
	Study Completion:	<u>12/2018</u>
	Final Report Submission:	<u>06/2019</u>

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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 and bipolar disorder are more common in the adult population. Therefore, the pharmacokinetics, efficacy and safety of cariprazine in adults need to be established before we request pediatric studies.

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

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

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

A pediatric study is required under PREA to obtain data on the pharmacokinetic, safety and tolerability of cariprazine in pediatric patients 10 to 17 years of age. This study can be an open-label study in pediatric patients with adequate sample size to determine relevant pharmacokinetic parameters.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

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

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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

PMR/PMC Description: 2947-4  
Deferred pediatric study under PREA for the treatment of schizophrenia in patients aged 13 to 17. A study of the efficacy and safety of cariprazine in the relevant pediatric population.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2018</u>
	Study/Trial Completion:	<u>11/2022</u>
	Final Report Submission:	<u>05/2023</u>

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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 more common in the adult population. Therefore, the efficacy and safety of cariprazine in adults needs to be established before we request pediatric studies.

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

The goal of this pediatric study is to explore the efficacy and safety of cariprazine for the treatment of schizophrenia in patients 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.

Deferred pediatric study under PREA for the treatment of schizophrenia in patients aged 13 to 17. A study of the efficacy and safety of cariprazine in the relevant pediatric population.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- 
- Other
- 

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

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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

PMR/PMC Description: 2947-5  
A deferred pediatric study under PREA for the treatment of bipolar disorder, manic episode in patients aged 10 to 17. A study of the efficacy and safety of cariprazine in the relevant pediatric population.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2019</u>
	Study/Trial Completion:	<u>10/2022</u>
	Final Report Submission:	<u>03/2023</u>

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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

Bipolar disorder is more common in the adult population. Therefore, the efficacy and safety of cariprazine in adults needs to be established before we request pediatric studies.

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

The goal of this pediatric study is to explore the efficacy and safety of cariprazine for the treatment of bipolar disorder in patients 10 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.

Deferred pediatric study under PREA for the treatment of bipolar disorder, manic episodes in patients aged 10 to 17. A study of the efficacy and safety of cariprazine in the relevant population.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- 
- Other
- 

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

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- 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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

PMR/PMC Description: 2947-6  
A long-term, open-label safety study in pediatric patients with schizophrenia (ages 13 to 17) and bipolar I disorder, recent manic episodes (ages 10 to 17).

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2022</u>
	Study/Trial Completion:	<u>06/2024</u>
	Final Report Submission:	<u>06/2025</u>

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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

This study will include patients that have completed the efficacy and safety (PMR 2947-4). Therefore, it is not feasible to begin this study prior to the completion of pediatric safety and efficacy 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.”

A long-term, open-label safety study in pediatric patients with schizophrenia (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.

Pediatric patients with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) primary diagnosis of schizophrenia (aged 13 to 17) based on Structured Clinical Interview for DSM-V (SCID) who have completed (PMR 2947-4 and responded to treatment at the end of that study.

Required

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

Continuation of Question 4

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

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
    Long-term pediatric safety and tolerability 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?  
(PMR 2947-4 or 2947-5)
- 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

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**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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## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

PMR/PMC Description: 2947-7  
An *in vivo* drug-drug interaction study to assess cariprazine exposure when cariprazine is coadministered with a proton pump inhibitor.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2016</u>
	Study/Trial Completion:	<u>09/2017</u>
	Final Report Submission:	<u>03/2018</u>

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

There is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of cariprazine.

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.”

Cariprazine has pH-dependent solubility. Coadministration with PPIs could affect its absorption. The goal is to evaluate 1) if coadministration with PPIs could affect the exposure, and thus the safety or efficacy of cariprazine; 2) whether dose adjustment is needed in that scenario.

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.

(b) (4)

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  
Drug interaction clinical trials
- 

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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

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PMR/PMC Description: 2947-8  
*In vitro* evaluation of :  
1) inhibition potential of cariprazine, and the metabolites DCAR and DDCAR toward CYP2C8;  
2) inhibition potential of DCAR and DDCAR toward CYP2B6 and CYP2C19;  
3) induction potential of cariprazine, DCAR and DDCAR toward CYP2B6;  
4) induction potential of cariprazine toward CYP3A4 and CYP1A2  
Depending on the study results, in vivo drug interaction studies may or may not be needed.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2016</u>
	Study Completion:	<u>12/2016</u>
	Final Report Submission:	<u>04/2017</u>

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

There is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of cariprazine.

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.”

Per the Drug Interaction Studies guidance (February 2012), inhibition and induction potential of the investigational new drug and major active metabolites toward major CYP enzymes need to be evaluated. The goal of the study is to evaluate whether cariprazine and/or its major active metabolites (i.e., DCAR and DDCAR) have any potential to affect the activities of the major enzymes.

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.

(b) (4)

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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**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)

## 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 # 204370  
Product Name: Vraylar (cariprazine) capsules

PMR/PMC Description: 2947-9  
Conduct a placebo-controlled, randomized withdrawal, dose-response trial in adult patients with schizophrenia to assess the long-term, dose-related serious adverse effects of cariprazine, including tardive dyskinesia, akathisia, adrenal dysfunction, and extrapyramidal symptoms. The trial will also assess both the efficacy and tolerability of several fixed doses of cariprazine as maintenance treatment. Patients stabilized on treatment with cariprazine for at least 12 weeks would be randomized to fixed doses of cariprazine. These would include doses lower than those used to achieve a response in the acute phase.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2017</u>
	Trial Completion:	<u>12/2020</u>
	Final Report Submission:	<u>08/2021</u>

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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

Acute studies indicate that the drug was generally well-tolerated at the doses used. Most sponsors agree to conduct a post marketing maintenance study as a post marketing commitment (PMC), but we believe there is the possibility for significant safety concerns with long-term use. Thus, a longer-term study is needed.

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.”

Most sponsors agree to conduct a post marketing maintenance study as a post marketing commitment (PMC), but we believe there is the possibility for significant safety concerns with long-term use (most notably akathisia and pulmonary issues). Thus, a longer-term study is needed.

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? (akathisia)
- Assess signals of serious risk related to the use of the drug? (phospholipidosis/fibrosis)
- Identify an unexpected serious risk when available data indicate the potential for a serious risk? (phospholipidosis/fibrosis)

– **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.

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

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**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)

## 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.

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NDA/BLA # 204370  
Product Name: Vraylar (cariprazine) capsules

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PMR/PMC Description: 2947-10  
Conduct a placebo-controlled, randomized withdrawal, dose-response trial in adult patients with bipolar I disorder to assess the long-term, dose-related serious adverse effects of cariprazine, including tardive dyskinesia, akathisia, adrenal dysfunction, and extrapyramidal symptoms. The trial will also assess both efficacy and tolerability of several fixed doses of cariprazine as maintenance treatment. Patients stabilized on treatment with cariprazine for at least 12 weeks would be randomized to fixed doses of cariprazine. These would include doses lower than those used to achieve a response in the acute phase.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/2016</u>
	Trial Completion:	<u>06/2020</u>
	Final Report Submission:	<u>12/2020</u>

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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

Acute studies indicate that the drug was generally well-tolerated at the doses used. We believe there is the possibility for significant safety concerns with long-term use.

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.”

Most sponsors agree to conduct a post marketing maintenance study as a post marketing commitment (PMC), but we believe there is the possibility for significant safety concerns with long-term use (most notably akathisia and EPS). Thus, a longer-term study is needed.

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? (akathisia)
- Assess signals of serious risk related to the use of the drug? (phospholipidosis/fibrosis)
- Identify an unexpected serious risk when available data indicate the potential for a serious risk? (phospholipidosis/fibrosis)

– **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.

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

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**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)

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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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KIMBERLY S UPDEGRAFF  
09/16/2015

MARC B STONE  
09/17/2015

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## 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)

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**Date of This Memorandum:** September 16, 2015  
**Requesting Office or Division:** Division of Psychiatry Products (DPP)  
**Application Type and Number:** NDA 204370  
**Product Name and Strength:** Vraylar (cariprazine) Capsules  
1.5 mg, 3 mg, 4.5 mg, and 6 mg  
**Submission Date:** September 15, 2015  
**Applicant/Sponsor Name:** Forest Laboratories, Inc.  
**OSE RCM #:** 2015-186-01  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Danielle Harris, PharmD, BCPS

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#### 1 PURPOSE OF MEMO

The Division of Psychiatry Products requested that we review the revised carton and container labels and labeling for Vraylar (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to DMEPA's request for resubmission of the carton and container labels and labeling for review following recent changes made by the Sponsor to the NDC numbers in Section 16, *How Supplied/Storage and Handling*, of the proposed prescribing information to confirm that these NDC changes are aligned with the carton and container labels and labeling.

#### 2 CONCLUSION

The revised carton and container labels and labeling for Vraylar is acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/  
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DEBORAH E MYERS  
09/16/2015

DANIELLE M HARRIS  
09/16/2015

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

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

## Memorandum

**Date:** August 25, 2015

**To:** Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products (DPP)

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

**Subject:** **NDA 204370**  
VRAYLAR™ (cariprazine) capsules, for oral use

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OPDP has reviewed the draft product labeling (PI) and carton/container labeling for VRAYLAR™ (cariprazine) capsules, for oral use (Vraylar) as requested in the consult from DPP dated February 4, 2015.

OPDP's comments on the draft PI for Vraylar are based on the version provided by Kim Updegraff via email on August 18, 2015.

OPDP reviewed the proposed carton/container labeling obtained from the EDR ([\\CDSESUB1\evsprod\NDA204370\204370.enx](#)) on August 19, 2015, and has no comments at this time.

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

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

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/s/  
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SUSANNAH O'DONNELL  
08/25/2015



## Memorandum

Date: August 12, 2015

From: Sabine Francke, D.V.M., Ph.D., FIATP and Steven Mog, D.V.M., DACVP, Senior Science and Policy Staff, Office of Food Additive Safety, CFSAN (HFS-205)

Subject: Division of Psychiatry Products - NDA 20430 (cariprazine) Request for consultation regarding lung histopathology observed in dogs in the one-year cariprazine toxicity study

To: Kimberly Updegraff, RPh, MS, RAC, Senior Regulatory Project Manager, Division of Psychiatry Products, FDA/CDER/ODEI, (HFD-130)

### References:

1. E-mail from Updegraff to Francke dated July 21, 2015 subject: Division of Psychiatry Products - NDA 20430 (cariprazine) Request for consultation regarding lung histopathology observed in dogs in the one-year cariprazine toxicity study with three attachments:
  - a. Questions and background to Dr. Francke
  - b. Study number 05-3126, RGH-188 HCl: A one-year oral (capsule) toxicity study in dogs with a 2-month recovery period; final report dated 3 October, 2008.
  - c. Appendix I Expert Report on the lung findings in study number 05-3126 pg. 39-47 signed 6 June, 2015 (out of the 1.12.4 Request for comments and advice Forest Research Institute, Inc. entitled: Response to FDA request, Cariprazine (RGH-188), NDA 204370, dated 8 June, 2015.
2. E-mail from Chalecka-Franaszek to Francke dated August 5, 2015 subject: review by Drs. West and Cohen with attachment:
  - a. Medical expert report 20150720 entitled Histopathologic Review of Lung Tissue, Study Number 05-3126 RGH-188 HCl: A ONE-YEAR ORAL (CAPSULE) TOXICITY STUDY IN DOGS WITH A 2-MONTH RECOVERY PERIOD, SUMMARY PATHOLOGY
3. E-mail from Updegraff to Francke dated July 22, 2015 subject: Re: Division of Psychiatry Products - NDA 20430 (cariprazine) Request for consultation regarding lung histopathology observed in dogs in the one-year cariprazine toxicity study with one attachment:
  - a. 204370 Digital slide info cover-letter- 20150721- seq0077.pdf From Forest Research Institute, Inc. (Melina Cioffi, PharmD) to FDA (Mitchell V. Mathis, MD); dated 21 July, 2015
    - i. pg. 2 .....124 total slides have been shipped to FDA
    - ii. pg. 3.....70 slide images are digitally available with instructions for access

Based on your request (reference 1) we both have reviewed the materials that were provided to us; we have focused our evaluation on documents listed above, relevant to answering your specific questions (reference 1a) which we addressed below in this memorandum.

In addition, we both have reviewed the 124 glass slides and the 70 digital images of lung tissue. The results of our assessment are recorded in the Excel spreadsheet (attachment) and the summary tables below.

Background:

A one year (Dec. 2005-Feb 2007) study in 5-6 month old Beagle dogs (reference 1b) was conducted by [REDACTED]<sup>(b) (4)</sup>, sponsored by Forest Laboratories, Inc., NJ.

Briefly, the test article RGH-188 HCl (Cariprazine) was administered orally by capsule at 0, 1, 2, 4, and 6 mg/kg/day. The study consisted of 5 groups with 6 animals per sex per group, encompassing a total of 60 animals. Two animals per sex per group were maintained on study for an additional 2 months without treatment during a recovery period.

Results of the one year dog study report (reference 1b):

Specific to the lung, the following microscopic observations were recorded in the individual animal tables of the study report (reference 1b, Appendix N):

- Alveolar /Intraalveolar Foamy Macrophages (With / Without “Cholesterol” Clefts)
- Subacute (Chronic Active) / Chronic Inflammation/Fibrosis

In the pathology narrative of the study report (reference 1b, pg. 1350-51) the study pathologist reported the following lung findings...

- “ ....at the end of the treatment alveolar/intra-alveolar foamy macrophages accompanied by subacute/chronic inflammation were present in all males and females at 4 and 6 mg/kg/day, in 2 males and 2 females at 2 mg/kg/day and in 2 males at 1 mg/kg/day; severity ranged from minimal to moderate with a dose related increase in severity. These findings were considered to be compatible with phospholipidosis, commonly seen with cationic amphiphilic drugs in this and several other therapeutic classes.
- *At the end of the 2-month recovery phase, alveolar/intra-alveolar foamy macrophages accompanied by subacute/chronic inflammation were present in one male and one female at 4 and in 2 males and 2 females at 6 mg/kg/day. Severity ranged from minimal to slight and was most severe at the high dose. The decrease in the incidence and severity of the findings indicated that some regression had occurred but was incomplete”.*

In addition, the study pathologist summarized the pulmonary findings (incidences only) as follows in the Table entitled: TEST ARTICLE-RELATED MICROSCOPIC FINDINGS: DOSING PHASE – (reference 1b, pg. 1353)

	Peer Review Statement	Appendix N
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GROUP	1		2		3		4		5	
DOSE: mg/kg/day	0		1		2		4		6	
SEX	M	F	M	F	M	F	M	F	M	F
<b>DOSING PHASE (number/group)</b>	<b>4</b>									
<b>LUNGS (number examined)</b>	<b>4</b>									
Alveolar/intraalveolar foamy macrophages	0	0	2	0	2	2	4	4	4	4
Subacute/chronic inflammation	0	0	2	0	2	2	4	4	4	4

The FDA review of the dog study submission questioned specifically why the microscopic observation of “Fibrosis” was not carried forward to the pathology narrative and subsequently was not discussed in the overall study report.

Pathology comment:

It needs to be noted, that other microscopic observations also were not specifically addressed, in the pathology narrative, these include: “**cholesterol clefts**” and the observation of “**chronic active**” inflammation.

FDA requested clarification on the “Fibrosis” observations in lung tissues of the dog study from the sponsor; in response, the sponsor initiated a review specifically of the lung findings by 4 veterinary pathologists, resulting in an expert pathology report (reference 1c). This expert review entailed an evaluation of the lung tissues (slides and digital images) and resulted in a narrative report, but did not generate new data tables.

The sponsor provided a new data table of histopathological lung findings through a second review of the digital slides by two expert medical pathologists (reference 2a).

For an internal regulatory review of the slides specifically addressing “Fibrosis” in the dog lung tissues, FDA requested the slides /digital images from the sponsor for a review by CFSAN Pathology.

**CFSAN-Pathology’s review of the 124 glass slides and the 70 digital images of the one year Cariprazine dog study:**

Materials evaluated (reference 3a):

For most of the 60 study animals, 2 glass slides (slide number 13 and 14) with lung tissue were presented with the exception of animals 3291, 3293, and 4794; for these three dogs, additional lung

sections were provided: 2 (slide number 35 and 36), 1 (slide number 35), and 1 (slide number 35) sections, respectively. The quality of the glass slides was limited with regard to fading of the differential staining along the outer perimeter of the tissue section (up to 1mm depth) in almost all lung specimens. These coverslip artifacts resulting in loss of differential (Hematoxylin and Eosin [H&E]) staining hampered the detailed histomorphological evaluation to a degree, as treatment related findings tended to localize in the subpleural space. However, given the relative age (about 8 years old) of the slide specimens, some degree of slide deterioration can be expected.

In addition, we evaluated the 70 digital images; for most dogs, one digital slide image (either slide 13 or 14) was presented. For animals 2291, 2292, and 3290 both sections of slides 13 and 14 were scanned. For animals 3793, 4291, 4292 and 4294 identical images of slide 14 were submitted twice; a reason for this was not apparent. Animal 3291 presented with 4 images, one for each of its glass slides (13, 14, 35 and 36).

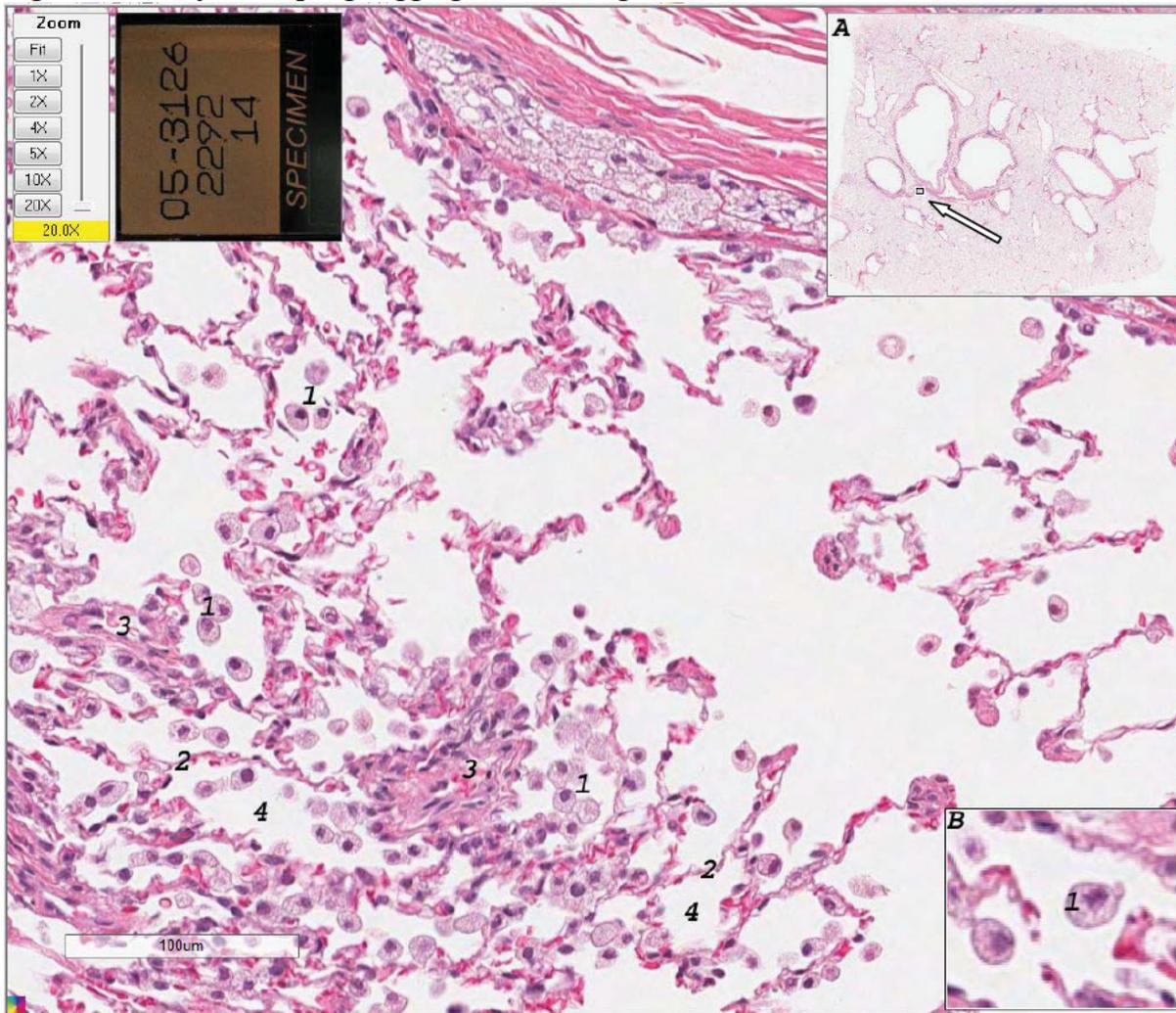
We also used the digital images as a source for representative photomicrographs presented below to illustrate key histological features of the treatment related findings discussed in this memorandum.

#### Pulmonary Changes identified by CFSAN Pathology:

In the dog lungs all Cariprazine related findings were microscopic in size and overall a minor component of the tissue section presented, most often occupying less than 10% of the tissue evaluated. Findings were of minimal to mild severity (see grading scale below) and of focal to multifocal distribution.

At all concentration of Cariprazine, the predominant treatment related change consisted of focal to multifocal aggregates of **foamy** (cytoplasm expanded by a clear vacuolar to light pinkish-brown granular material) alveolar **macrophages**. Foamy macrophage aggregates occupied the alveolar lumen as well as the interstitial space. They were located more commonly in the subpleural space but also adjacent to larger airways often in association with the lymphatic vasculature. At the lowest dose (group 2) of Cariprazine, very small to small **macrophage aggregates** were the only change observed.

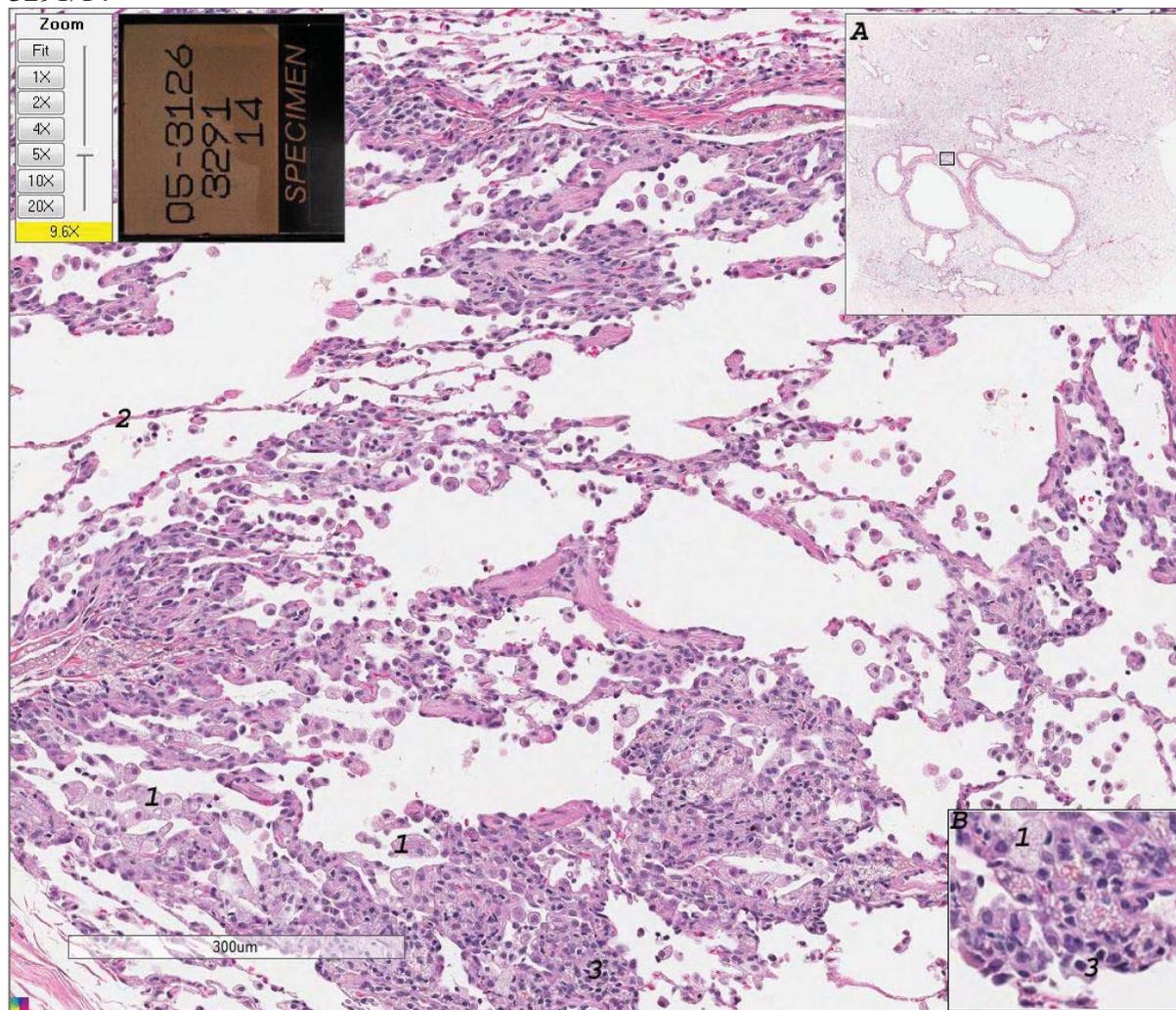
Figure 1: Foamy macrophage aggregate, male dog number 2292/14



Upper right corner inset A: low power – shows the entire tissue section presented – see small box at arrow tip, demonstrates the low percentage of overall tissue affected by the change; representing most of the lung tissue as normal. Inset B – high power – detailed view of foamy macrophage (1 – two macrophages are present in the view). Main image: upper left shows the slide identification and to the very left the objective magnification at which the image was captured (20x). Lower left – scale bar, provides reference for the relative size of focus shown. Image shows: small focal foamy macrophage aggregate; 1=foamy alveolar macrophage, 2=alveolar septal wall, 3=small vessel, 4=alveolar space.

Starting with group 3 and also seen at all higher doses (Group 4 and 5), the macrophage aggregates were accompanied by variable numbers of mixed individual **inflammatory cells** consisting mostly of lymphocytes, neutrophils and plasma cells. The individual inflammatory cell components varied but were most often loosely scattered around the macrophage aggregates. Neutrophils were at times more apparent in the inflammatory infiltrate warranting the term “**chronic active**” as used by the study pathologist (reference 1b, Appendix N). The inflammatory infiltrate (minimal to mild) was consistently similar or less cellular than the macrophage aggregates.

Figure 2: Inflammation, mixed cellularity associated with foamy macrophage aggregate – male dog 3291/14

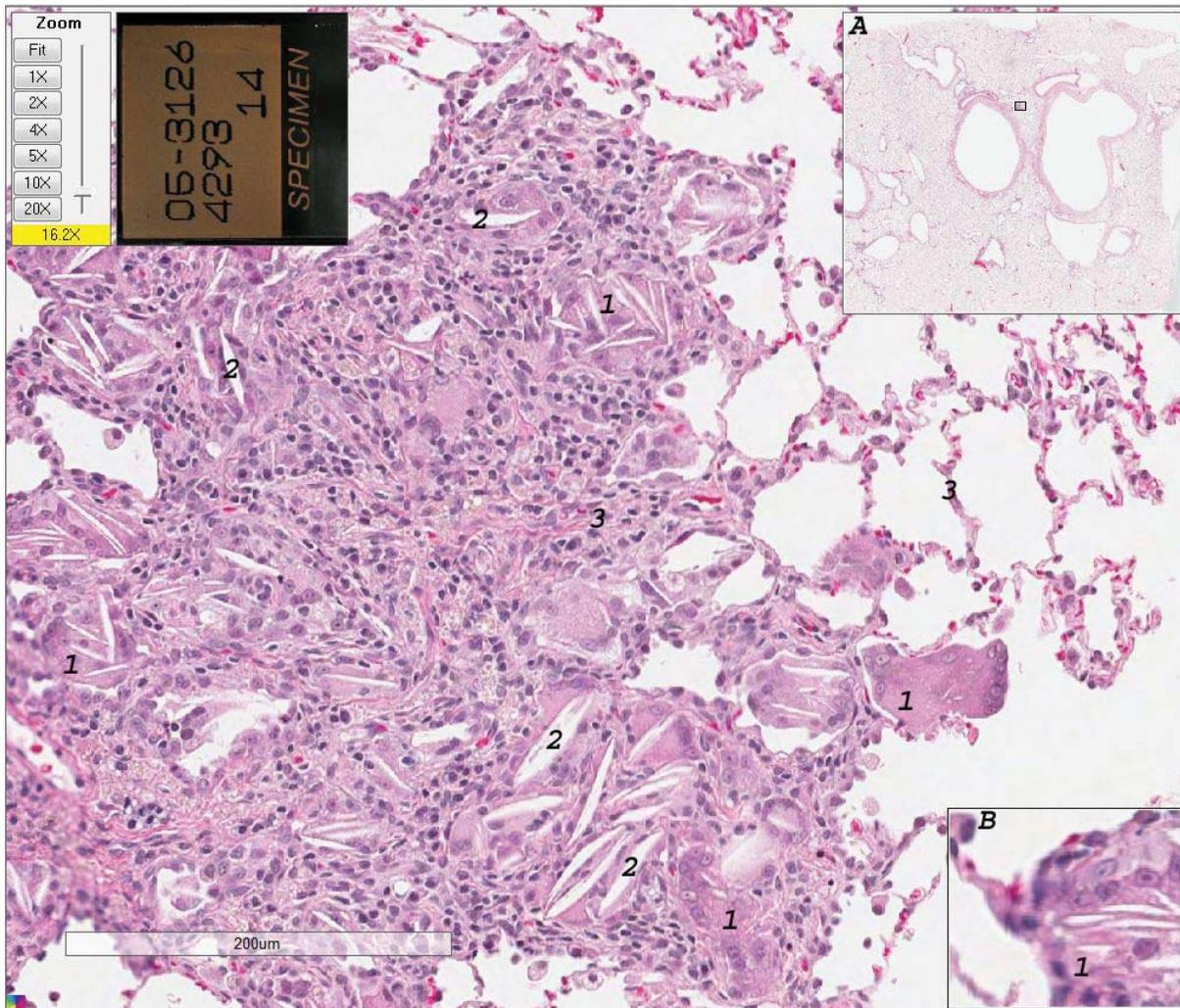


Upper right corner inset A: low power – shows the entire tissue section presented – see small box, demonstrates the low percentage of overall tissue affected by the change; representing most of the lung tissue as normal. Inset B – high power – detailed view of mixed inflammatory cell aggregate composed of foamy macrophage (1) – lymphocytes, plasma cells and few neutrophils (3). Main image: upper left shows the slide identification and to the very left the objective magnification at which the image was captured (9.6x). Lower left – scale bar,

provides a reference for the relative size of foci depicted. Image shown: small focal foamy macrophage aggregate with mixed inflammatory cells; 1=foamy alveolar macrophage, 2=alveolar septal wall, 3=mixed inflammatory cells.

With increasing dose (groups 4 and 5) the morphology of the macrophage aggregates changed to also include macrophages that were significantly larger (2-15x the size of foamy macrophages) containing 2-20 nuclei (**multinucleated giant cells**). These cells often contained an angular clear space of crystalline shape (ranging in length from 10-50 microns) consistent with **intracellular cholesterol clefts**.

Figure 3: Macrophage aggregate with multinucleated giant cells and cholesterol clefts – male dog 4293/14

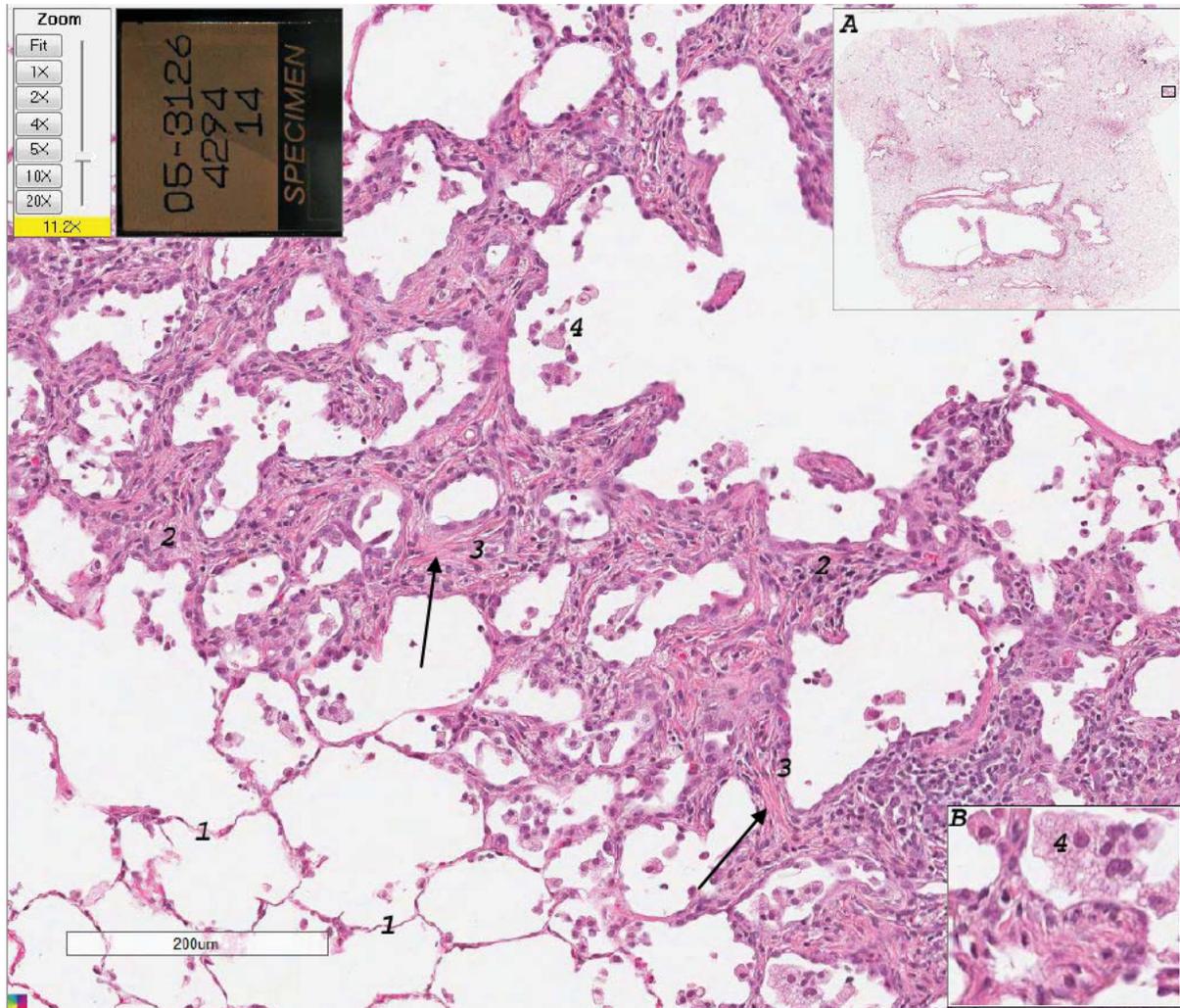


Upper right corner inset A: low power – shows the entire tissue section presented – see small box, demonstrates the low percentage of overall tissue affected by the change; representing most of the lung tissue as normal. Inset B – high power – detailed view of multinucleated giant cell containing cholesterol clefts (1). Main image: upper left shows the slide identification and to the very left the objective magnification at which the image was captured (16.2x). Lower left – scale bar, provides a reference for the relative size of the focus shown. Image shows:

aggregates consisting of mostly multinucleated giant cells with cholesterol clefts, few foamy macrophages and mixed inflammatory cells; 1=multinucleated giant cell, 2=cholesterol cleft, 3=alveolar septal wall.

Some foci with chronic inflammation (7 /24 animals in groups 4 and 5) were observed only in the 2 highest dose groups of both sexes. In those foci, macrophage accumulations manifested occasionally as small sub-pleural areas involving the septae of multiple alveoli. Macrophages and few, mostly chronic inflammatory cells (lymphocytes, fibroblasts/fibrocytes) occupied a widened interstitial space. Inflammatory chronicity (fibrosis) manifested in these foci evidenced as cellular 'organization' characterized by the occasional production of minor amounts of collagen by fibroblasts/fibrocytes resulting in the embedding of the remaining macrophages and other inflammatory cells in fibrous connective tissue.

Figure 4: Macrophage aggregates with chronic inflammation and secondary fibrosis - male dog 4294/14



Upper right corner inset A: low power – shows the entire tissue section presented – see small box, demonstrates the low percentage of overall tissue affected by the change; representing most of the lung tissue as normal. Inset B – high power – detailed view of foamy alveolar macrophages in the

alveolar space (4) next to an expanded alveolar septal wall. Main image: upper left shows the slide identification and to the very left the objective magnification at which the image was captured (11.2x). Lower left – scale bar, provides a reference for the relative size of the focus depicted. Image shows: focus with thickened septal walls due to chronic (minimal fibrosis) mixed inflammation; 1=normal alveolar septal wall, 2=expanded alveolar septal wall, 3/arrow=collagen deposition (fibrosis), 4=foamy alveolar macrophages.

### CFSAN Pathology Histopathology Grading: *Foamy macrophage / Inflammation*

#### Scoring scale:

For consistency, we utilized the scoring scale outlined in the one year dog study pathology report (reference 1b, pg. 521), but we modified the scale (*changes made are italicized below*), to ensure that the severity of the same parameter is consistently addressed. Since “total tissue affected” is a driving consideration in the determination of lung functionality, we anchored the severity scoring scale around the parameter of “percent of change, occupying the total amount (100%) of the tissue presented”. Additional features of changes observed, such as cell morphology (e.g. multinucleated giant cells, cholesterol clefts) or contributing components of inflammation (e.g. fibrosis) were identified and recorded qualitatively base on their presence or absence, to not artificially influence the distribution severity upward or downward.

Grade 0: WITH IN NORMAL LIMITS = there are no changes or changes cannot be differentiated from changes occurring in control animals with regard to quality and quantity; *100% = total tissue present on each slide section examined*

Grade 1: MINIMAL = the change is barely discernible and/or very few (multifocal)/very small foci or areas are affected; *change affects less than 10% of the total tissue present on each slide section examined.*

Grade 2: SLIGHT = the change is more noticeable but only evident as few/small foci or areas affected; *change affects 10 to 25% of the total tissue present on each slide section examined.*

Grade 3: MODERATE = the change is obviously present, and of appreciable size and/or number; *change affects 25-50%of the total tissue present on each slide section examined.*

Grade 4: MARKED = the change is abundant in many areas of the section and/or is of prominent size; *change affects 50-75% of the total tissue present on each slide section examined.*

Grade 5: SEVERE = the change affects a large proportion of the tissue and/or is of a large size; *change affects greater than 75% of the total tissue present on each slide section examined.*

Distribution: Focal = one focus only, Multifocal = 2 or more foci

Table 1 summarizes the incidences of the lung findings identified in the one year dog study with Cariprazine of treated and recovery dogs consolidated from our individual animal recordings presented in the Excel spreadsheet attachment to this document.

Summary Table 1. CFSAN Pathology Evaluation: Incidences of one year-dosed dog pulmonary Histopathological Findings

One Year <b>Dosed</b> Animals	Males N=4					Females N=4				
	1	2	3	4	5	1	2	3	4	5
Treatment groups	1	2	3	4	5	1	2	3	4	5
Dose mg/kg/day	0	1	2	4	6	0	1	2	4	6
Alveolar Foamy Macrophages	0	2	2	4	4	0	2	3	4	4
Multinucleated Giant Cells with Cholesterol Clefts	0	0	0	3	4	0	0	0	3	4
Inflammation	0	0	2	3	4	0	0	2	3	4
Fibrosis secondary to Inflammation	0	0	0	1	2	0	0	0	1	0

Summary Table 2. CFSAN Pathology Evaluation: Incidences of recovery dog pulmonary Histopathological Findings

2 Month <b>Recovery</b> Animals	Males N=2					Females N=2				
	1	2	3	4	5	1	2	3	4	5
Treatment groups	1	2	3	4	5	1	2	3	4	5
Dose mg/kg/day	0	1	2	4	6	0	1	2	4	6
Alveolar Foamy Macrophages	0	0	0	1	2	0	0	0	1	2
Multinucleated Giant Cells with / or without Cholesterol Clefts	0	0	0	1	2	0	0	0	1	2
Inflammation	0	0	0	1	2	0	0	0	1	1
Fibrosis secondary to Inflammation	0	0	0	1	1	0	0	0	1	0

Interpretation of Results:

The treatment related findings in term dogs were alveolar foamy macrophage aggregates in all treatment groups (groups 2-5) of minimal to mild severity in both sexes. Inflammation was observed in both sexes in the highest 3 dose groups (groups 3-5). Fibrosis secondary to organizing, chronic inflammation was present in groups 4 (both males and females) and 5 (males only). Multinucleated giant cell with /or without cholesterol clefts were observed only in the two highest dose groups of both sexes.

The recovery animals in groups 2 and 3 (males and females) did not show any histological lung changes compared to control animals indicating complete recovery at these dose levels. Foamy macrophage aggregates were still present at both high dose groups (groups 4 and 5) of male and female recovery animals. Macrophage accumulations in groups 4 and 5 of both sexes also contained multinucleated giant cells with or without cholesterol clefts as well as inflammation. In the two high dose groups, fibrosis as part of chronic inflammation was not observed in the recovery females of group 5.

## Discussion:

Based on the data presented above and in the attachment to this memorandum, our evaluation is in many aspects consistent with findings of the study pathologist and /or the first or second expert review. However, some differences are also noted.

The incidence of the lung changes summarized in Tables 1 and 2, ranged in severity from 1 to 2 (minimal to slight) indicating, according to our scoring scale above, that in all animals the total area occupied by alveolar macrophage aggregates and inflammation was always less than 25% of the total lung tissue presented in the slide. Compared to the study pathologist, we recorded an overall higher number of incidences but the overall severity score was lower. As previously mentioned, we anchored our evaluation on one parameter –tissue % affected - while the study pathologist did not provide a semi-quantitative numerical gauge for the grading parameters used in his scale (reference 1b, pg. 521)

## Macrophage aggregates:

Specifically, for lower doses, we agree with the study pathologist and the expert reviewers that the quality of the described treatment related findings consist of very few and very small **aggregates of foamy alveolar macrophages** (see Figure 1). These changes were stated to be compatible with **phospholipidosis** in the study pathology report and in both expert reviews (reference 1b, Appendix N pg. 1350, reference 1c and 2a). However, the study pathologist recorded in the individual animal tables an observation of **cholesterol clefts** (reference 1b, Appendix N), but failed to describe this observation further in the pathology report.

The first expert review report (reference 1c) did not comment on the observation of cholesterol clefts at all. The second expert review report (reference 2a, pg. 5) described the “occasional giant cells and a few cholesterol clefts” but did not elaborate further on the relevance of this finding in the context of a phospholipidosis change.

Our evaluation determined that the cholesterol clefts were consistently located in **multinucleated giant cells** (see Figure 3), found only in the macrophage aggregates of the two highest dose groups, and not in the typical foamy macrophages comprising the early (low dose) manifestation of the changes described here. Multinucleated giant cells generally result from macrophage fusion secondary to an inability of the macrophage to digest phagocytosed material; intracellular cholesterol clefts in macrophages are indicative of lipid rich materials stored within the macrophages. The manifestation of both of these features is theoretically conceivable considering the drug-class context of phospholipidosis. Multinucleated giant cells as well as cholesterol clefts are, however, not a typical feature of phospholipidosis; therefore these observations may warrant further consideration and investigation.

In general multinucleated giant cells are considered inflammatory cells comprising granulomatous inflammation; as the presentation of macrophages involved in this change, manifests as a morphologic continuum, it is difficult to determine if ‘foamy macrophage aggregates’ at higher concentrations of cariprazine would be better described as foci of ‘granulomatous inflammation’. However, although the appearance of multinucleated cells and cholesterol clefts increased with dose they were only present in the 2 highest doses of both sexes and foci remained overall very small and

infrequent considering the entirety of the lung parenchyma affected, which makes the overall relevance of this observation uncertain.

#### Fibrosis:

We further agree with the conclusion of the first expert report that the description of ‘**fibrosis**’ made by the study pathologist (reference 1b, pg. 46) is different from primary pulmonary fibrosis and that there is no resemblance, of changes observed in this study, to human pulmonary fibrosis.

We further agree with the second expert report (reference 2a, pg. 5) , that the “findings are not suggestive of the spectrum of pathologic changes usually associated with the group of chronic diffuse lung disorders or acute lung injury associated with adverse drug reactions in humans.”

We disagree, however, with the second expert report (reference 2a, pg. 4) stating that there was “no histologic evidence to suggest ongoing organization with fibrosis”. As outlined in the first expert review (reference 1b, pg. 46), we agree that there were focal chronic foci where “*The infiltrations resulted in thickening of the alveolar walls.*” And that “*in some cases, depending on the chronicity and severity, the chronic inflammation was associated with minimal degrees of organization interpreted as fibrosis, but the “fibrosis” was only a minor component of the lesions and is interpreted as being a secondary consequence of the inflammatory reaction” (see Figure 4).*

Fibrosis (newly produced collagen) at very small amounts is difficult to discern histologically in an H&E stained slide from preexisting collagen as both stain eosinophilic (pink). To more readily identify and visualize the degree of fibrosis, a special stain (Masson’s trichrome) for collagen is generally used.

Overall it appears that the issue of “fibrosis” in this case is mainly a consequence of failed communication. The study pathologist diagnosed: “Subacute (Chronic Active) / Chronic Inflammation/Fibrosis” which makes the Inflammation and the Fibrosis appear to be separate entities. A recording of “Subacute (chronic active)/Chronic Inflammation (with or without fibrosis)” would likely have caused less confusion. The pathologist’s even greater communication omission was not to comment on the finding of fibrosis in the pathology report narrative by explaining that some degree of collagen deposition (fibrosis) constitutes the hallmark of chronic inflammation, by definition.

#### Recovery:

Our findings in lungs of recovery animals were similar to those recorded by the study pathologist (reference 1b, Appendix N, pg. 1351) with regard to incidence and severity (see attached spreadsheet). Therefore we agree with the study pathologist’s statement that there is indication of some regression of the treatment changes but recovery is overall incomplete after 2 months in the two highest dose groups of both sexes.

## Your specific Questions:

**1. Do you agree with the Applicant's statement that the "fibrosis" component of the composite description "subacute/chronic inflammation/fibrosis" was not an observation of primary pulmonary fibrosis and bears no resemblance to pulmonary fibrosis in humans, which is a progressive condition with obliteration of normal architecture?**

As outlined above, we agree with the interpretation of the study pathologist's findings by the authors of the first expert report that the changes described are consistent with an observation of chronic inflammation that was associated with minimal degrees of organization manifesting as collagen deposition (fibrosis). This change is depicted in Figure 4 above. In agreement with the second expert report (human pulmonary physicians), we did not see evidence that the changes observed resembled any of the established patterns of adverse pulmonary drug reactions in humans.

**2. Do you agree with the Applicant's statement that "only in some cases", depending on the chronicity and severity, the chronic inflammation was associated with minimal degrees of organization interpreted as fibrosis, but the "fibrosis" was only a minor component of the lesions and is interpreted as being a secondary consequence of the inflammatory reaction.**

Our evaluation identified a total of 7/24 animals in groups 4 and 5 (See Summary Incidence Tables above) with focal, minimal to mild chronic inflammation in which fibrosis was a minor component of the lesion and was considered to be a secondary consequence to inflammation. As stated above, the definition of chronicity with regard to inflammatory processes is the presence of some degree of fibrosis.

**3. Do you agree with the Applicant's assessment that in two males at 1 mg/kg/day, at the minimal severity of inflammation, these lesions were comprised of inflammatory cells without fibrosis and, therefore, the 1 mg/kg/day could be a NOEL?**

Based on our assessment of the lung tissues, neither inflammation nor fibrosis was observed at the 1mg/kg/day dose level in either sex. However, foamy alveolar macrophage aggregates were observed in both sexes at this dose level. Therefore, a lung NOEL was not achieved in this dog study.

Inflammation is a known confounding factor of phospholipidosis, therefore we consider the lowest dose level at which inflammation is observed, the lung LOAEL of this study. Accordingly, the NOAEL would be at the 1mg/kg/day dose level. However, as described above, the morphological manifestation of multinucleated giant cell and cholesterol clefts at higher doses are unusual for phospholipidosis and may therefore warrant consideration in the safety assessment.

**4. Do you agree that chronic active inflammatory lesions were focal and the areas of the lung unaffected by the inflammatory processes were histologically normal?**

For illustration purposes, we have included 4 representative photomicrographs of the treatment related changes observed in the one year dog study. The upper right hand inset in these photomicrographs depicts the entirety of the lung tissue presented for evaluation. A very small box within this overview inset outlines the dimensions of the actual image presented in the main frame of the photo. This relation illustrates the relative low distribution of changes observed within the lung tissues of this study. Therefore, we agree with the study pathologist and the expert reviewers that the lesions were very focal, very small and that the lung tissue overall was histologically normal.

**5. Please comment, if possible, on effects of fibrosis, inflammation, phospholipidosis and/or thickening of the alveolar wall caused by inflammation on lung function in dogs.**

Assessments of lung function are best extrapolated from in life data rather than the two-dimensional, histomorphological assessment of tissue slides. However, in the absence of any reported pulmonary clinical signs we do not anticipate any functional deficits given the relative rare occurrence of alveolar macrophage aggregates, inflammation, thickening of the alveolar walls and fibrosis secondary to inflammation in the entirety of the lung tissue evaluated.

Please let us know if you have any questions.

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Date: 2015.08.12 15:05:44 -04'00'

Sabine Francke, D.V.M., Ph.D., FIATP and Steven Mog D.V.M., DACVP

Dog ID-slide #	R = Recovery	Diagnosis (Phospholipidosis-like)				Diagnosis associated with Phospholipidosis-like findings	
		Alveolar Foamy Macrophages	MN giant cells	Cholesterol clefts	Interstitial Foamy Macrophages	Inflammation	with/without Fibrosis
<b>GROUP 1</b>							
1290-13		0	n	n	n	0	n
1290-14		0	n	n	n	0	n
1291-13		0	n	n	n	0	n
1291-14		0	n	n	n	0	n
1292-13		0	n	n	n	0	n
1292-14		0	n	n	n	0	n
1293-13		0	n	n	n	0	n
1293-14		0	n	n	n	0	n
1294-13	R	0	n	n	n	0	n
1294-14		0	n	n	n	0	n
1295-13	R	0	n	n	n	0	n
1295-14		0	n	n	n	0	n
1790-13		0	n	n	n	0	n
1790-14		0	n	n	n	0	n
1791-13		0	n	n	n	0	n
1791-14		0	n	n	n	0	n
1792-13		0	n	n	n	0	n
1792-14		0	n	n	n	0	n
1793-13		0	n	n	n	0	n
1793-14		0	n	n	n	0	n
1794-13	R	0	n	n	n	0	n
1794-14		0	n	n	n	0	n
1795-13	R	0	n	n	n	0	n
1795-14		0	n	n	n	0	n

Dog ID-slide #	R = Recovery	Alveolar Foamy Macrophages	MN giant cells	Cholesterol clefts	Interstitial Foamy Macrophages	Inflammation	with/without Fibrosis
<b>GROUP 2</b>							
2290-13		1, mf	n	n	y	0	n
2290-14		1, mf	n	n	y	0	n
2291-13		0	n	n	n	0	n
2291-14		0	n	n	n	0	n
2292-13		1, mf	n	n	y	0	n
2292-14		1, mf	n	n	y	0	n
2293-13		0	n	n	n	0	n
2293-14		0	n	n	n	0	n
2294-13	R	0	n	n	n	0	n
2294-14		0	n	n	n	0	n
2295-13	R	0	n	n	n	0	n
2295-14		0	n	n	n	0	n
2790-13		0	n	n	n	0	n
2790-14		0	n	n	n	0	n
2791-13		1, mf	n	n	y	0	n
2791-14		0	n	n	n	0	n
2792-13		0	n	n	n	0	n
2792-14		0	n	n	n	0	n
2793-13		0	n	n	n	0	n
2793-14		1, mf	n	n	y	0	n
2794-13	R	0	n	n	n	0	n
2794-14		0	n	n	n	0	n
2795-13	R	0	n	n	n	0	n
2795-14		0	n	n	n	0	n

Dog ID-slide #	R = Recovery	Alveolar Foamy Macrophages	MN giant cells	Cholesterol clefts	Interstitial Foamy Macrophages	Inflammation	with/without Fibrosis
<b>GROUP 3</b>							
3290-13		0	n	n	n	0	n
3290-14		0	n	n	n	0	n
3291-13		0	n	n	n	0	n
3291-14		1, f	n	n	y	1, f	n
3291-35		0	n	n	n	3*, mf	n
3291-36		0	n	n	n	3*, mf	n
					*character of inflammation = aspiration pneumonia		
3292-13		0	n	n	n	0	n
3292-14		0	n	n	n	0	n
3293-13		0	n	n	n	0	n
3293-14		1, f	n	n	n	0	n
3293-35		1, f	n	n	n	1, f	n
3294-13	R	0	n	n	n	0	n
3294-14		0	n	n	n	0	n
3295-13	R	0	n	n	n	0	n
3295-14		0	n	n	n	0	n
3790-13		1, mf	n	n	n	1, f	n
3790-14		1, mf	n	n	n	0	n
3791-13		0	n	n	n	0	n
3791-14		0	n	n	n	0	n
3792-13		0	n	n	n	0	n
3792-14		1, f	n	n	y	1, f	n
3793-13		0	n	n	n	0	n
3793-14		1, f	n	n	y	0	n
3794-13	R	0	n	n	n	0	n
3794-14		0	n	n	n	0	n
3795-13	R	0	n	n	n	0	n
3795-14		0	n	n	n	0	n

Dog ID-slide #	R = Recovery	Alveolar Foamy Macrophages	MN giant cells	Cholesterol clefts	Interstitial Foamy Macrophages	Inflammation	with/without Fibrosis
<b>GROUP 4</b>							
4290-13		0	n	n	n	0	n
4290-14		1, mf	n	n	y	0	n
4291-13		0	n	n	n	0	n
4291-14		1, f	y	n	n	1, mf	n
4292-13		1, f	n	n	n	0	n
4292-14		1, mf	y	y	y	1, mf	n
4293-13	R	2, mf	y	y	y	2, mf	y
4293-14		2, mf	y	y	y	2, mf	n
4294-13		1, mf	y	y	y	1, mf	n
4294-14		2, mf	y	y	y	2, mf	y
4295-13	R	0	n	n	n	0	n
4295-14		0	n	n	n	0	n
4790-13		1, mf	y	y	y	1, mf	n
4790-14		1, f	n	n	y	0	n
4791-13		2, mf	y	y	y	1, mf	n
4791-14		2, mf	y	y	y	1, mf	y
4792-13		2, mf	y	y	y	1, mf	n
4792-14		2, mf	y	y	y	1, mf	n
4793-13		1, mf	n	n	y	0	n
4793-14		0	n	n	n	0	n
4794-13	R	0	n	n	n	0	n
4794-14		0	n	n	n	0	n
4794-35		1, mf	y	y	y	1, mf	y
4795-13	R	0	n	n	n	0	n
4795-14		0	n	n	n	0	n

Dog ID-slide #	R = Recovery	Alveolar Foamy Macrophages	MN giant cells	Cholesterol clefts	Interstitial Foamy Macrophages	Inflammation	with/without Fibrosis
<b>GROUP 5</b>							
5290-13		2, mf	y	y	y	1, mf	n
5290-14		2, mf	y	y	y	2, mf	n
5291-13		1, mf	y	y	y	1, mf	n
5291-14		1, mf	y	y	y	1, mf	n
5292-13		0	n	n	n	0	n
5292-14		2, mf	y	y	y	2, mf	y
5293-13		2, mf	y	y	y	1, mf	y
5293-14		2, mf	y	y	y	2, mf	y
5294-13	R	1, mf	y	y	y	1, mf	n
5294-14		1, mf	y	y	y	1, mf	n
5295-13	R	1, mf	n	n	n	1, mf	y
5295-14		1, mf	y	y	y	1, mf	n
5790-13		1, mf	n	n	n	1, mf	n
5790-14		2, mf	y	y	y	1, mf	n
5791-13		2, mf	y	y	y	2, mf	n
5791-14		1, mf	y	y	y	1, mf	n
5792-13	R	0	n	n	n	0	n
5792-14		2, mf	y	y	y	1, mf	n
5793-13	R	1, mf	y	y	n	0	n
5793-14		1, f	y	y	n	0	n
5794-13		2, mf	y	y	y	1, mf	n
5794-14		2, mf	y	y	y	1, mf	n
5795-13		1, mf	y	n	y	1, mf	n
5795-14		2, mf	y	y	y	1, mf	n

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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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KIMBERLY S UPDEGRAFF

08/17/2015

CFSAN reviewed entered into DARRTS by RPM

**Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Pharmacology/Toxicology and Clinical Consultation**

**NDA:** 204370

**Sponsor:** Forest Pharmaceutical Research Institute

**Drug:** Cariprazine (for Schizophrenia and Bipolar disorder)

**Route of Administration:** Oral

**Date of consult:** July 1, 2015

**From:**

Timothy W. Robison, Ph.D., D.A.B.T.  
Pharmacology/Toxicology Team Leader  
DPARP

Sally Seymour, M.D.  
Deputy Division Director for Safety  
DPARP

**Through:**

Badrul Chowdhury, M.D., Ph.D.  
Division Director  
DPARP

**To:** Kim Updegraff  
Project Manager  
Division of Psychiatric Products

**Background:** Forest Pharmaceutical Research Institute resubmitted NDA 204370, which proposes the use of cariprazine for schizophrenia and bipolar disorder. The Division of Psychiatry Products (DPP) issued a complete response letter on November 19, 2013.

In the nonclinical program, cariprazine-induced phospholipidosis was observed in the lungs of mice, rats, and dogs. In many cases, these findings were accompanied by additional progressive findings of inflammation, hemorrhage, and/or fibrosis. During the first cycle review for this application, DPP consulted DPARP to help evaluate the potential of cariprazine to cause pulmonary toxicity in humans. In a review dated August 23, 2013, Dr. Sally Seymour, the DPARP Medical Officer, stated that although the clinical data did not identify a pulmonary safety signal, pulmonary safety could not be assured based upon comparable adverse histopathological findings in the lungs of three different nonclinical test species.

A complete response (CR) letter was issued on November 19, 2013, but the pulmonary non-clinical toxicity issue was not identified as a deficiency. A response to the CR letter was submitted to DPP on December 17, 2014. In May 2015, DPP contacted DPARP to

discuss the non-clinical pulmonary toxicity issues with cariprazine. A meeting was held May 26, 2015. During the meeting, it was determined that there were outstanding concerns with the non-clinical pulmonary findings with cariprazine and more information from the sponsor was needed.

On May 29, 2015, DPP requested additional information about the clinical relevance of the animal toxicity findings.

*With regard to PLD in the presence of inflammation/fibrosis in dogs, please provide an explanation, along with any supportive information, of the clinical relevance (or lack thereof) of phospholipidosis in human subjects. We note that, if inflammation and/or fibrosis were to occur in humans, this would be an unmonitorable event. Thus, if this toxicity is relevant to humans, the risks associated with cariprazine would probably outweigh its potential benefits. Please provide any information to support the position that this observed animal toxicity is not relevant to humans.*

In addition, DPP on June 4, 2015 sent the following request:

*We recommend that you review the lung histopathology findings in the dog 1-year toxicity study, specifically in relation to phospholipidosis in presence of inflammation and fibrosis and, if necessary, re-evaluate the slides.*

*We note the following from the study report:*

*Page 55, Table 3.10.2-2, lists microscopic findings in the lungs as “subacute/chronic inflammation;” however, on page 533 of the report, the table of incidence summary lists “subacute (chronic active)/chronic inflammation/**Fibrosis** [emphasis added].”*

*There are discrepancies between Table 2, below, submitted in your response to an FDA request for information dated May 22, 2013, and the two tables listed above with regard to the total number of dogs with lung findings. The study report tables state that four female dogs each in the 4 and 6 mg/kg/day groups had lung findings of interest, but the table below lists only three female dogs in each of those groups. Moreover, the table below does not list “fibrosis.” Please explain these discrepancies.*

**Table 2. Incidence of Adrenal and Lung Findings in the 52-Week Dog Study**

Dose (mg/kg/day)	0		1		2		4		6	
	Male	Female								
<b>N=4</b>										
<b>Adrenals</b>										
Phospholipidosis	0	0	0	2	1	2	4	1	4	4
Phospholipidosis Inflammation	0	0	0	0	0	1	0	0	0	0
<b>Lung</b>										
Phospholipidosis	0	0	0	0	0	0	0	0	0	0
Inflammation	0	0	0	0	0	1	0	0	0	0
Hemorrhage	2	0	0	0	0	0	0	0	0	1
Phospholipidosis Inflammation	0	0	2	0	2	2	3	2	3	3
Phospholipidosis Inflammation Hemorrhage	0	0	0	0	0	0	1	1	1	0

On June 8, 2015, the Sponsor provided a response. DPP qualified the response as a major amendment and subsequently issued a letter informing the Sponsor of their decision to extend the review cycle. The revised PDUFA date is September 17, 2015; however, the Division is prepared to act prior the PDUFA date if possible.

DPP requested DPARP's input regarding the nonclinical interpretation and the clinical relevance of these findings based on the recent submission.

**DPARP Assessment of Lung Findings from the Sponsor's Nonclinical Toxicology Studies with Mice, Rats, and Dogs (From Dr. Seymour's Consultation dated August 23, 2013):**

In the non-clinical program, phospholipidosis (PLD), characterized by the presence of foamy alveolar macrophages (AM), was observed in the lungs of rats, dogs, and mice. In many cases, these findings were accompanied by additional progressive findings of inflammation, hemorrhage, and/or fibrosis. In DPARP's experience, PLD in the lungs is a common finding in rats, especially with inhaled drugs, but PLD in the lungs of dogs is not a common finding. Findings of AM alone in the lungs are generally not considered adverse unless there is evidence of progression, such as histopathological findings of inflammation, hemorrhage, and/or fibrosis that accompany findings of foamy AM. For findings of PLD associated with these progressive changes, it is general DPARP practice to determine a NOAEL (e.g., no evidence of foamy AMs given concerns that macrophages are mediating the lung damage) and limit clinical dosing to ensure an adequate safety margin for PLD. These microscopic changes are not considered monitorable in a clinical setting. Therefore, it is important to have an adequate safety margin based upon the non-clinical studies.

**Histopathological Findings in the Lungs from the 12-month Toxicology Study with Dogs:** The DPARP PharmTox Consultation focuses on histopathological findings in the lungs from the 12-month oral toxicology study with beagle dogs.

The following information was taken from the review of Dr. Elzbieta Chalecka-Franaszek dated July 22, 2013.

In the 12-month toxicology study, Beagle dogs (6/sex/group) received cariprazine in oral gelatin capsules at doses of 0, 1, 2, 4, and 6 mg/kg/day. Four dogs/sex/group were sacrificed after the 12-month dosing period. The remaining 2 dogs/sex/group were sacrificed following a 2-month recovery period.

At the end of the 12-month dosing period, gross pathological examination of the lungs found scattered foci of slight to severe discolorations (white, tan, yellow) for 2 of 4 males at 2 mg/kg/day and all males and females at the 4 and 6 mg/kg/day. These findings were still evident in the lungs at the end of the 2-month recovery period for 1 of 2 males and 1 of 2 females at 4 mg/kg/day and all males and females at 6 mg/kg/day. These findings in the lungs were judged to be partially reversible at 4 mg/kg/day and not reversible at 6 mg/kg/day.

**Table 1 Gross pathological findings in the lungs at the end of 12-month dosing period and 2-month recovery period**

**Table 3.10.1-1: Test Article-Related Macroscopic Findings**

Group	1		2		3		4		5	
Dose(mg/kg/day)	0		1		2		4		6	
Sex	M	F	M	F	M	F	M	F	M	F
<b>Dosing Phase (number/group)</b>	4	4	4	4	4	4	4	4	4	4
<i>Eyes:</i>										
Discolored (white)/Opacity	0	0	0	0	0	0	1	2	1	2
<i>Lungs:</i>										
Discolored (white/tan/yellow foci)	0	0	0	0	2	0	4	4	4	4
<i>Adrenal Glands:</i>										
Enlarged	0	0	0	0	0	0	1	3	0	4
<i>Gall Bladder</i>										
Discolored (green/black material)	0	0	0	0	0	0	2	0	1	2
<b>Recovery Phase (number/group)</b>	2	2	2	2	2	2	2	2	2	2
<i>Eyes:</i>										
Discolored (white)	0	0	0	0	0	0	0	0	0	1
<i>Lungs:</i>										
Discolored (tan/yellow foci)	0	0	0	0	0	0	1	1	2	2

Histopathological examination of the lungs from dogs after the 12-month dosing period found alveolar/intra-alveolar foamy macrophages with or without cholesterol clefts, consistent with phospholipidosis, at all doses for males and at doses  $\geq 2$  mg/kg/day for females. The severity of these findings (minimal to moderate) increased with dose. Findings of foamy macrophages were accompanied by additional findings of subacute/chronic inflammation/fibrosis for 2 of 4 males at 1 mg/kg/day, 2 of 4 males and 2 of 4 females at 2 mg/kg/day, and all males and females at 4 and 6 mg/kg/day (see page 533 and 557 of the study report). The severity of these findings increased with dose (minimal to moderate). At the end of 2-month recovery period, findings of foamy macrophages were still evident at doses  $\geq 4$  mg/kg/day, although the severity was reduced (minimal to slight). Accompanying findings of subacute/chronic inflammation/fibrosis were also observed at doses  $\geq 4$  mg/kg/day and the severity was similarly reduced. The findings of foamy macrophages and subacute/chronic inflammation/fibrosis were only partially reversible.

The report was judged to be problematic in that findings of subacute inflammation, chronic inflammation, and fibrosis were pooled together rather than describing the findings separately.

**Table 2 Histopathological findings in the lungs at the end of the 12-month dosing period**

RGH-188 HCl: A One-Year Oral (Capsule) Toxicity Study  
in Dogs with a Two Month Recovery Period

Incidence Summary of Microscopic Findings with Severity Levels  
Terminal Sacrifice

Controls from group(s): 1		-- Animals --					Affected --					
		-- Males --					-- Females --					
Tissues	With Diagnoses	Animal sex: Dosage group: No. in group:	Ctls	2	3	4	5	Ctls	2	3	4	5
Lungs .....Number examined:			4	4	4	4	4	4	4	4	4	4
CONGESTION												
	->		1	2	0	2	0	0	0	0	2	0
	2>		3	2	4	2	4	4	4	4	2	4
.....Total Incidence of Finding Observed:			3	2	4	2	4	4	4	4	2	4
HEMORRHAGE(S)												
	->		2	3	4	2	3	4	4	4	2	4
	1>		1	1	0	2	1	0	0	0	1	0
	2>		1	0	0	0	0	0	0	0	1	0
.....Total Incidence of Finding Observed:			2	1	0	2	1	0	0	0	2	0
ALVEOLAR/INTRAALVEOLAR FOAMY MACROPHAGES (WITH/WITHOUT -"CHOLESTEROL" CLEFTS)												
	->		4	2	2	0	0	4	4	2	0	0
	1>		0	2	1	2	0	0	0	2	2	0
	2>		0	0	1	1	1	0	0	0	1	1
	3>		0	0	0	1	3	0	0	0	1	3
.....Total Incidence of Finding Observed:			0	2	2	4	4	0	0	2	4	4
LYMPHOID CELL AGGREGATE(S)												
	->		4	3	4	3	4	4	3	3	4	3
	1>		0	1	0	1	0	0	1	1	0	1
.....Total Incidence of Finding Observed:			0	1	0	1	0	0	1	1	0	1
SUBACUTE (CHRONIC ACTIVE)/CHRONIC INFLAMMATION/FIBROSIS												
	->		4	2	2	0	0	4	4	2	0	0
	1>		0	2	1	2	0	0	0	2	2	0
	2>		0	0	1	1	1	0	0	0	1	1
	3>		0	0	0	1	3	0	0	0	1	3
.....Total Incidence of Finding Observed:			0	2	2	4	4	0	0	2	4	4

All Diagnoses; Phases: P4; Death types: All; Date of death range: 07-Dec-06 To 21-Dec-06

**Table 3 Histopathological findings in the lungs at the end of the 2-month recovery period that followed the 12-month dosing period**

RGH-188 HCl: A One-Year Oral (Capsule) Toxicity Study  
in Dogs with a Two Month Recovery Period

Incidence Summary of Microscopic Findings with Severity Levels  
Recovery Sacrifice

---

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	-- Animals --					Affected --				
		-- Males --					-- Females --				
		Ctls	2	3	4	5	Ctls	2	3	4	5
Controls from group(s): 1											
Lungs	Number examined:	2	2	2	2	2	2	2	2	2	2
ALVEOLAR/INTRAALVEOLAR FOAMY MACROPHAGES (WITH/WITHOUT -"CHOLESTEROL" CLEFTS)	->	2	2	2	1	0	2	2	2	1	0
	1>	0	0	0	0	0	0	0	0	1	1
	2>	0	0	0	1	2	0	0	0	0	1
.....Total Incidence of Finding Observed:		0	0	0	1	2	0	0	0	1	2
Lymphoid Cell Aggregate(s)	->	2	2	2	2	2	2	1	2	2	2
	1>	0	0	0	0	0	0	1	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	1	0	0	0
Subacute (Chronic Active)/Chronic Inflammation/Fibrosis	->	2	2	2	1	0	2	2	2	1	0
	1>	0	0	0	0	0	0	0	0	1	1
	2>	0	0	0	1	2	0	0	0	0	1
.....Total Incidence of Finding Observed:		0	0	0	1	2	0	0	0	1	2
Granulomatous Inflammation	->	2	2	2	1	2	2	2	2	2	2
	1>	0	0	0	1	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	1	0	0	0	0	0	0
Interstitial: Mineral Deposit(s)	->	2	2	2	2	2	2	2	2	2	2
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	0	0
Interstitial: Osseous Metaplasia	->	2	2	2	2	1	2	2	2	2	2
	1>	0	0	0	0	1	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	0	1	0	0	0	0	0

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All Diagnoses; Phases: P5; Death types: All; Date of death range: 08-Feb-07 To 22-Feb-07

**Sponsor's Re-evaluation of Lung Lesions from the 12-month Toxicology Study with Dogs:** On June 8, 2015, the Sponsor provided a response to DPP that included a re-evaluation of the lung lesions from the 12-month dog study conducted by four Veterinary Pathologists with a focus on the fibrosis component of "subacute/chronic inflammation/fibrosis" composite description in the original toxicology report.

The Sponsor provided the following comments regarding the re-evaluation of lung lesions from 12-month dog study. "Upon re-examination of all of the lung slides from the 12-month study, the changes described as subacute (chronic active)/chronic inflammation/fibrosis were characterized as minimal to moderate infiltrations of leukocytes, including foamy macrophages and lymphocytes, in the alveolar septae and the alveolar spaces. The infiltrations resulted in thickening of the alveolar walls. At all severities, the findings were focal even after a year of daily treatment. The chronic inflammation was only rarely associated with minimal degrees of organization which was originally referred to as "fibrosis". In addition, organization represented only a minor component of this composite histologic observation, and is an expected secondary effect to the inflammatory process, and was absent at the lowest dose in the study (1 mg/kg/day). The use of the term "fibrosis" in the composite observation is not indicative

of an observation of pulmonary fibrosis with structural organ changes and as such bears no resemblance to pulmonary fibrosis in humans.”

#### **DPARP PharmTox Evaluation of the Sponsor’s Response:**

The Sponsor’s re-evaluation of lung tissue slides was judged to be somewhat unusual in that there were no tables listing the histopathological findings in the lungs from the re-evaluation. Further, no photomicrographs of the lung lesions in question were provided. Setting these issues aside, the findings appear to be generally focal in nature and consist of inflammation and thickening of the alveolar walls. Fibrosis was not a prominent feature (i.e., organization represented a minor component of the composite histopathological observation) and reported to be absent at the low dose of 1 mg/kg/day. Lung findings at lower doses of 1 and 2 mg/kg/day were reported to be reversible, while findings at doses of 4 and 6 mg/kg/day were only partially or not reversible. The reversibility of findings at lower doses of 1 and 2 mg/kg/day might further confirm that fibrosis was absent or not a prominent feature at these doses with the assumption that fibrosis is not generally reversible.

The findings of lung inflammation are a concern for a chronically administered drug. For the low dose of 1 mg/kg/day, there were no findings in the lungs for females and limited findings in the lungs for 2 of 4 males, which appears to provide a 2-fold safety margin on an AUC basis. The larger exposure margin provides some separation from only partial or no reversibility of lung findings at higher doses.

Overall, based upon the focal nature of the lung findings, which consisted of inflammation and some thickening of the alveolar walls, and given that fibrosis was not a prominent feature, the level of concern would be reduced. The findings of lung inflammation are a concern for a chronically administered drug. These findings might be reported in the drug product label in Section 13.2.

#### **Clinical Summary of the June 8, 2015 submission**

In the response to IR, the sponsor also provided information on the safety data from the clinical trial database. There were over 1800 patients treated with cariprazine in studies 16 weeks duration or longer. The sponsor provided a summary of the respiratory adverse event data, laboratory data, and concomitant medication use for pulmonary conditions. Not surprisingly, there was no pulmonary safety signal identified in the sponsor’s review of the clinical pulmonary safety data.

The sponsor also provided a literature review of drugs with phospholipidosis findings in animals, including case reports of pulmonary adverse outcomes with these drugs. The sponsor noted the small number of literature reports given the number of drugs and years of marketing.

The sponsor also provide expert pulmonology consultation. The consultants noted that the clinical relevance of PLD findings in animals is unclear. The consultants noted that there would be more concern if the PLD was associated with inflammation or fibrosis,

but that inflammation may be reversible with discontinuation of the drug. The consultants recommended the sponsor review the histopath findings from the 1 year dog study to clarify the risk and extent of fibrosis.

**DPARP Clinical Evaluation of the Sponsor's Response:**

The additional clinical data provided by the sponsor do not adequately address the safety concern of pulmonary toxicity identified in the toxicology studies. As noted in my original consult dated August 23, 2013, the histological changes in the animal studies are not clinically monitorable. The lack of a signal in the clinical program does not assure that cariprazine does not have adverse effects on the lungs. The effects of inflammation and fibrosis in the lungs could take years to manifest clinically.

The re-review of the animal toxicity studies does suggest that fibrosis was not a prominent feature and the findings were reversible at low doses and partially reversible at higher doses. This does raise questions about the fibrosis findings, since fibrosis is generally not reversible. The finding of pulmonary inflammation remains, which is a concern especially for a drug intended for long-term use. According to Dr. Robison's evaluation of the chronic dog toxicity study, there is a 2-fold safety margin (AUC) for the lung inflammation for the low dose, if you discount that the male dogs had minimal inflammation at the low dose. This provides some reassurance.

Overall, the finding of pulmonary fibrosis in the lungs in dogs is in question and while the concern for pulmonary inflammation remains, this is less a concern than fibrosis. Strictly speaking, there is no safety margin for the inflammation, but if you discount that the male dogs had minimal inflammation at low dose, there is a 2 fold safety margin.

While the animal studies do not provide clean non-clinical support with regards to adverse findings in the lungs, the risk of fibrosis seems less likely, which is reassuring. The potential for pulmonary inflammation is still unclear, but the findings at lower doses in animals were minimal. We cannot predict the likelihood of pulmonary inflammation in humans, but the more serious concern about fibrosis appears to be less likely. Overall, the non-clinical data do not provide compelling evidence of serious pulmonary safety risk that would preclude approval of a beneficial drug. Given the nature of the findings, no specific pulmonary monitoring is recommended.

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/s/  
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TIMOTHY W ROBISON  
07/01/2015

SALLY M SEYMOUR  
07/01/2015

BADRUL A CHOWDHURY  
07/01/2015



Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
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### MEMORANDUM TO FILE

**Date:** August 9, 2013

**From:** Amy M. Taylor, MD, MHS Medical Officer  
Pediatric and Maternal Health Staff

**Through:** Hari Cheryl Sachs, MD Acting OND Associate Director  
Pediatric and Maternal Health Staff

**NDA Number:** 204-370

**Sponsor:** Forest Research Institute

**Drug:** cariprazine

**Dosage form and route of administration:** capsule, oral

**Proposed Adult Indications:**

- Treatment of schizophrenia
- Treatment of manic or mixed episodes associated with bipolar I disorder

**Consult request:** The Division of Psychiatry Products requested PMHS' input on "all relevant section of the label."

#### Background

The applicant's NDA 204-370 is currently under review by the Division of Psychiatry Products for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. DPP request PMHS' assistance with the labeling language for subsection 8.4 Pediatric Use. The product has not been studied in pediatric patients.

#### Current labeling (August 1, 2013)

##### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

*Reviewer comment: The Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (Pediatric Labeling Guidance) states that:*

*“When substantial evidence does **not** exist to support an indication in **any** pediatric population, or the drug has not been studied in any pediatric population, the following statement (or a reasonable alternative) must be included (21 CFR 201.57(c)(9)(iv)(F)): “Safety and effectiveness in pediatric patients have not been established.” The basis for this statement should be provided (e.g., stating that studies have not been conducted or providing an explanation of why the available evidence does not support a pediatric approval).”*

*A statement should be added that the drug hasn't been studied. The Division should confirm with the sponsor that there are no studies in pediatric patients that have not been reported. In addition, subsection 8.1 Pregnancy discusses neonatal withdrawal symptoms. The current labeling states:*

*Fetal/Neonatal Adverse Reactions*

*Monitor neonates (b) (4) extrapyramidal or withdrawal symptoms. (b) (4) agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in neonates exposed to antipsychotic drugs during the third trimester of pregnancy. These (b) (4) have varied in severity; (b) (4) prolonged hospitalization.*

*A brief statement on this topic should be included in the Pediatric Use subsection referring the reader to section 8.1 since the providers caring for the neonate will be pediatric providers.*

**Recommendations**

Subsection 8.4 Pediatric Use should contain the following language:

Safety and effectiveness in pediatric patients have not been established since pediatric studies of TRADENAME have not been conducted. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [see *Use in Specific Populations (8.1)*]

**Addendum May 29, 2015**

The cariprazine NDA received a complete response after the first cycle review primarily because of difficulty establishing a dosing regimen with the data submitted and safety concerns (b) (4). The sponsor resubmitted the NDA on December 17, 2014. The Division of Pediatric and Maternal Health reviewed the labeling again and has no changes to their recommendations from August 9, 2013.

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/s/  
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AMY M TAYLOR  
06/01/2015

LINDA L LEWIS  
06/01/2015



Food and Drug Administration  
Office of New Drugs  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
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### PLLR Labeling Memorandum

**Date:** May 26, 2015

**From:** Carrie Ceresa, Pharm D, MPH  
Clinical Analyst, Maternal Health Team  
Division of Pediatric and Maternal Health

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

Lynne P. Yao, M.D., Acting Division Director,  
Division of Pediatric and Maternal Health

**To:** The Division of Psychiatry Products (DPP)

**Drug:** Cariprazine

**NDA:** 204370

**Applicant:** Forest Research Institute

**Drug Class:** Antipsychotic

**Indication(s)** schizophrenia and bipolar disorder, manic episodes

**Subject:** Pregnancy and Lactation Labeling Rule (PLLR) Conversion

**Submission Date:** December 17, 2014

**Consult Date:** March 11, 2015

**Materials Reviewed:**

- July 19, 2013: DPMH maternal health labeling consult (formerly PMHS)
- December 17, 2014: NDA 204370 submission

**BACKGROUND**

**Pregnancy and Lactation Labeling Rule (PLLR)**

On December 4, 2014, the Food and Drug Administration (FDA) published the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). 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 creates a new subsection for information with regard to females and males of 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 format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format.

**DISCUSSION**

On December 17, 2014, Forest Research Institute submitted a resubmission to NDA 204370 for cariprazine in response to the November 19, 2013, Complete Response letter they received from the FDA due to [REDACTED] <sup>(b) (4)</sup> and “safety” issues cited as major deficiencies.

Of note, DPMH (formerly PMHS) completed a labeling review on July 19, 2013, for cariprazine in the PLLR hybrid format. The content of the labeling has not changed substantively since the initial review provided by DPMH. The only change this memo documents is updating of labeling recommendations for subsection 8.1 and 8.2 in the “final” PLLR format because the hybrid format is no longer being used.

**CONCLUSION**

DPMH recommends the applicant add cariprazine to the National Pregnancy Registry for Atypical Antipsychotics upon approval. DPMH refers to the final NDA action for final labeling.

**RECOMMENDATIONS**

**HIGHLIGHTS**

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

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

## **8.1 Pregnancy**

### ***Pregnancy Exposure Registry***

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VRAYLAR 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***

Based on animal data VRAYLAR may cause fetal harm. Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dose (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day[see Data]. The clinical relevance of findings in rabbits is not known. Studies have not been conducted with VRAYLAR in pregnant women to inform any drug-associated risk for birth defects or miscarriage. Consider the benefits and risks of VRAYLAR and possible risks to the fetus when prescribing VRAYLAR to a pregnant woman. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### ***Clinical Considerations***

#### **Fetal/Neonatal Adverse Reactions**

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose 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***

Administration of cariprazine to pregnant rats at oral doses of 0.5, 2.5, and 7.5 mg/kg/day during the period of organogenesis caused reduced fetal weights and male anogenital distance, malformations (bent limb bones and localized fetal thoracic edema), visceral variations (undeveloped/underdeveloped renal papillae and/or distended urethrae), and skeletal developmental variations (bent ribs, unossified sternbrae) at  $\geq 0.5$  mg/kg/day (0.2 times the MRHD of 6 mg/day based on AUC of total cariprazine [i.e., sum of cariprazine, DCAR, and DDCAR]). These effects occurred in the absence of maternal toxicity at the 0.5 mg/kg/day dose; however maternal toxicity, observed as reduction in body weight and food consumption, occurred in dams treated at 2.5 mg/kg/day and above. Cariprazine had no effect on fetal survival.

Administration of cariprazine to pregnant rats during the period of organogenesis, throughout pregnancy and lactation at oral doses up to 1 mg/kg/day (0.4 times the MRHD of 6 mg/day based on AUC) decreased postnatal survival, birth weight, and post-weaning body weight of first generation pups. In addition, pale, cold bodies and developmental delays (renal papillae not developed/underdeveloped and decreased auditory startle response in males) were observed in the absence of significant maternal toxicity at this dose. Reproductive performance of the first generation pups was unaffected; however, second generation pups also had similar clinical signs and lower body weight.

No teratogenic effects were observed following administration of cariprazine to pregnant rabbits at doses up to 5 mg/kg/day (4.6 times the MRHD of 6 mg/day based on AUC). Maternal body weight and food consumption were decreased at the 5 mg/kg/day dose, however, no adverse effects were observed on pregnancy parameters or reproductive organs.

## **8.2 Lactation**

### ***Risk Summary***

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

## **17 Patient Counseling Information**

### **Pregnancy**

Advise patients that third trimester use of VRAYLAR may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy. [*see Use in Specific Populations (Error! Reference source not found.)*].

### **Pregnancy Registry**

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

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CARRIE M CERESA  
05/26/2015

LYNNE P YAO  
05/27/2015

Medical Officer's Review of NDA 204-370  
Ophthalmology Consult Review #2

NDA Resubmission Date: 12/17/14  
Review completed: 5/22/15

Name: Cariprazine (RGH-188)

Applicant: Forest Research Institute, Inc.

**Requested:** Forest Pharmaceutical Research Institute resubmitted NDA 204370 which proposes the use of cariprazine for schizophrenia and bipolar disorder. The Division of Psychiatry Products issued a complete response letter on November 19, 2013, stating (b) (4) and "safety" as the major deficiencies. The safety evaluation revealed ocular toxicity as one of the concerns. Dr. Wiley Chambers reviewed the original NDA submission (review dated August 27, 2013- see attachment).

In the resubmission, the ophthalmologic data from the NDA database of studies for the treatment of Schizophrenia (Group 1) and bipolar mania (Group 2) has been reanalyzed by cariprazine (b) (4). In addition, data are available from 4 new studies: RGH-MD-06 (20-week, open-label phase of ongoing study in schizophrenia relapse prevention), RGH-MD-56 (bipolar depression study), RGH-MD-75 (adjunctive therapy I major depressive disorder), and A002-A11 (PK and efficacy/safety in schizophrenia conducted in Japan). The updated ocular data includes up-to-date narratives for all cases of SAEs and non-serious AEs coded to preferred terms within the MedDRA Eye Disorders (SOC) and a summary of ocular findings to date. Based on the reanalysis of the cumulative efficacy and safety data, as well as additional PK data, the sponsor proposes to (b) (4)

We would appreciate your assessment of the most recent ophthalmology data, including updated patient narratives, LOCS III findings, ocular examinations and ocular adverse events. Narratives for ocular AEs are located in the respective study folders within Module 5. For ease of review, a list of narratives has been included as Appendix II of the Safety Update Report (Module 5.3.5.3) and an update to the ophthalmology report is provided as Appendix IV of the Safety Update Report (Module 5.3.5.3). A summary of the sponsor's ocular findings and the sponsor's conclusions can be found in the Clinical Overview, Section 4.5, and the Safety Update Report, Section 9.

**Specific questions:**

- 1) Based on the updated ocular data, does your assessment of the risk of cataract remain unchanged since your previous consult?
- 2) Based on the updated ocular data, does your assessment of the risk of retinal toxicity remain unchanged since your previous consult?
- 3) Does the sponsor's recommendation to (b) (4) change your assessment of ocular risk?
- 4) In your previous consult, you recommended that labeling include information on the potential for cariprazine to cause cataracts in dogs and retinal degeneration in rats. You also recommended that the adverse reactions section of the labeling include blurred vision an event which was observed in clinical trials in 2-3% of patients, and cataract development as a rare event. If cariprazine is approved for treatment of schizophrenia and bipolar disorder, do you have any changes or additions to your recommendations, based on the new data?

The submission is electronic and can be found via:

- EDR Location: <\\CDSESUB1\evsprod\NDA204370\204370.enx>
- SharePoint link to materials: [NDA 204370](#)

If you need additional information, please contact the clinical team leader, Dr. Lucas Kempf at 301-796-1140.

Mid-Cycle meeting: 3/17/15; Labeling discussion: 5/27/15; PDUFA: 6/17/15

Ophthalmology Consult #2

Cariprazine NDA 204-370

## Nonclinical Ocular Findings

### Cataract

Cataract formation was noted in 13-week and 1-year toxicity studies in dogs. The no-observed-effect levels (NOELs) for cataract formation in dogs (3 mg/kg/day and 2 mg/kg/day, respectively) provide approximately 6- and 4-fold exposure margins (cariprazine AUC) at the maximum recommended human dose (MRHD) (b) (4).

**Reviewer's Comments:** *The finding of cataract development in dogs appears to be reproducible. The clinical significance in humans is unknown without at least a two year study in humans.*

### Adverse Reactions:

#### Number (%) of Patients Who Had TEAEs of the Eye Disorders SOC During the Double-blind Treatment Period in Group 1A (Controlled Schizophrenia Studies)—Safety Population – 2 or more subjects

	Placebo (N = 584)	Cariprazine Modal Daily Dose			Overall Cariprazine (N = 1317)	Risperidone 4 mg (N = 140)	Aripiprazole 10 mg (N = 152)
		1.5-3 mg (N = 539)	4.5-6 mg (N = 575)	9-12 mg (N = 203)			
Eye disorders	15 (2.6)	15 (2.8)	22 (3.8)	13 (6.4)	50 (3.8)	4 (2.9)	5 (3.3)
Vision blurred	2 (0.3)	6 (1.1)	10 (1.7)	4 (2.0)	20 (1.5)	3 (2.1)	2 (1.3)
Dry eye	2 (0.3)	2 (0.4)	2 (0.3)	3 (1.5)	7 (0.5)	0	1 (0.7)
Eye irritation	3 (0.5)	1 (0.2)	0	2 (1.0)	3 (0.2)	0	0
Oculogyric crisis	1 (0.2)	2 (0.4)	0	1 (0.5)	3 (0.2)	0	0
Blepharitis	0	1 (0.2)	1 (0.2)	0	2 (0.2)	0	0
Eye pain	0	0	2 (0.3)	0	2 (0.2)	0	1 (0.7)
Eye swelling	0	1 (0.2)	0	1 (0.5)	2 (0.2)	0	0
Ocular hyperaemia	1 (0.2)	0	1 (0.2)	1 (0.5)	2 (0.2)	0	1 (0.7)
Visual acuity reduced	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.2)	0	0

Source: Safety Update Report Appendix VI, Table 5 1 1

#### Number (%) of Patients Who Had TEAEs of the Eye Disorders SOC During the Open-label Treatment Period in Group 1B (Long-term, Open-label Schizophrenia Studies)—Safety Population – 2 or more subjects

	Cariprazine Modal Daily dose			Overall Cariprazine (N = 679)
	1.5-3 mg (N = 170)	4.5-6 mg (N = 361)	9 mg (N = 148)	
Eye disorders	17 (10.0)	15 (4.2)	5 (3.4)	37 (5.4)
Vision blurred	4 (2.4)	6 (1.7)	2 (1.4)	12 (1.8)
Dry eye	2 (1.2)	1 (0.3)	2 (1.4)	5 (0.7)
Conjunctivitis	2 (1.2)	0	0	2 (0.3)
Eye irritation	0	2 (0.6)	0	2 (0.3)
Lacrimation increased	1 (0.6)	1 (0.3)	0	2 (0.3)
Normal tension glaucoma	1 (0.6)	0	0	1 (0.1)
Oculogyric crisis	1 (0.6)	0	0	1 (0.1)

**Number (%) of Patients Who Had TEAEs of the Eye Disorders SOC During the Double-blind Treatment Period in Group 2A (Double-blind Bipolar Mania Studies)—Safety Population – 2 or more subjects**

	Placebo (N = 442)	Cariprazine Modal Daily dose		Overall Cariprazine (N = 623)
		3-6 mg (N = 263)	9-12 mg (N = 360)	
Eye disorders	8 (1.8)	17 (6.5)	20 (5.6)	37 (5.9)
Vision blurred	5 (1.1)	10 (3.8)	13 (3.6)	23 (3.7)
Diplopia	0	0	3 (0.8)	3 (0.5)
Photophobia	0	1 (0.4)	1 (0.3)	2 (0.3)

**Number (%) of Patients Who Had TEAEs of the Eye Disorders SOC During the Open-label Treatment Period in Group 2B (Long-term, Open-label Bipolar Mania Study)—Safety Population – 2 or more subjects**

	Cariprazine Modal Daily dose		Overall Cariprazine (N = 402)
	3-6 mg (N = 234)	9-12 mg (N = 168)	
Eye disorders	25 (10.7)	10 (6.0)	35 (8.7)
Vision blurred	8 (3.4)	3 (1.8)	11 (2.7)
Dry eye	7 (3.0)	2 (1.2)	9 (2.2)
Blepharospasm	3 (1.3)	0	3 (0.7)
Conjunctivitis	3 (1.3)	0	3 (0.7)
Excessive eye blinking	1 (0.4)	1 (0.6)	2 (0.5)
Lacrimation increased	1 (0.4)	1 (0.6)	2 (0.5)

**Number (%) of Patients Who Had Ocular TEAEs During the Open-label Phase in Study RGH-MD-06—Run-in Phase Safety Population- 2 or more subjects**

	Cariprazine Modal Daily dose			Overall Cariprazine (N = 765)
	1.5-3 mg (N = 105)	4.5-6 mg (N = 255)	9 mg (N = 405)	
Eye disorders SOC	2 (1.9)	12 (4.7)	13 (3.2)	27 (3.5)
Vision blurred	1 (1.0)	5 (2.0)	5 (1.2)	11 (1.4)
Dry eye	0	1 (0.4)	1 (0.2)	2 (0.3)
Eye irritation	0	1 (0.4)	1 (0.2)	2 (0.3)
Intraocular pressure increased	0	2 (0.8)	0	2 (0.3)

**Number (%) of Patients Who Had TEAEs of the Eye Disorders SOC During the Double-blind Treatment Period in Study RGH-MD-56—Safety Population – 2 or more subjects**

Preferred Term	Placebo (N = 145) n (%)	Cariprazine 0.75 mg (N = 141) n (%)	Cariprazine 1.5 mg (N = 146) n (%)	Cariprazine 3 mg (N = 146) n (%)
Eye Disorders	3 (2.1)	1 (0.7)	2 (1.4)	3 (2.1)
Vision blurred	1 (0.7)	0	2 (1.4)	2 (1.4)

**Number (%) of Patients Who Had TEAEs of the Eye Disorders SOC During the Double-blind Treatment Period in Study RGH-MD-75—Safety Population – 2 or more subjects**

Preferred Term	Placebo (N = 266) n (%)	Cariprazine 1-2 mg/day (N = 273) n (%)	Cariprazine 2-4.5 mg/day (N = 273) n (%)
Eye disorders	4 (1.5)	8 (2.9)	15 (5.5)
Vision blurred	2 (0.8)	4 (1.5)	10 (3.7)

**Reviewer's Comments:** *There is consistent reporting of blurred vision being more common in the cariprazine group than in the placebo group in each of the study populations.*

## From Sponsor's Ophthalmic Consultant Report

### Lens: LOCS III

Assessment for cataract formation was performed in all studies in which ophthalmologic assessments were done. The LOCS III system for nuclear opalescence, nuclear color, cortical cataract, and posterior subcapsular cataract was used for each eye. The largest positive change from baseline for each patient was evaluated.

The definitions of positive lenticular shifts Class I, II, III were:

- Class I: increase from baseline in LOCS III grade of  $\geq 0.5$  (nuclear opalescence), or  $\geq 0.8$  (cortical), or  $\geq 0.5$  (posterior subcapsular)
- Class II: increase from baseline in LOCS III grade of  $\geq 0.9$  (nuclear opalescence),  $\geq 1.5$  (cortical), or  $\geq 0.9$  (posterior subcapsular)
- Class III: LOCS III grade of  $\geq 2.0$  for any type of opacity (nuclear opalescence, cortical, or posterior subcapsular) and increase from baseline in LOCS III grade of  $\geq 0.9$  (nuclear opalescence),  $\geq 1.5$  (cortical), or  $\geq 0.9$  (posterior subcapsular), or cataract surgery since baseline

Incidence of Lenticular Shifts in Group 1B (Long-term, Open-label Schizophrenia Studies)—Safety Population

	Cariprazine Modal Daily Dose			Overall Cariprazine n/N1 (%)
	1.5-3 mg n/N1 (%)	4.5-6 mg n/N1 (%)	9 mg n/N1 (%)	
Positive lenticular shifts at the end of treatment				
Class I	5/102 (4.9)	10/239 (4.2)	13/120 (10.8)	28/461 (6.1)
Class II	4/102 (3.9)	8/239 (3.3)	6/120 (5.0)	18/461 (3.9)
Class III	0/102	1/239 (0.4)	5/120 (4.2)	6/461 (1.3)
Negative lenticular shifts at the end of treatment				
Class I	11/102 (10.8)	20/239 (8.4)	13/120 (10.8)	44/461 (9.5)
Class II	3/102 (2.9)	7/239 (2.9)	2/120 (1.7)	12/461 (2.6)
Class III	1/102 (1.0)	1/239 (0.4)	1/120 (0.8)	3/461 (0.7)

LOCS III = Lens Opacities Classification System III; N1 = number of patients with nonmissing baseline and at least one postbaseline LOCS III assessment or with cataract surgery.

Source: Safety Update Report Appendix VI, [Table 13.6.1](#) and [Table 13.6.1.2](#).

Incidence of Lenticular Shifts in Group 1B (Long-term, Open-label Schizophrenia Studies)—Safety Population

	Cariprazine Modal Daily Dose			Overall Cariprazine n/N1 (%)
	1.5-3 mg n/N1 (%)	4.5-6 mg n/N1 (%)	9 mg n/N1 (%)	
Positive lenticular shifts at the end of treatment				
Class I	5/102 (4.9)	10/239 (4.2)	13/120 (10.8)	28/461 (6.1)
Class II	4/102 (3.9)	8/239 (3.3)	6/120 (5.0)	18/461 (3.9)
Class III	0/102	1/239 (0.4)	5/120 (4.2)	6/461 (1.3)
Negative lenticular shifts at the end of treatment				
Class I	11/102 (10.8)	20/239 (8.4)	13/120 (10.8)	44/461 (9.5)
Class II	3/102 (2.9)	7/239 (2.9)	2/120 (1.7)	12/461 (2.6)
Class III	1/102 (1.0)	1/239 (0.4)	1/120 (0.8)	3/461 (0.7)

LOCS III = Lens Opacities Classification System III; N1 = number of patients with nonmissing baseline and at least one postbaseline LOCS III assessment or with cataract surgery.

Source: Safety Update Report Appendix VI, [Table 13.6.1](#) and [Table 13.6.1.2](#).

**Reviewer's Comments concerning Cataracts:** *While there are individual cases of increasing lens opacification, there are relatively few cases. It remains possible that the follow-up period was not long enough to detect lens changes. It is recommended that cataract development be listed in the adverse reaction section of the labeling.*

**Intraocular pressure (IOP):** Mean changes from baseline to the end of treatment in IOP were negligible in both short- and long-term studies, and in controlled studies changes were similar across treatment groups. Only 4 patients had IOP readings of > 25 mm Hg, and based on normal ocular examination findings, 3 of these 4 patients are likely to be ocular hypertensive. The remaining patient, who had a report of increased cup disc ratio, is likely to have had undiagnosed chronic open-angle glaucoma.

**Reviewer's Comments:** *Concur with consultant's findings.*

**Retina:** Dilated examination of the eyes, including the posterior segment, revealed no significant ocular changes from baseline in either the short- or long-term cariprazine studies.

OCT scans were performed in long-term study RGH MD-11. Approximately 172 cariprazine-treated patients had OCT performed and about 85 of these patients received cariprazine therapy for 1 year. Three independent ophthalmologists assessed the OCT scans separately. Although a number of abnormalities were observed, some of which were artifact, abnormalities such as drusen or a pseudo-macular hole were also noted. Only 1 patient was noted to have macula edema. The patient had a known history of diabetes, was on insulin therapy, and was noted to have diabetic retinopathy at baseline. Therefore, based on OCT, no abnormality of note related to

separation of the retinal layers or in the retinal pigment epithelium was seen in patients receiving long-term cariprazine treatment.

**Reviewer's Comments:** *Concur with consultant's findings.*

**Questions from Division:**

1) Based on the updated ocular data, does your assessment of the risk of cataract remain unchanged since your previous consult?

**Reviewer's Comment:** *The risk assessment remains unchanged. While there are individual cases of increasing lens opacification, there are relatively few cases. It remains possible that the follow-up period was not long enough to detect lens changes. It is recommended that cataract development be listed in the adverse reaction section of the labeling.*

2) Based on the updated ocular data, does your assessment of the risk of retinal toxicity remain unchanged since your previous consult?

**Reviewer's Comment:** *The risk assessment remains unchanged. The applicant has used currently available methodologies to investigate the potential for cariprazine to cause ocular events. Limitations exist in the number of patients available (85 patients) for one year follow-up in study MD-11. Due to the limited number of patients studied, adverse events at frequencies less than 4% may not have been detected, however, retinal degeneration in a manner similar to that seen in rats was not observed in human clinical trials.*

3) Does the sponsor's recommendation to [REDACTED] (b) (4) change your assessment of ocular risk?

**Reviewer's Comment:** *The risk assessment is not significantly changed although there is a lower frequency of cataract events [REDACTED] (b) (4).*

4) In your previous consult, you recommended that labeling include information on the potential for cariprazine to cause cataracts in dogs and retinal degeneration in rats. You also recommended that the adverse reactions section of the labeling include blurred vision an event which was observed in clinical trials in 2-3% of patients, and cataract development as a rare event. If cariprazine is approved for treatment of schizophrenia and bipolar disorder, do you have any changes or additions to your recommendations, based on the new data?

**Reviewer's Comment:** *All previous recommendations remain unchanged.*

**Summary:**

1. Animal data demonstrated a risk to dogs of developing cataracts following administration of cariprazine and a risk to rats of developing retinal degeneration following administration of cariprazine.
2. The review of potential cataract development was confounded by apparent errors in assessment, grading and/or recording of lens scores during the clinical trials, but no evidence of rapid cataract development or high frequencies of cataract development were observed in the human clinical trials. The findings in humans are therefore not consistent with the findings in dogs. Long term development or low frequencies of cataract development cannot be ruled out without carefully monitoring in clinical trials or practice over a period of at least 3 years.
3. Limitations exist in the number of patients available (85 patients) for one year follow-up with macular OCT testing, and limitations exist in the methods available to detect early peripheral retina changes. With the technology currently available, there was no signal of retinal degeneration in human studies similar to that seen in rat studies. Due to the limited number of patients studied, adverse events at frequencies less than 4% may not have been detected.
4. Ocular adverse reactions were reported in 5-6% of patients. The most frequently reported ocular adverse reaction was blurred vision which accounted for approximately half of the reported ocular adverse reactions. The physiologic cause of the blurred vision was not identified in the clinical trials.

**Recommendations:**

There is no objection to the approval of NDA 204-370 for cariprazine from an ophthalmologic prospective. If the application is approved, it is recommended that the labeling include information on the potential for cariprazine to cause cataracts in dogs and retinal degeneration in rats. It is also recommended that the adverse reactions section of the labeling include blurred vision as an event which was observed in clinical trials in 2-3% of patients, and cataract development as a rare event.

Wiley A. Chambers, M.D.  
Supervisory Medical Officer, Ophthalmology

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/s/  
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WILEY A CHAMBERS  
05/25/2015

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**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\*\*\***

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**Date of This Review:** April 27, 2015  
**Requesting Office or Division:** Division of Psychiatry Products (DPP)  
**Application Type and Number:** NDA 204370  
**Product Name and Strength:** Vraylar (cariprazine) capsules 1.5 mg, 3 mg, 4.5 mg, and 6 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Forest Laboratories, Inc.  
**Submission Date:** December 17, 2014  
**OSE RCM #:** 2015-186  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Danielle Harris, PharmD, BCPS

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## 1 REASON FOR REVIEW

This review is written in response to a request from the Division of Psychiatry Products (DPP) to review the Vraylar (cariprazine), a new molecular entity (NME), [NDA 204370] proposed container label, carton, and package insert labeling for vulnerabilities to medication errors.

Forest Laboratories, Inc. submitted a Class 2 resubmission on December 17, 2014 to respond to the Complete Response (CR) letter issued on November 19, 2013 stating dose-response and safety as major deficiencies for Vraylar. This CR resulted in the revision of the (b) (4)

## 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.

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

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEW

Our review of the proposed labels and labeling identified areas that can be improved to increase the readability and prominence of important information, as well as provide more clarity to promote the safe use of Vraylar. (b) (4)

The section can be revised to decrease the potential for wrong dose errors.

Additionally, in the *How Supplied* section of the Prescribing Information, the imprint code for each of the capsule strengths is not provided. This section can be revised with inclusion of the imprint codes to facilitate product identification.

The Applicant also proposed a [REDACTED] (b) (4). According to the *Dosage and Administration* section of the insert labeling, the starting dose is one 1.5 mg [REDACTED] (b) (4). Depending upon clinical response and tolerability, dose adjustments can be made upward or downward in 1.5 mg or 3 mg increments. The maximum recommended dose is 6 mg.

[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED] Physicians will still have the ability [REDACTED] (b) (4) dose for a patient by utilizing the 7-count professional sample blisters or providing the patient with a prescription.

#### 4 CONCLUSION & RECOMMENDATIONS

Our review did not identify and areas of vulnerability from a medication errors perspective on the carton and container labels. However, we conclude that the [REDACTED] (b) (4) [REDACTED] is not supported by the proposed [REDACTED] (b) (4) for Vraylar.

The proposed labeling (Prescribing Information) identified areas that can be improved to decrease the potential for medication errors. We provide recommendations in Section 4.1.

##### 4.1 RECOMMENDATIONS FOR THE DIVISION

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

A.

[REDACTED] (b) (4)

B. Prescribing Information

1. Section 2. *Dosage and Administration*

- a. Please consider the removal of [REDACTED] (b) (4) that appear in this Section. Currently it states; [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Inclusion of this information may cause confusion given the [REDACTED] (b) (4)

[REDACTED].

- b. To mitigate the risk of prescribing in excess the 6 mg maximum dose during dose adjustments, consider adding “not to exceed the maximum recommended dose of 6 mg/day.” to the end of the last statements in Sections 2.1 *Schizophrenia* and 2.2 *Manic or Mixed Episodes Associated with Bipolar I Disorder*, such that they read: “Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments; not to exceed the maximum recommended dose of 6 mg/day.”

2. Section 16. *How Supplied/Storage and Handling*

- a. We recommend adding the imprint code for each of the capsule strengths to the table in Section 16 *How Supplied*, to facilitate product identification in case of a mix-up between capsules of different strengths and to prevent wrong strength errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vraylar that Forest Laboratories, Inc. submitted on December 17, 2014.

Table 2. Relevant Product Information for Vraylar	
Initial Approval Date	N/A
Active Ingredient	cariprazine; cariprazine is a new molecular entity (NME)
Indication	treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder
Route of Administration	oral
Dosage Form	capsule
Strength	1.5 mg, 3 mg, 4.5 mg, and 6 mg
Dose and Frequency	<p>once daily with or without food</p> <p><b>Schizophrenia:</b> The recommended dose range is 1.5 mg to 6 mg once daily. The starting dose of Vraylar is 1.5 mg and can be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments.</p> <p><b>Manic or Mixed Episodes Associated with Bipolar I Disorder:</b> The recommended dose range is 3 mg to 6 mg once daily. The starting dose of Vraylar is 1.5 mg and (b) (4). Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments.</p>
How Supplied	all strengths are supplied as a 30-count bottle, 90-count bottle, and 100-count box (hospital unit dose); 7-count blister packs of 7 in two configurations: 7 x 1.5 mg capsules and 1 x 1.5 mg plus 6 x 3.0 mg
Storage	Storage: Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect 3 mg and 4.5 mg capsules from light to prevent potential color fading.

## APPENDIX C. PREVIOUS DMEPA REVIEWS

### C.1 Methods

We searched the L:Drive on February 23, 2015 using the terms, Vraylar to identify reviews previously performed by DMEPA.

### C.2 Results

Our search identified two previous reviews<sup>1,2</sup>, and we confirmed that most of our previous recommendations were implemented.

## 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,<sup>3</sup> along with postmarket medication error data, we reviewed the following Vraylar (cariprazine) labels and labeling submitted by Forest Laboratories, Inc. on October 15, 2013, November 1, 2013, and December 17, 2014 (specific submission dates associated with each label are notated below in italics).

All labeling submitted October 15, 2013 and November 1, 2013 have been previously reviewed. In the Forest Laboratories, Inc. NDA resubmission, dated December 17, 2014, Forest has

(b) (4)  
. There were no changes to the original configurations for the 1.5 mg, 3 mg, 4.5 mg, and 6 mg; therefore these were not resubmitted with the NDA resubmission.

In the NDA resubmission, Forest introduced additional packaging for two (1.5 mg and 3 mg) out of the four strengths under review that include:

- Blister Packs, 7-count, 7 x 1.5 mg; Blister Pack Carton Labeling (sleeve), 7-count, 7 x 1.5 mg; and Blister Pack Carton Labeling, 7-count, 7 x 1.5 mg
- Blister Packs 7-count, 1 x 1.5 mg plus 6 x 3.0 mg; Blister Pack Carton Labeling (sleeve), 7-count, 1 x 1.5 mg plus 6 x 3.0 mg; and Blister Pack Carton Labeling, 7-count, 1 x 1.5 mg plus 6 x 3.0 mg
- Professional Sample Container Label for 1.5 mg, 30-count; associated Professional Sample Carton Labeling, Professional Sample Sleeve (contents: 5 kits | Each Patient Kit

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<sup>1</sup> Holmes L. Label, Labeling and Packaging Review for Vraylar (NDA 204370). 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); 2013 JUL 30. 17 p. OSE RCM No.: 2013-146.

<sup>2</sup> Holmes L. Label, Labeling and Packaging Memorandum for Vraylar (NDA 204370). 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); 2013 NOV 19. 11 p. OSE RCM No.: 2013-146.

<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Contains 30 Capsules) Labeling, Professional Sample Trays (contents: 5 kits | Each Patient Kit Contains 30 Capsules)

- Professional Sample Container Label for 3 mg, 30-count; associated Professional Sample Carton Labeling, Professional Sample Sleeve (contents: 5 kits | Each Patient Kit Contains 30 Capsules) Labeling, Professional Sample Trays (contents: 5 kits | Each Patient Kit Contains 30 Capsules)

An Information Request (IR) was submitted to Forest on March 13, 2015 to obtain a single list of all proposed labels for all configurations that the Sponsor intends to market, including professional samples. This information was received in a response dated March 16, 2015 and was used to determine the following labels for review:

- 30-count and 90-count retail bottle labels for 1.5 mg, 3 mg, 4.5 mg, and 6 mg
- Hospital Unit-Dose (HUD) blisters, 10-count for 1.5 mg, 3 mg, 4.5 mg, and 6 mg
- Hospital Unit Dose (HUD) Carton Labeling 100-count for 1.5 mg, 3 mg, 4.5 mg, and 6 mg
- Retail Blister Packs, Blister Pack Carton Labeling (sleeve), and Blister Pack Carton Labeling for 7-count; 7 x 1.5 mg and 7-count; 1 x 1.5 mg and 6 x 3 mg
- Professional Sample Container Label 30-count, Professional Sample Carton Labeling 30-count, Professional Sample Sleeve (contents: 5 kits | Each Patient Kit Contains 30 Capsules), and Professional Sample Trays (contents: 5 kits | Each Patient Kit Contains 30 Capsules) for 1.5 mg and 3 mg
- Professional Sample Blister, 7-count and corresponding Professional Sample Blister Carton for 1.5 mg, 3 mg, 4.5 mg, and 6 mg
- Professional Sample Blister, 7-count and corresponding Professional Sample Blister Carton for 1 x 1.5 mg and 6 x 3 mg
- [REDACTED] (b) (4)  
[REDACTED]

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

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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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DEBORAH E MYERS  
04/27/2015

DANIELLE M HARRIS  
04/27/2015

## Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 2 April 2015

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)

TO: Mitchell Mathis M.D., Acting Director, Division of Psychiatric Products (DPP), Office of New Drugs (OND), Office of Drug Evaluation 1 (ODE-1)  
Victor Crentsil, M.D., Deputy Director for Safety, DPP  
Lucas Kempf, M.D., Medical Reviewer and Team Leader, DPP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of Forest Laboratories product cariprazine (previously RGH-188) for treatment of schizophrenia and bipolar mania or mixed episodes under NDA 204370, resubmission of 17 December 2014

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Documents reviewed:

- 1) Consultation request dated 29 January 2015 with desired completion date 17 April 2015, to Louis Flowers (OSE Regulatory Project Management Staff)
- 2) My previous consultation on cariprazine dated 23 September 2013
- 3) Previous clinical review by Dr. Francis Becker, 22 July 2013, 278 pages
- 4) Sponsor re-submission to NDA 204370 on 17 December 201 (Seq. 6700), Section 5.3.5.4 for studies -06, -56, -75, and 5.3.5.2 pharmacokinetic study a001-a11 (Japan)
- 5) Minutes of mid-cycle meeting 17 March 2015
- 6) eDISH data displays for Studies -06, -56, and -75
- 7) Hepatic safety update report 4 December 2014 in MDA module 5.3.5.3 of resubmission
- 8) Medical literature (still has no articles on liver toxicity of cariprazine)

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The original submission 19 November 2012 by Forest Laboratories, was not approved and a “complete response” was sent on 13 November 2013, for concerns mainly about the (b) (4) accumulated central nervous, ocular, muscle, and hepatic toxicities of the parent drug and its active long-lived metabolites, especially the didesmethylcariprazine metabolite (DDCAR) that far outlasted the parent drug and the desmethylcariprazine metabolite (DCAR).

The request for consultation dated 29 January from the review division asked us to consider the problem of serum transaminase elevations in the newly submitted data from the four studies RGH MD-06 (open-label cariprazine prevention of schizophrenia relapse, 20-weeks), RGH

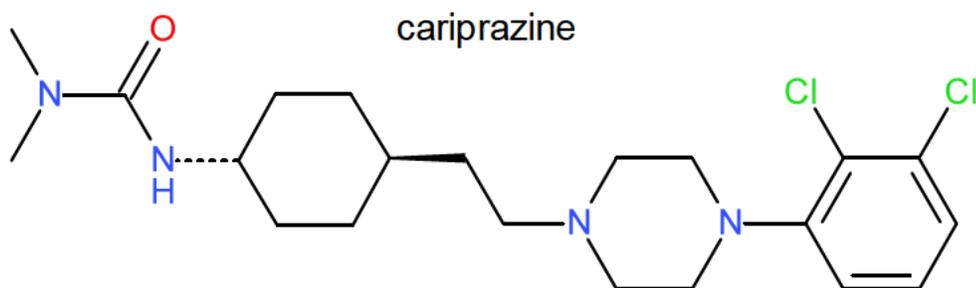
MD-56 (bipolar depression study), RGH MD-75 (major depressive disorder adjunctive therapy, and A002-A11 (pharmacokinetic study in Japanese schizophrenic patients). The sponsor proposes to set the maximum daily dose at 6 mg for both indications, to reduce the risks of adverse effects.

The questions posed in the consultation request were:

- 1) In your previous consult, you concluded that the liver findings from the studies were not impressive or predictive of serious drug-induced injury. Based on the new data, are your conclusions the same?
- 2) Based on the new data, do you have any additional recommendations for labeling if cariprazine is approved?
- 3) Based on the new data and considering that cariprazine-induced liver findings appear to be dose-related, does the (b) (4) substantially decrease the risk of hepatic adverse events?

The newly submitted data included three clinical studies: RGH-MD-06 (765 patients on open-label cariprazine to prevent relapse of schizophrenia), RHG-MD-56 (433 patients on cariprazine, 145 on placebo, for bipolar depression, 8 weeks), and RGH MD-75 (546 patients on cariprazine, 269 on placebo, as adjunctive therapy for major depressive disorder, 8 weeks), and study A002-A11, a new pharmacokinetic study (38 schizophrenic Japanese patients: 11 on 3 mg, 16 on 6 mg, and 11 on 9 mg/day). The sponsor submitted data to Dr. Guo for eDISH analyses of the three clinical studies but did not include with those data the baseline liver tests for studies -56 and 75 nor narratives that had been prepared and re-submitted to the NDA 204370 . The latter were submitted with the NDA resubmission in section 5.3.5.4 under Other Study Reports, Study Report Body, for each of the three studies, rgh-06, rhg-56, and tgh-75.

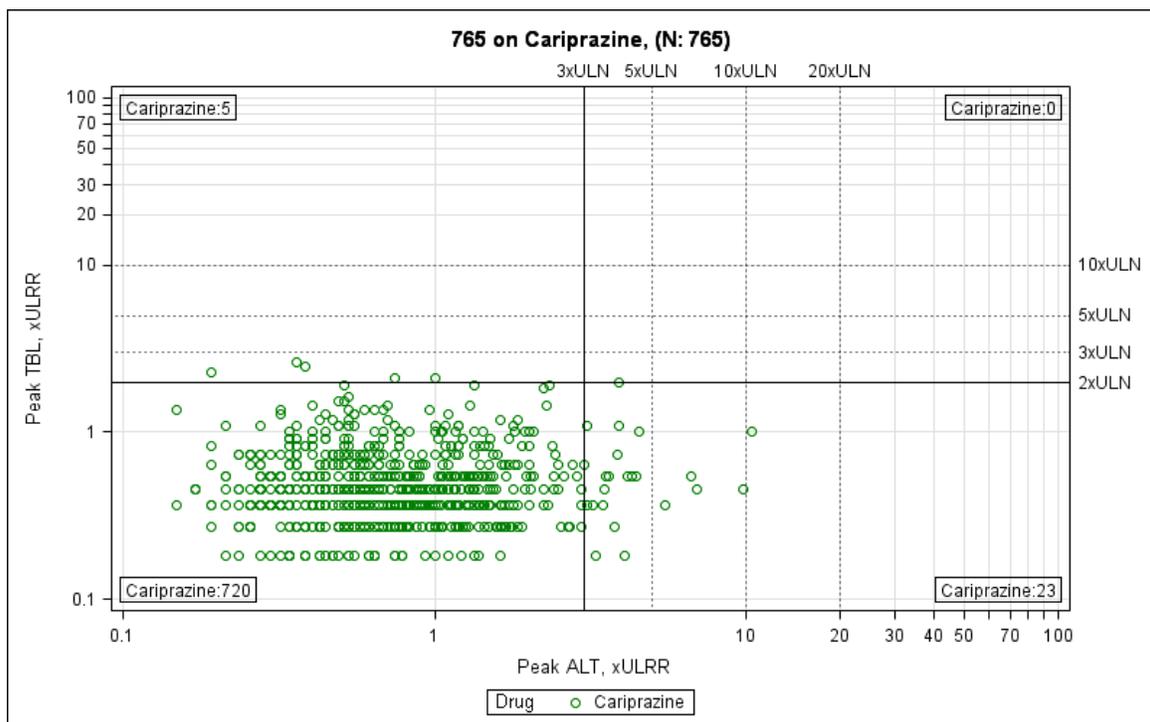
Cariprazine was discovered and developed in Hungary about 2005 by Gideon Richter Plc, and was found to have agonist activity at doapamine (D) receptors as a D<sub>2</sub> and partial D<sub>3</sub> agonist for the treatment of schizophrenia (IND 071958, 21 March 2005) and for bipolar mania (IND 077726, 7 May 2007).. It is metabolized by CYP3A4, somewhat by CYP2D6, with removal of one or both urea-methyl groups; the metabolites are equally potent with the parent compound. The mono-desmethyl (DCAR) concentrations are lower than cariprazine, but slowly removed di-demethyl cariprazine (DDCAR) accumulates. Cariprazine structure may be seen below:



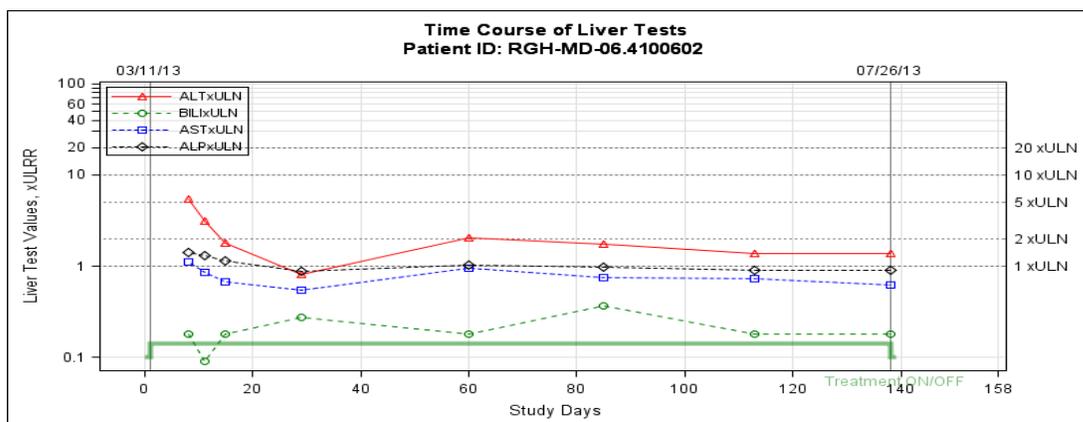
N<sup>''</sup>-[trans-4-[2-[4-(2,3-dichlorophenyl)-1-piperazinyl]ethyl]cyclohexyl]-N,N-dimethylurea

The compound is very lipophilic, and demethylation of the terminal urea moiety only modestly increases its polarity. It is therefore can easily penetrate membranes and enter tissues all over the body, the brain included. Its absorption by the intestine is probably highly diverted to lymph chylomicrons and into the systemic circulation before reaching the liver where it is primarily metabolized, mostly by demethylation but some by hydroxylation. Further pharmacologic details are in the review by Dr. Zhang (19 July 2013).

With regard to the central questions for this consultation, we found the eDISH analyses to be much more useful than the convoluted and extremely voluminous statistical analyses submitted by the sponsor. It is the aim of eDISH to scan over the hundreds of subjects studied and focus on the few potentially more serious cases of whole-liver dysfunction in addition to hepatocyte injury that can be attributable to causation by the study drug and not by disease or some other chemical or drug substance, and pay little attention to the much more frequent but clinically meaningless rises in serum aminotransferase activities that measure no liver function whatsoever and are unreliable indicators of severity. It is only when there is enough injury to the liver cells that the remaining cells are not able to perform the many true liver functions that serious hepatotoxicity is seen. The liver is amazingly resilient, far more than other organs able to change itself, even to regenerate and quickly grow a new and functional organ when as much as two thirds of its mass is resected or damaged! Not only can it regenerate, but its cells often adapts to challenges posed by exposure to new compounds, and they develop tolerance so that a new drug no longer causes progressive injury and functional loss. For serious drug-induced liver injury with dysfunction (meaning disability, need for hospitalization, liver failure with secondary renal or neurological dysfunction, death or need for transplantation), we are looking for quite rare problems. This is not really a problem if only serum transaminase activities are raised. This is the basis for our developing eDISH. Let us look at the eDISH plot for the schizophrenic patients of study -06, open-label, 20-week cariprazine prevention of schizophrenia recurrence:



Note that there were no subjects whose on-study liver tests showed both ALT elevation above 3xUNB and TBL above 2xULN (right upper quadrant), but there were five who showed peak ALT greater than 5xULN and five others with no ALT elevation but total bilirubin peaks between 2 and 3xULN, suggesting that there were no cases of potentially serious liver injury with dysfunction that required closer inspection for determination of the most likely cause of the slight abnormalities. Working back-and-forth between the eDISH plots of the time course of on-study liver test data and the narratives with baseline (pre-treatment) data in the submission list of narratives provided in section 5.3.5.4 – Other Study Reports, rghMD-06, Study Report Body, vols. 1 to 4 of 191 narratives, it was possible to find all 10 cases with TBL but no ALT elevations and ALT but no TBL elevations, an example of which was subject 410-0602 (on above graph @ ALT 5.49, TBL 0.36) for whom the eDISH time course and NDA narrative are shown below:



Patient 4100602, a 39-year-old male with a diagnosis of schizophrenia, enrolled in Study RGH-MD-06 in Romania and received treatment with open-label cariprazine for 138 days (from 2013-03-11 to 2013-07-26). The patient's modal daily dose of cariprazine in the open-label phase was 3 mg/day; the final daily dose was 3 mg/day. The patient reported no medical history. The patient received the following prior medications within 2 weeks before the first dose of cariprazine in the open-label phase of the study: diazepam and olanzapine. The patient received the following concomitant medication during the open-label phase of the study: trimetazidine. Baseline serology was positive for hepatitis B core antibody and hepatitis B surface antibody, and negative for hepatitis B surface antigen and hepatitis B core antibody IgM (compatible with immunity due to prior natural hepatitis B infection), and negative for hepatitis C virus antibody. ALT was within the reference range at baseline; GGT was elevated at 84 U/L (reference range: 0-51 U/L).

On 2013-03-18 (Study Day 8), ALT had increased to 258 U/L (> 5 × ULN; reference range: 0-47 U/L), alkaline phosphatase had increased to 192 U/L (reference range 40-135 U/L), and GGT had increased to 298 U/L; AEs of alanine aminotransferase abnormal (Investigator term: abnormal ALT) and gamma-glutamyltransferase abnormal (Investigator term: abnormal GGT)

were reported. ALT decreased to 84 U/L ( $< 2 \times$  ULN) on Study Day 15 and varied between 38-95 U/L at the following visits; alkaline phosphatase and GGT decreased gradually, with the former becoming normal at Study Day 85, but the latter remaining elevated (143 U/L) at the final visit (Study Day 138). The AEs of abnormal alanine aminotransferase and gamma-glutamyltransferase were ongoing as of the last visit. Bilirubin was within the reference range at all assessments. Liver biochemistry test results during treatment were as follows:

	ALT (U/L)	AST (U/L)	T. Bili (mg/dL)	D. Bili (mg/dL)	I. Bili (mg/dL)	AlkPhos (U/L)	GGT
<i>Reference Range</i>	0-47	0-37	0-1.1	0-0.2	0-0.9	40-135	0-51
2013-03-06 Visit 01 (-5)	38	23	0.2	0.1	0.1	109	84
2013-03-18 Visit 03 (8)	258	41	0.2	0.1	0.1	192	298
2013-03-21 Unscheduled	148	32	0.1	0.1	0	178	268
2013-03-25 Visit 04 (15)	84	25	0.2	0.1	0.1	154	237
2013-04-08 Visit 06 (29)	38	20	0.3	0.1	0.2	119	129
2013-05-09 Visit 08 (60)	95	35	0.2	0.1	0.1	139	204
2013-06-03 Visit 10 (85)	81	28	0.4	0.1	0.2	133	163
2013-07-01 Visit 12 (113)	64	27	0.2	0.1	0.1	123	143
2013-07-26 Visit 14 (138)	65	23	0.1	0.1	0.1	123	144

The abnormal alanine aminotransferase and gamma-glutamyltransferase were considered by the Investigator to be mild and related to treatment with investigational product. No abdominal pain, anorexia, fatigue, jaundice, nausea, or vomiting were reported. The only other AE reported was an abnormal electrocardiogram. Confounding factor for this case was the baseline elevation of GGT (84 U/L). The patient completed the open-label phase of the study.

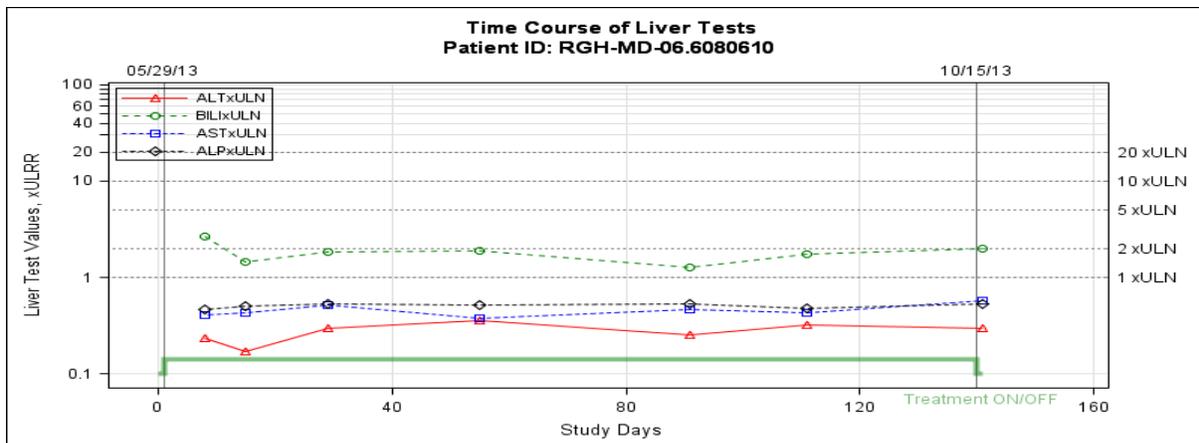
*Comment: This patient had a history of hepatitis B from which he recovered and showed antibodies. It was not clear if any residual liver damage was present, but ALT rose to 5.5xULN soon after he started cariprazine, then subsided toward normal despite continuing the drug, presumably by adaptation. There was no evidence of any whole-liver dysfunction or symptoms. Hy's Law was not fulfilled because there was no jaundice and the case was not serious.*

In similar fashion, all nine of the other cases for whom narratives were prepared were investigated by both eDISH time course and resubmission narratives with serial liver test data. No serious cases of liver injury were found in any of them. Three of the five cases with mild bilirubin increases appeared in young males with presumed Gilbert syndrome of reduced glucuronide conjugation of bilirubin. An example of that is shown below:

Patient 6080610, a 29-year-old male with a diagnosis of schizophrenia, enrolled in Study RGH-MD-06 in Ukraine and received treatment with open-label cariprazine for 140 days (from 2013-05-29 to 2013-10-15). The patient's modal daily dose of cariprazine in the open-label phase was 6 mg/day; the final daily dose was 6 mg/day. The patient had a

medical history of bronchitis, chronic sinusitis, concussion, dysbacteriosis, fat embolism, femur fracture, gastritis, Gilbert’s syndrome, haematoma, haematoma evacuation, open reduction of fracture, pneumonia, upper limb fracture and varicella. No prior medication was reported. No concomitant medication was reported. Baseline serology was negative for hepatitis B core antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis C virus antibody. Total bilirubin was elevated at baseline at 1.6 mg/dL (reference range: 0-1.1 mg/dL) with indirect fraction also elevated at baseline at 1.3 mg/dL (reference range: 0-0.9 mg/dL). On Study Day 8, total bilirubin had increased to 2.9 mg/dL ( $> 2 \times$  ULN), while direct bilirubin was within the reference range and indirect bilirubin was 2.7 mg/dL. Total bilirubin ranged between 1.4 and 2.2 mg/dL at the remaining study visits; the highest reported direct bilirubin value was 0.3 mg/dL (reference range: 0-0.2 mg/dL). No AE was reported in this patient with Gilbert’s syndrome, and ALT, AST and alkaline phosphatase were within reference ranges at all assessments. No AEs of abdominal pain, anorexia, fatigue, jaundice, nausea or vomiting were reported. No AEs were reported for the patient. The likely cause of this patient’s bilirubin elevation was Gilbert’s syndrome. The patient completed the open-label phase of the study. Liver biochemistry test results during the open-label phase were as follows:

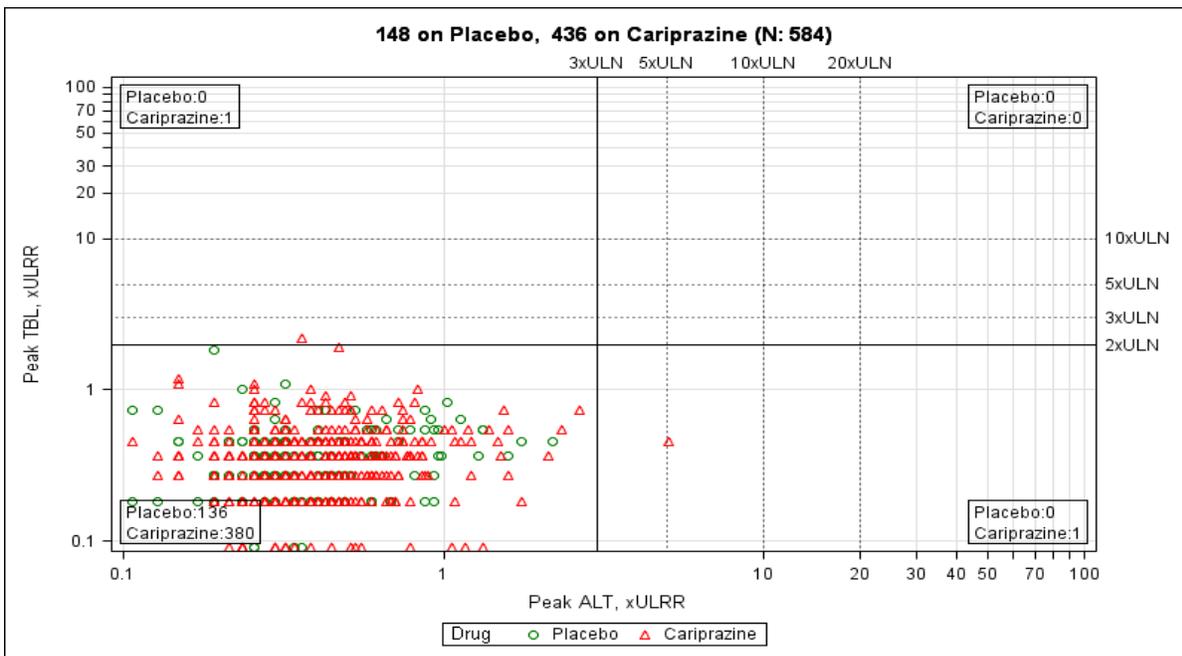
Date & Visit Name (Study Day)	ALT (U/L)	AST (U/L)	T. Bili (mg/dL)	D. Bili (mg/dL)	I. Bili (mg/dL)	Alk Phos (U/L)	GGT (U/L)	
	Reference Range	0-47	0-37	0-1.1	0-0.2	0-0.9	40-135	0-51
2013-05-22 Visit 01 (-7)	14	13	1.6	0.3	1.3	71	10	
2013-06-05 Visit 03 (8)	11	15	2.9	0.1	2.7	62	8	
2013-06-12 Visit 04 (15)	8	16	1.6	0.3	1.3	68	7	
2013-06-26 Visit 06 (29)	14	19	2.0	0.3	1.7	72	9	
2013-07-22 Visit 08 (55)	17	14	2.1	0.3	1.8	70	13	
2013-08-27 Visit 10 (91)	12	17	1.4	0.3	1.1	72	8	
2013-09-16 Visit 12 (111)	15	16	1.9	0.3	1.6	65	10	
2013-10-16 Visit 14 (141)	14	21	2.2	0.2	2.0	72	8	



Similar results were obtained for the other four subjects (0180825, 0210629, 4040606, and 404-615) who showed mild total bilirubin elevations during treatment (and before) but did not have ALT elevations at any time during observation. The four other subjects who showed ALT elevations but no elevations of total bilirubin, nor symptoms of liver dysfunction. All showed ALT elevations greater than AST increases and without alkaline phosphatase elevations;

number	site	sex-age	BMI	dose mg-days	ALT <-----peak, xULN----->	TBL	AST	ALP
3070607	India	M24	25.5	9 x 21	9.77	0.45	5.78	0.89
3070608	India	M22	19.9	9 x 21	10.45	1.00	6.43	0.58
6070611	Ukraine	F 34	24.3	3 x 137	6.66	0.55	4.08	0.76
6090603	Ukraine	F 48	26.4	3 x 138	6.96	0.45	3.41	0.99

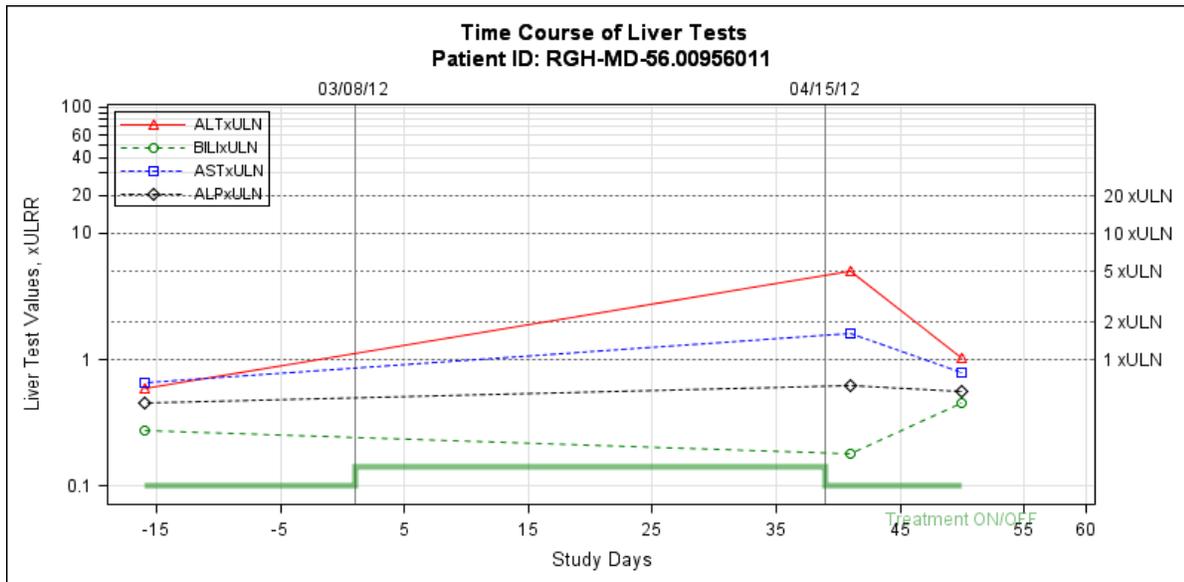
For study -56 of bipolar depression, there were 578 patients studied, 145 on placebo, and 433 on cariprazine (141 on 0.75, 146 on 1.5 and 146 on 3 mg/day) for 8 weeks. The sponsor sent only limited data to Dr. Guo for presentation in eDISH, and submitted only 4 narratives for patients with elevated liver tests, none of which were notable and there were no cases of liver injury or dysfunction detected that warranted detailed investigation.



The lone patient who showed elevated ALT was a U.S. white female 50 (#56-0095-6011), not obese (BMI 22.3), and showed normal values for liver tests before starting cariprazine 3 mg/day on 8 March 2012. She was severely depressed and failed to take medication regularly and was dropped from the study for non-compliance on 15 April (Day 39), but showed elevated ALT of 237 U/L (5.04 xULN) and AST of 60 U/L (1.62 xULN) on 17 April (Day 41) without elevations

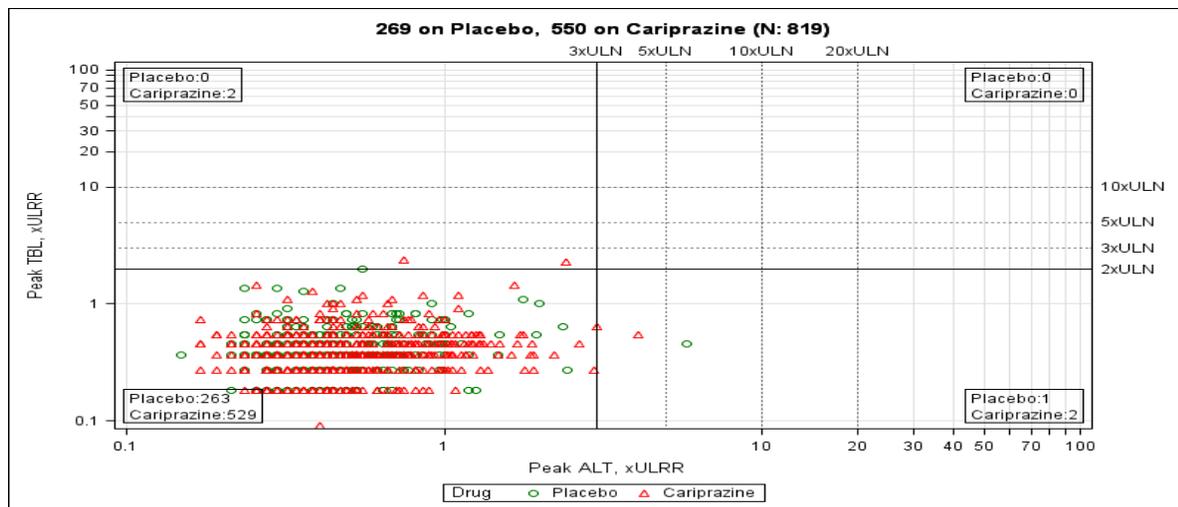
in total bilirubin or ALP, and no symptoms. The serum aminotransferases returned to normal on April 26 (Day 50).

*Comment: Only limited liver test data were gathered for Study -56, at pre-study visit-01 and at visit -07, after treatment, so lack of findings of test abnormalities cannot be taken as evidence that they did not occur during treatment (see time-course graph of the limited data below) An 8=page narrative and dtat summary was found in the NDA resubmission.*

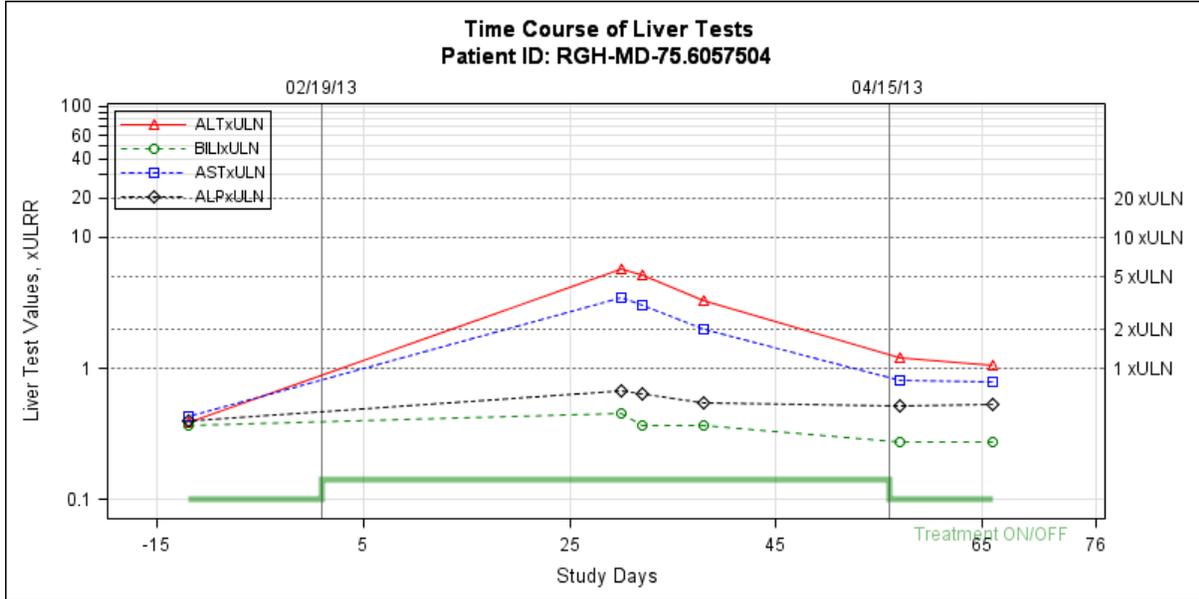


*What may have occurred during the 39 days she was on cariprazine treatment cannot be known and only speculated about. It was unclear why the sponsor did not do laboratory tests during treatment in this or the other depressed patients on Study -56.*

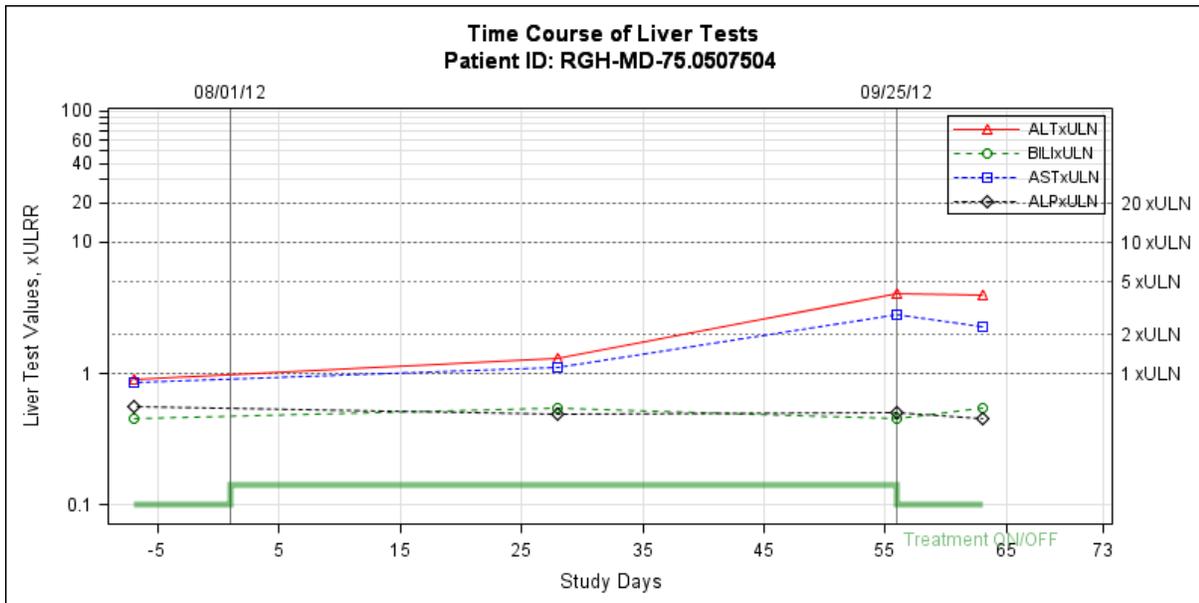
In Study -75 of adjunctive therapy of depression, 550 patients were randomized to cariprazine and 269 to placebo for 8 weeks.



Again, there were no patients found to have both ALT and TBL elevations, but only limited testing was done, as in Study -56. One patient on placebo and one on cariprazine showed peak aminotransferases > 3xULN. A narrative was provided for the patient randomized to placebo #75-605-7504, but no explanation for the enzyme elevations that was found after 4 weeks on placebo, but they resolved by 4 weeks later (see below):



For the patient on cariprazine (#75-0507-504) no narrative was submitted to the NDA for Study -75, and the mild elevations of ALT and AST after 8 weeks on treatment were not explained and no symptoms were reported (see below):



*Comment: Not much can or should be made of mild serum aminotransferase elevations alone, without evidence of whole organ dysfunction or clinical symptoms, nor is it probably worth the effort to investigate for causality, especially if transient and reversible.*

---

In the small Study A002-A11 done in Japan in 2013 to investigate the pharmacokinetics of doses of 3, 6, or 9 mg/day, and especially to determine when peak steady state concentrations of parent cariprazine and its two metabolites DCAR and DDCAR would be reached, there were 2 patients randomized to 9 mg/day who showed aminotransferase elevations and the study discontinued for them:

site-no.	sex-age		dose	start	date	ALT	AST	stop	recovered
110-01	F 33	fatty liver	9	2/19	4/8	308	138	4/10	5/7
111-01	M 45	BMI 24.9	9	2/28	3/13	121	67	3/15	3/27

*Comment: In this this closely monitored study, the investigators very conservatively stopped the drug at the first indication of asymptomatic serum enzyme elevations.*

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Review of the new data submitted for these additional patients appears to confirm and support the conclusions reached in the previous consultation of September 2013, that there does not appear to have been any evidence of serious hepatotoxicity attributable to cariprazine. This conclusion must be interpreted with some misgiving because of the rather spotty measurement of liver test data, especially in Study -56 and somewhat in Study -75. What might happen when the drug is prescribed for thousands of patients, and perhaps for quite long periods cannot be known with any confidence. There is no justification for requiring monitoring, and it cannot be expected that psychiatrists treating these patients with schizophrenia and bipolar depression will become expert or even competent hepatologists. The incidence of mild to moderate serum transaminase elevations is uncommon but not rare; if any of these patients should fail to adapt to the drug and show progressive transaminase elevations leading to liver dysfunction and serious hepatotoxicity it would likely be very rare but not impossible. The benefits of treatment appear to be modest in most patients, and probably outweigh the risk of serious harm from liver injury. The principal concerns of DPP were more on dosing and other possible toxicities (neurologic, ocular, muscle) in issuing a complete response ruling in November 2013.

Therefore, let us return to the questions posed for the consultation:

- 1) In your previous consult, you concluded that the liver findings from the studies were not impressive or predictive of serious drug-induced injury. Based on the new data, are your conclusions the same?

**The new studies permit only confirmation of the earlier conclusions, but not because of robust and convincing new data, but only because nothing new was found or reported, or even looked for. One easy way not to find trouble is not to look too hard for it.**

- 2) Based on the new data, do you have any additional recommendations for labeling if cariprazine is approved?

**It should be mentioned in the labeling that dose-related serum aminotransferase elevations have been observed not infrequently. Treating physicians should not exceed the recommended dosing schedule, and should be on the lookout for symptoms or complaints suggesting possible liver injury, such as fatigue, anorexia, nausea, and especially jaundice, which should trigger prompt and thorough investigation of possible cause, and tests of liver injury, with interruption in treatment until liver injury is ruled out.**

- 3) Based on the new data and considering that cariprazine-induced liver findings appear to be dose-related, does the [REDACTED] (b) (4) substantially decrease the risk of hepatic adverse events?

**The data are too sparse to allow any quantitative support for saying that [REDACTED] (b) (4) will substantially decrease the risk of hepatotoxicity, but other toxicities provide stronger support for this proposal.**

Thank you for sending this most interesting and challenging consultation request.

---

John R. Senior, M.D.

cc: M. Mathis, DPP  
V. Crentsil, DPP  
L. Kempf, DPP  
S. Iyasu, OPE

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/s/  
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JOHN R SENIOR  
04/06/2015

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

**Label, Labeling and Packaging Memorandum**

Date: November 19, 2013

Reviewer: Loretta Holmes, BSN, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Vraylar (Cariprazine) Capsules  
1.5 mg, 3 mg, 4.5 mg, 6 mg (b) (4)

Application Type/Number: NDA 204370

Applicant: Forest Laboratories, Inc.

OSE RCM #: 2013-146

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

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## **1 INTRODUCTION**

This memorandum evaluates the revised labels and labeling for Vraylar (Cariprazine) Capsules, submitted on October 11, 2013 and November 1, 2013 (see Appendices A through E), for areas of vulnerability that could lead to medication errors.

## **2 METHODS AND MATERIALS REVIEWED**

DMEPA evaluated the revised labels and labeling submitted on October 11, 2013 and November 1, 2013. We compared the revised labels against our previous recommendations from OSE Review 2013-146, dated August 1, 2013, as well as recommendations sent by email on October 30, 2013, to assess whether the revised labels address our concerns from a medication error perspective. We did not provide comments on the proposed [REDACTED]<sup>(b) (4)</sup> labeling submitted on October 11, 2013 because the initial and maintenance dosing of this product have not been finalized. We reserve comment on acceptability of the [REDACTED]<sup>(b) (4)</sup> and associated labeling until dosing determinations have been finalized.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Our review of the revised labels and labeling determined the Applicant has implemented all of our recommendations. Therefore, we have no further recommendations at this time.

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

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

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/s/  
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LORETTA HOLMES  
11/19/2013

IRENE Z CHAN  
11/19/2013

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

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

**Memorandum**

**Date:** November 13, 2013

**To:** Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products (DPP)

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

**Subject:** **NDA #204370**  
Cariprazine Capsules

---

OPDP acknowledges receipt of the January 22, 2013, consult request from DPP for proposed product labeling (PI) for cariprazine. OPDP notes that DPP indicated on November 12, 2013, that final labeling negotiations will not be initiated during the current review cycle because a Complete Response letter will be issued. Therefore, OPDP will not provide comments on the proposed PI during this review cycle.

OPDP requests that DPP submit a new consult request during a subsequent review cycle to provide comments regarding labeling for this application.

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

Thank you!

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/s/  
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SUSANNAH O'DONNELL  
11/13/2013

## Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 30 September 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology(OPE) , Office of Surveillance and Epidemiology (OSE)

TO: Mitchell Mathis M.D., Acting Director, Division of Psychiatric Products (DPP),  
Office of New Drugs (OND, Office of Drug Evaluation 1 (ODE-1)  
Victor Crentsil, M.D., Deputy Director for Safety, DPP  
Robert Levin, M.D., Team Leader, DPP  
Francis Becker, M.D., Medical Reviewer, DPP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of Forest Laboratories product cariprazine for treatment of bipolar I mania or mixed episodes and schizophrenia under NDA 204370

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### Documents reviewed:

- 1) Consultation request dated 8 August 2013 (DARRTS 9 August: Kim Updegraff), with desired completion date 27 September 2013, assigned OSE tracking number #2013-1842 by Louis Flowers (OSE Regulatory Project Management Staff)
  - 2) Medical literature has no articles on liver toxicity of cariprazine, but 24 others
  - 3) Clinical review by Dr. Francis Becker, 22 July 2013, 278 pages
  - 4) Sponsor submission (original) 19 November 2012 (Seq. 0000), Section 5.3.5.3 Integrated Summary of Safety, Vol. 1, pp. 217-255 and 279-294 (of 32,323 pages in Vols. 1 & 2)
  - 5) Clinical Response to Request for Information, 1 July 2012 (Seq.0030), 1372 patient profiles from schizophrenia, and 569 from bipolar studies, total 24,452 pages
  - 6) Minutes of late-cycle meeting 16 August (DARRTS 13 September) and sponsor's version of 23 August 2013 (Seq.0038)
  - 7) Selected submissions by sponsor as Clinical Responses to Information Requests, including statistical data on adverse event tables (Seq. 0041, 11 September); laboratory values for CPK, Cr, bilirubin, other serum enzymes (Seq. 0043, 17 September); long-term safety (Seq. 0045, 18 September); adverse events update (Seq. 0047, 29 September)
- 

Dr. Robert Levin very thoughtfully arranged a preliminary meeting with me on 2 August to give some background about the thinking and concerns of DPP concerning this NDA submission and to explain that a request to me via OSE would be coming in the next few days. He also sent that day a detailed email message indicating exactly where among the 34 sponsor's data submissions up to that time (from 19 November 2012 Seq. 0000 until 25 July 2013 Seq. 0033) the key items

of interest could be found. As he warned this was a very large set of submissions up to then, and even more since in subsequent voluminous statistical submissions in August and September.

The request for consultation dated 8 August from the review division asked us to consider the problem of serum transaminase elevations, several  $.10 \times \text{ULN}$  and one  $>220 \times \text{ULN}$ , as well as serum bilirubin elevations with or without transaminase elevations, apparently dose-related, with more in patients receiving more than 6 mg/day, but no cases of evidently serious liver injury. In addition, there were frequent elevations of creatine phosphokinase (CK) activity, as has been noted with other anti-psychotic drugs. These concerns were augmented by the very long half-life of clearance of the drug and its two principal metabolites in which one or both methyl groups are removed from the urea end of the molecule.

The questions posed in the consultation request were:

- 1) We would appreciate your assessment and recommendations regarding the liver findings,
- 2) Do the findings suggest there is a risk of serious drug-induced liver injury?
- 3) Is there any concern that the risk should be an approval issue?
- 4) Do you recommend a warning in the label regarding the hepatic findings?
- 5) Would you recommend that we request additional data from the sponsor during this NDA review cycle?
- 6) If the NDA is approved, do you recommend any particular postmarketing studies, enhanced pharmacovigilance, or any other regulatory actions regarding the hepatic findings and risk?
- 7) If the drug is approved, do you recommend that we require any routine clinical laboratory monitoring or drug discontinuation criteria for patients treated with cariprazine?

They stated further that data for eDISH analysis was requested 8/9 of the sponsor, and that they would like consult recommendations by 9 September.

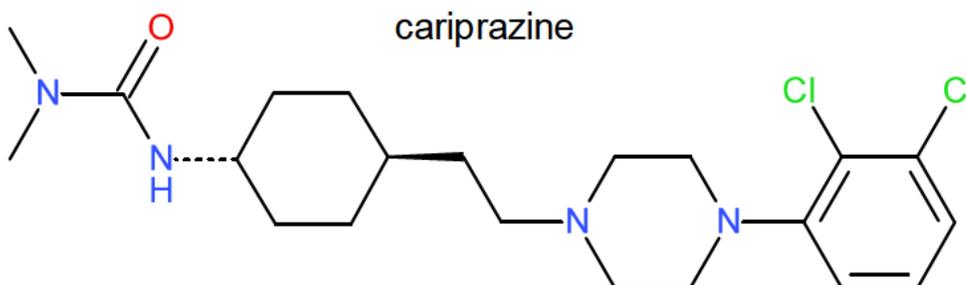
In response to all these requests and questions, and the vast amount of material to be reviewed and considered, it was simply not possible to provide a comprehensive answer in the time that was requested, particularly since we had to wait for the sponsor to respond and format the key clinical data on liver tests in eDISH format. It was futile to try to make sense of the thousands and thousands of pages of statistical data, patients profiles, submitted by the sponsor. The whole idea of our eDISH analyses is to separate wheat from chaff, to extract a few needles of special patient interest from the haystack of thousands who did not need it. We have learned long ago that just serum aminotransferase activities are not good or even useful measures of liver function or loss thereof, and not particularly specific to the liver, and usually go away unless accompanied or followed by true indicators of whole liver dysfunction such as increasing concentration of serum bilirubin, indicating diminished liver function of clearing plasma of that pigment, or evidence of rising prothrombin time or its international normalized ratio (INR) indicating reduced ability of the liver to synthesize the prothrombin protein and regulate its concentration. Therefore, we had to wait until the sponsor prepared and submitted their data for entry into the eDISH data base, and for Dr. Ted Guo to make the eDISH file available for analyses, which took almost all the time allotted for a response from us. The sponsor was fairly prompt, but their data arrived when Dr. Guo was on leave in Europe, and some further work was necessary when he returned. Dr

Guo notified me on Friday 6 September that he had installed the newly received data on the eDISH server, as instructed by Dr. Levin:

- File 1A: schizophrenia placebo-controlled short-term studies MD-03, MD-04, MD-05, and MD16, with comparators (aripirazole and risperidone) in MD-04 and MD-16;
- File 1B: schizophrenia uncontrolled open label studies MD-11 and MD-17
- File 2A: bipolar mania placebo-controlled studies MD-31, MD-32, MD-33
- File 2B: bipolar mania uncontrolled open label extension study MD-36

As noted in the clinical review by Dr. Francis Becker, cariprazine (RGH-188, VRAYLAR<sup>®</sup>, Forest Laboratories) is not yet approved anywhere in the world. It has been studied in the United States, Asia (India and Malaysia), Europe (Russia, Ukraine, Romania, Serbia, Croatia), South America (Columbia), and a few patients in South Africa.

The drug was discovered and developed in Hungary by Gideon Richter Plc, and found to have agonist activity at dopamine (D) receptors as a D<sub>2</sub> and partial D<sub>3</sub> agonist, but may inhibit overstimulated receptors when endogenous dopamine levels are low. It shows high receptor affinity for the 5-hydroxytryptamine type 2B (5-HT)<sub>2B</sub> and slightly less for 5-HT<sub>1A</sub> receptors. It was found to be almost uniquely a “dopamine stabilizer” and has advantages over other first- and second-generation antipsychotic agents. It is metabolized by CYP3A4, somewhat by CYP2D6, with removal of one or both urea-methyl groups, and the metabolites are equally potent. The mono-desmethyl (DCAR) metabolite concentrations are lower than the parent, but the slowly formed di-demethyl cariprazibe (DDCAR) accumulates. Cariprazine structure may be seen below:



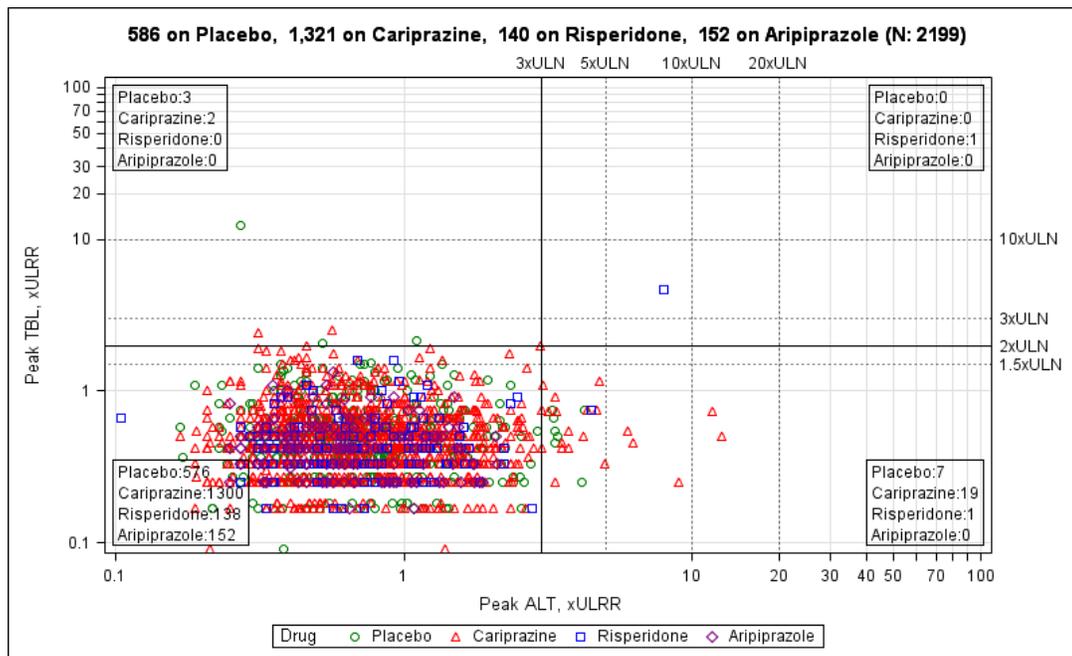
N<sup>''</sup>-[trans-4-[2-[4-(2,3-dichlorophenyl)-1-piperazinyl]ethyl]cyclohexyl]-N,N-dimethylurea

The compound is very lipophilic, and the demethylation of the urea only modestly increases its polarity. It is therefore can easily penetrate membranes and enter tissues all over the body, the brain included. Its absorption by the intestine is probably highly directed to lymph chylomicrons and therefore the systemic circulation before reaching the liver where it is primarily metabolized, mostly by demethylation but some by hydroxylation. Further details of pharmacology are in the review by Dr. Zhang (19 July 2013).

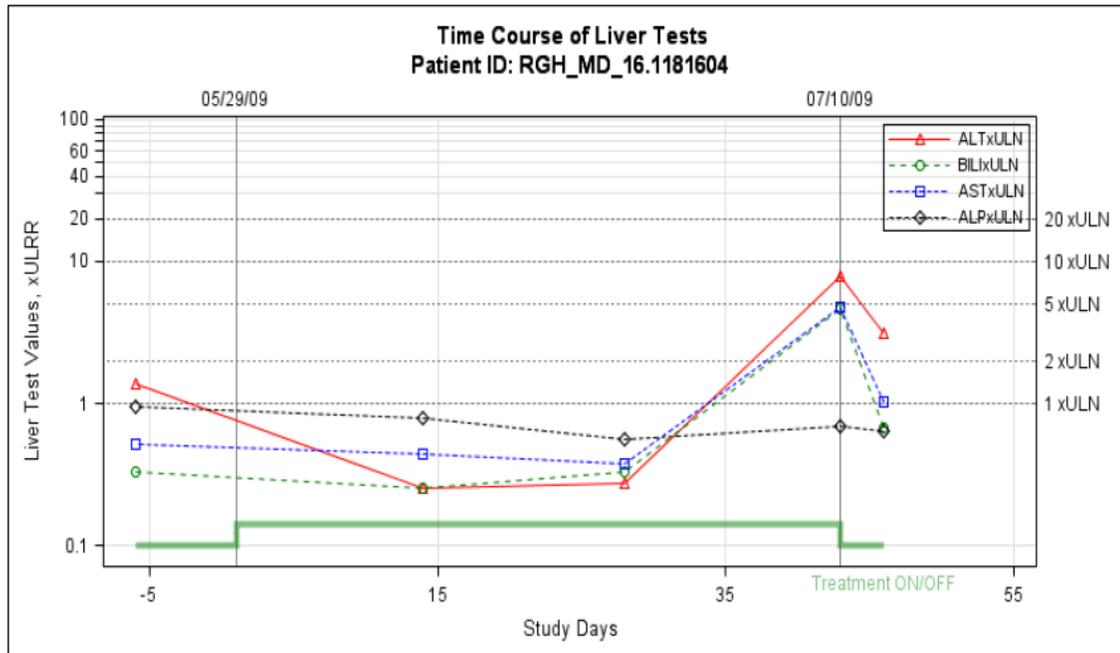
In the clinical review, Dr. Becker expressed more concern with the ocular adverse effects than the hepatic abnormalities. As with all the antipsychotic agents, akathasia (restlessness), nausea, vomiting, constipation, and extrapyramidal disorders were seen frequently, (b) (4)

With regard to the central questions for this consultation, we found the eDISH analyses to be much more useful than the convoluted and extremely voluminous statistical analyses submitted by the sponsor. It is the aim of eDISH to find and focus on the more serious cases of hepatic dysfunction, and pay little attention to the much more frequent but clinically meaningless rises in serum aminotransferase activities that measure no liver function whatsoever and are unreliable indicators of severity. It is only when there is enough injury to the liver cells that the remaining cells are not adequate to perform the many true functions of the liver that serious hepatotoxicity is seen. The liver is amazingly resilient, far more than other organs able to change itself, even to regenerate and quickly grow a new and functional organ when as much as two thirds of its mass is resected or damaged! Not only can it regenerate, but it often adapts to challenges posed by exposure to new compounds, and develops tolerance so that a new drug may be accepted without progressive injury and functional loss. This has been learned in recent decades, since the study of isoniazid, a drug very useful for preventing tuberculosis, but that initially injures from 15-20% of new users, but of them approximately 99% adapt and become tolerant, leaving only 1 or 2 per 1,000 who are unable to adapt, cannot tolerate the drug, and will show progressive liver injury, liver failure and death if the drug is not withdrawn from them. They are different from most people, but there is no biomarker or way to identify them in advance. Only by close observation, prompt investigation, and at least temporary interruption of treatment until the true cause of the problem is proved to be the drug and not some other process, can this be found out. For serious drug-induced liver injury with dysfunction (meaning disability, need for hospitalization, liver failure with secondary renal or brain dysfunction, death or need for transplantation), we are looking for quite rare problems. This is not a problem if only serum transaminase activities are raised. This is the basis for our developing eDISH, as may be understood better from the draft manuscript offered as the first reference.

Let us look at the first eDISH plot for the schizophrenic patients of group 1A:



This preliminary x-y plot of maximum observed serum ALT and bilirubin levels for each of the almost 2200 patients, as  $\log_{10}(xULN)$  values shows that the vast majority of them appear in the left lower quadrant, with normal or near-normal peak values reported at any time of their clinical trial observation. About 1.4% (19/1321) of patients randomized to cariprazine showed elevated serum ALTs at some time during their observation, compared to 1.2% (7/586) randomized to placebo. Only one patient, #11181604, an Indian male 24 randomized to risperidone in Study 16, can be seen in the right upper quadrant of the first eDISH x-y plot. His peak laboratory values of the liver tests ALT 7.9xULN, TBL 4.7xULN, AST 4.8xULN were found after 43 days on drug, which was stopped, and recheck 3 days later showed rapidly declining values.



The narrative provided stated that the patient had no symptoms, but that very little investigation of the possible cause for the findings beyond a test for acute viral hepatitis A was done, and that the findings “met the criteria for Hy’s Law” (see partial copy of narrative below).

*The patient received risperidone 4 mg/day for 43 days from 29 May 2009 through 10 Jul 2009, and completed the study. There was no other medical history reported. Concomitant medications taken during the treatment period included trihexyphenidyl (11 Jun 2009 to 02 Jul 2009) and paracetamol (a single dose of 500 mg was administered on 25 Jun 2009 for an adverse event of pyrexia of unknown origin, which resolved the same day). The patient had ALT of 381 U/L (approximately 8 × ULN), AST of 214 U/L (approximately 5 × ULN), and total bilirubin of 96 μmol/L (approximately 5 × ULN) on Day 43 (10 Jul 2009), which met the biochemical criteria for Hy’s Law. Hepatitis A Antibody (IgM) was nonreactive on 10 Jul 2009; hepatitis serology was negative at baseline. No INR was obtained. No associated adverse events were reported (ie, no report of jaundice or other hepatic events, and no report of nausea, vomiting, abdominal pain, fatigue, or itching).*

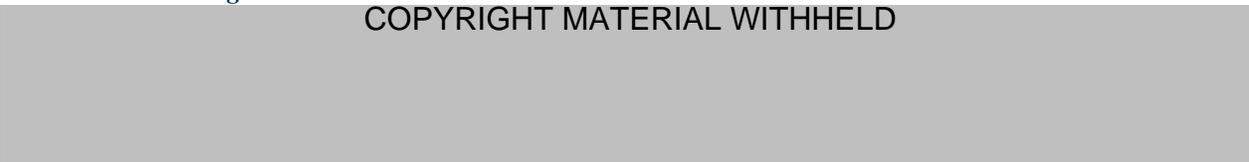
*Comment: The diagnosis of a “Hy’s Law case” cannot be made simply on biochemical findings but requires clinical investigation to rule out other causes. It is not a statistical diagnosis but must be a medical differential diagnosis, based on adequate workup and investigation of the*

patient's history and supplemental findings beyond those in the case report form, because there are many possible disease and other possible causes for such findings. Serious drug-induced liver injury is well worth clinical investigation, and premature conclusion of it is often falsely positive. The case was not investigated at the site. Our examination of the 13-page "patient profile" submitted 1 July 2013, does not provide any additional diagnostic information but simply confirms the correctness of the laboratory values submitted for and used in the eDISH plot. It is true that risperidone has been known to cause hepatic injury, as described in the excerpt below from the publicly available LiverTox website established by the hepatology experts at the National Institutes of Health (see reference).

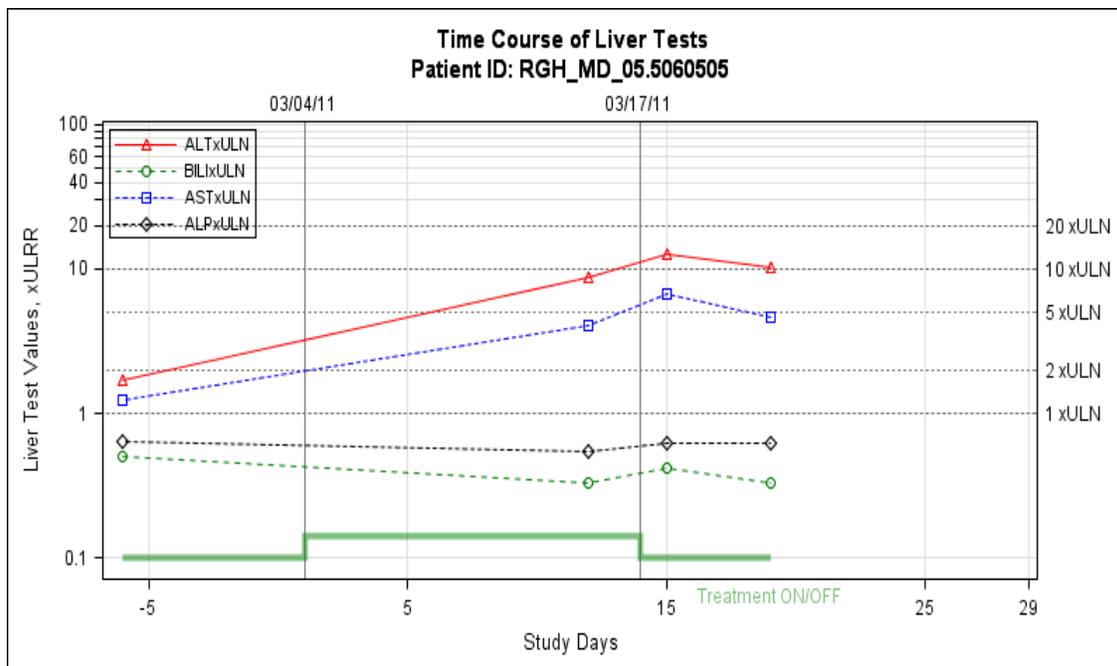
**Hepatotoxicity**



**Outcome and Management**



Shown in the first eDISH x-y plot above, there were two patients randomized to cariprazine with ALT elevations >10xULN but with no bilirubin increases. Let us now look at them, first at patient #5060505:

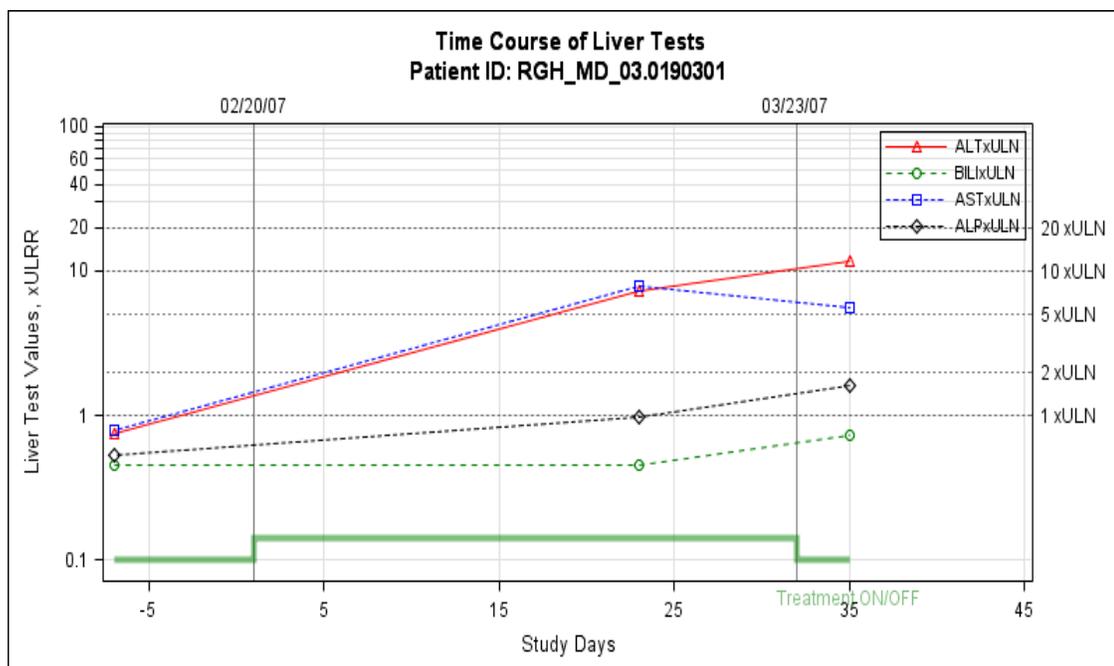


The time course for patient #5060505, an Indian male 25 randomized in Study -05 to receive cariprazine on 4 March 2011, is shown above, and as detailed in the narrative provided:

*Patient 5060505, a 27-year-old male diagnosed with acute schizophrenia and with medical history of jaundice (in 2009), enrolled in a 6-week double blind study (RGH MD-05). He received cariprazine 6-9 mg/day for 14 days from 04 Mar 2011 to 17 Mar 2011 (final dose: 7.5 mg/day). No concomitant medications were taken during the treatment period. An AE of hepatitis (Investigator term: drug induced hepatitis) was reported by the Investigator on the same day. On Study Day 15 (18 Mar 2011), his ALT increased to 608 U/L, AST increased to 299 U/L, and total bilirubin continued to be normal (8.55 umol/L). The AE of hepatitis was upgraded to an SAE; the patient was discontinued from the study. Bilirubin, alkaline phosphatase, and GGT levels remained within the reference range. The patient's abdominal ultrasound result was normal (18 Mar 2011). Serology for Hepatitis A, B, and C were negative at baseline, and Hepatitis A antibody (IgM) was negative on 15 Mar, 18 Mar, and 22 Mar 2011. The patient was treated with phospholipids, ursodeoxycholic acid, unspecified herbals (investigator term: Liv 52), oxazepam, loxapine and paliperidone. On Study Day 19 (22 Mar 2011), the patient's ALT decreased to 490 U/L and AST decreased to 210 U/L. On Day 25 (28 Mar 2011), ALT was 454.4 U/L (reference range: 10-40) and AST was 196.2 U/L (reference range: 10-35); his ALT continued to decrease to 176.8 U/L and AST decreased to 64.6 U/L on Day 32 (04 Apr 2011). The SAE of hepatitis was downgraded to a non-serious AE on Day 35. Per MedWatch, on Day 42 (14 Apr 2011), the patient was clinically asymptomatic and medically stable, there was no sign of hepatic pathology, and his liver enzymes returned to baseline levels, with ALT 67.1 U/L and AST 48.8 U/L. The AE of hepatitis resolved on Day 78 (20 May 2011). The SAE of hepatitis was considered by the Investigator to be moderate in intensity and related to investigational product.*

*Comment: The investigator at the site did make some attempt to rule out acute viral hepatitis A, but on finding the IgM negative concluded the reaction was drug-induced by study drug (found to be cariprazine), moderately severe, and made a diagnosis of "drug-induced hepatitis." The narrative appears to have been written from the MedWatch report submitted to the sponsor by the investigator. The diagnosis of an adverse event (AE) was upgraded to a serious adverse event (SAE) on the basis of a higher level of ALT and AST.*

The second case, a U.S male 47 #0190301 (Study -03 started cariprazine on 20 February 2007:

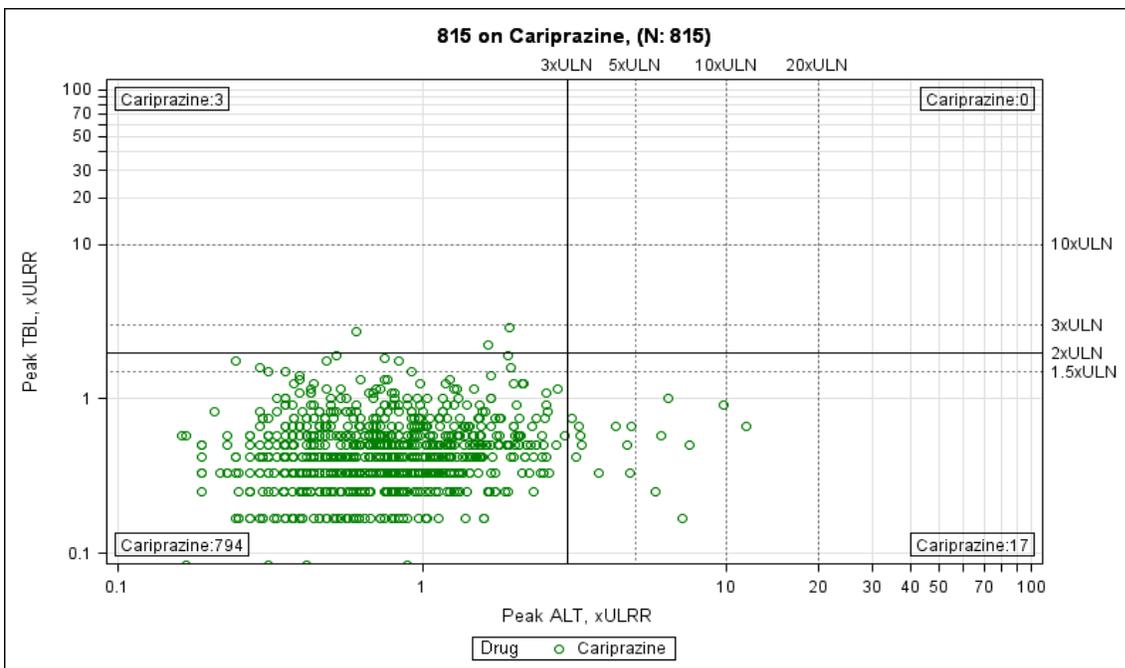


After 23 days on study drug elevated serum aminotransferases were found and the drug was stopped 9 days later, and he was discontinued from the study 3 days after that. The sponsor later contacted the study site and found that the serum enzyme tests had returned to normal over 6 months later.

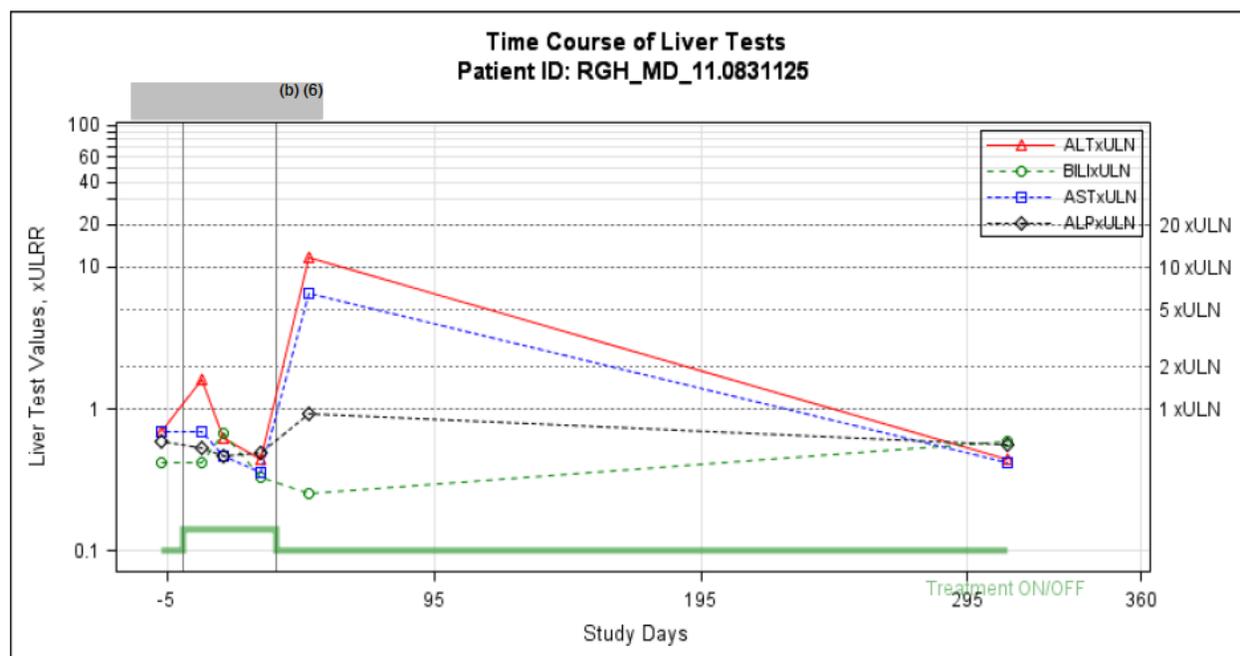
*Patient 0190301, a 47-year-old male diagnosed with schizophrenia, received double-blind cariprazine (1.5-4.5 mg/day) for 32 days from 20 Feb 2007 to 23 Mar 2007 (final dose: 1.5 mg/day). The patient had medical history that included anxiety, agitation, insomnia, depression, arthritis, herniated disc, asthma, hypertension, high cholesterol, and hyperlipidemia. Concomitant medication included simvastatin, initiated at the screening visit, lorazepam, ibuprofen, acetaminophen, zolpidem, and inhaled asthma medication.. The patient was discontinued from the study on Study Day 35 (26 Mar 2007) because of the AEs of increased ALT and increased AST, which were considered by the Investigator to be possibly related to treatment. Based on follow-up information from the site, the patient did not have elevated bilirubin, was presumably asymptomatic, and recovered without effect on hepatic function. After the patient discontinued the study, the study center provided follow-up information that the transaminase levels had returned to normal based on local laboratory tests obtained on 01 Oct 2007 (ALT, 25 U/L [reference range: 6-48]; AST, 27 U/L [reference range: 10-45]; and alkaline phosphatase, 72 U/L [reference range: 45-145]). Assessment of this case is confounded by the initiation of simvastatin 10 mg daily, a drug known to be associated with aminotransferase elevations, at the screening visit.*

*Comment: The analyses and retrospective diagnoses made by the sponsor in preparing the narratives requested six years later from information reported by the investigator are highly dubious. To say a case is “confounded” by the fact that some other drug than study drug was taken (simvastatin) does not remove the possibility that it was perhaps caused by study drug; all of the cases are confounded, and making a valid diagnosis of study drug-induced liver injury is never easy. The sparcity of data in this case is notable.*

For the smaller set of 815 schizophrenic patients followed on open-label cariprazine in eDISH extension Stdy -11 there was only one who showed ALT >10xULN, another 5 with >5-10xULN, and 10 others with >3-5xULN peak elevations at any time:



Let us look more closely at patient #0831125, a U.S. male 48 on cariprazine from (b) (6) when he was hospitalized for suicidal ideation and cariprazine was stopped, but the serum aminotransferases activities rose sharply 12 days later and were not followed closely or investigated. Elevated serum CPK levels were also noted and follow-up done for suspected rhabdomyolysis. A late set of serum liver tests was done on 16 December 2011, almost a year later and were in the normal range.

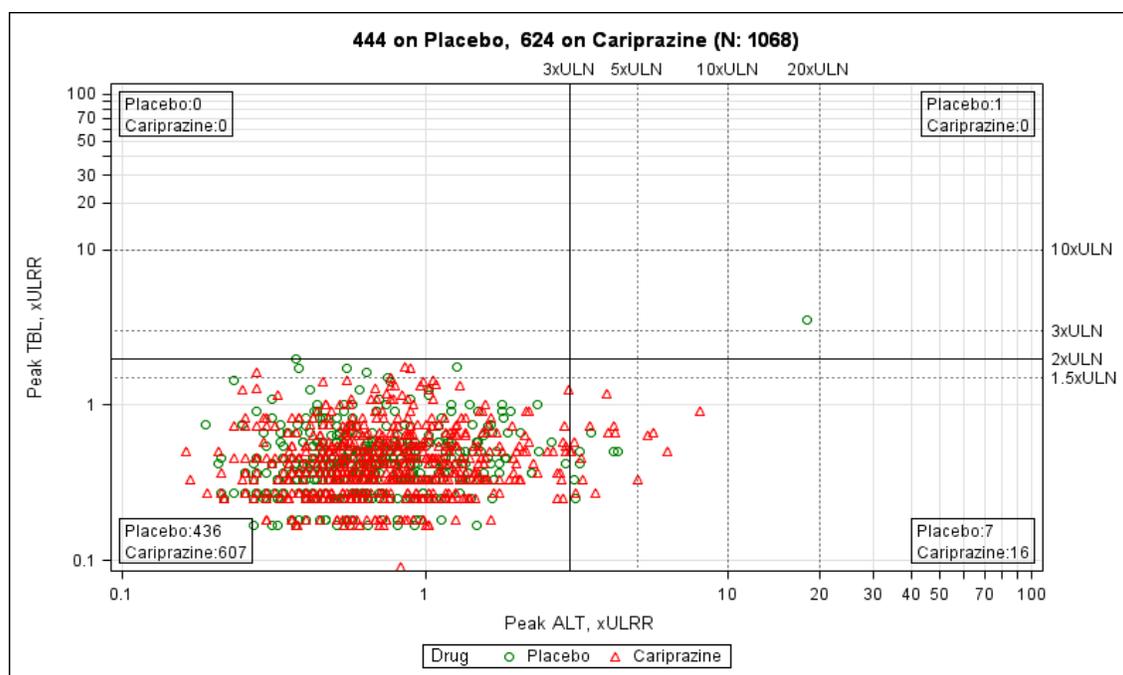


Patient 0831125, 48-year-old male diagnosed with schizophrenia without previous exposure to cariprazine, enrolled in a 48-week open-label study (RGH-MD-11) and received cariprazine for 36 days from (b) (6). He had a medical history of anxiety, depression, insomnia, restlessness, and chronic obstructive pulmonary disease. There were no relevant concomitant medications. Baseline CPK was 502 U/L, and creatinine, BUN, and ALT/AST were within the reference ranges. On Study Day 35 (b) (6), the patient experienced a nonserious AE of suicidal ideation (Investigator term: suicidal ideation secondary to increased psychosis). On Study Day 36 (b) (6), the patient was hospitalized with an SAE of psychotic disorder (Investigator term: increased psychosis). The patient was discontinued from the study because of the suicidal ideation and the psychotic disorder. Per C-SSRS, the patient did not have suicidal ideation or suicidal behavior during the study. AEs of GERD, COPD, renal insufficiency, rhabdomyolysis, left-arm numbness, troponin increased, CPK increased, and CPK-MB increased were reported over Days 36-39. Benztropine, paroxetine, and quetiapine were started. On Study Day 53, the patient had a second SAE of psychotic disorder. Per MedWatch (1000019561), on Day 36 (b) (6), the patient was hospitalized because of increased psychosis and suicidal ideation along with left arm numbness. The patient denied having any chest pain, paroxysmal nocturnal dyspnea, or orthopnea symptoms. Troponin I was 0.140 ng/mL (reference range: 0.00-0.056). Head CT scan was normal. On (b) (6), CPK was 2757 U/L (reference range: 39-308), CK-MB was 7.9 ng/mL (reference range: 0-3.6) at 06:10 and 5.4 ng/mL at 13:20; creatinine and BUN were within reference range. Echocardiogram was unremarkable, and carotid duplex study was normal. Myocardial infarction was ruled out by serial CPK and isoenzymes. On Day 38, CPK total was 1766 U/L, and creatinine was within the reference range. On Day 39, troponin I was < 0.04 ng/mL, and CK-MB was 1.7 ng/mL (within reference range). Urine myoglobin was not done. The patient was treated with pantoprazole, metoprolol, and aspirin as well as his quetiapine and lorazepam. The patient was transferred to an inpatient psychiatric facility. Medications with transfer included prednisone for 3 days, oral levofloxacin for 7 days, and his psychotropic medications. On Study Day 47 (b) (6) the suicidal ideation and the psychotic disorder resolved. The patient was discharged from the hospital. The AE of rhabdomyolysis was indicated as resolved on Study Day 310. On Study

Day 48 (b) (6), 12 days after the last dose of cariprazine, ALT was 558 U/L, AST was 293 U/L, and GGT was 132 U/L; these elevations were reported as AEs, considered by the Investigator to be related to treatment and resolved on Day 62. Total bilirubin remained within the reference range (5.13 umol/L on (b) (6)). Hepatitis serology was negative. Concomitant medications that were initiated shortly before the ALT and AST elevations were observed included quetiapine (50 mg twice daily), benztropine (0.5 mg twice daily), and paroxetine (10 mg daily), which were started on (b) (6), and metoprolol (25 mg daily), aspirin (81 mg daily), pantoprazole (40 mg daily), prednisone (20 mg daily), and levofloxacin (250 mg daily), which were started on (b) (6). Levofloxacin is known to cause increases in serum aminotransferase levels. Per MedWatch (1000019993), on Day 53 (b) (6), the patient again experienced increased psychosis and was hospitalized on the same day. He also had suicidal intent to overdose on his pills. He denied any medical symptoms. Urine drug screen was positive for THC. His regular medications quetiapine and benztropine were restarted and titrated as necessary, and paroxetine was added back to his regimen. The second SAE of psychotic disorder resolved on Study Day 58 (b) (6), and the patient was discharged from the hospital. Additional laboratory data available after discontinuation from study corresponding to Study Day 310 (b) (6) showed both liver biochemistries and CPK levels within their respective reference ranges.

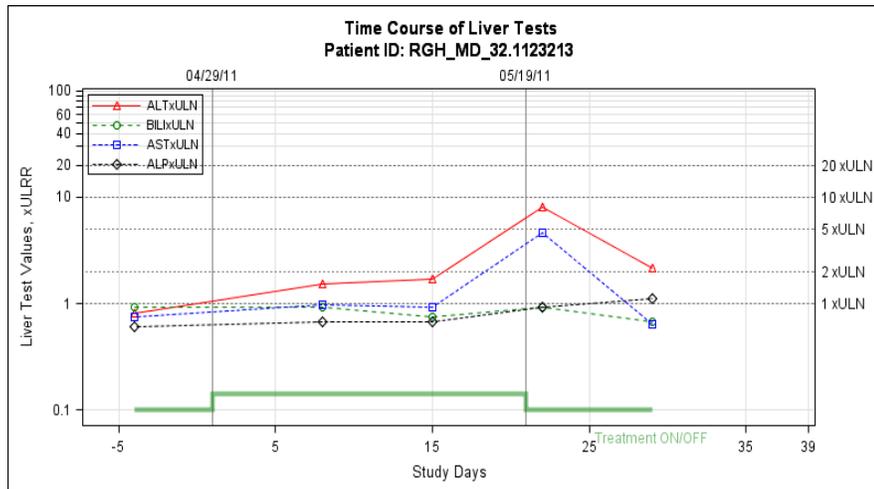
*Comment: It is not clear why the investigator, who was said by the sponsor in the narrative to have considered the aminotransferase elevated an adverse event related to treatment with the study drug cariprazine did no follow-up or repeat studies for almost a year, paying more attention to the CPK elevations. It is not stated in the narrative exactly when the aminotransferase elevations were conveyed to the sponsor, but a MedWatch report of (b) (6) is mentioned concerning the repeat hospitalization for psychosis.*

In the studies on bipolar mania, there were only a few patients who at any time showed modest elevations of serum aminotransferase activities, none associated with symptoms of evidence of liver dysfunction. Five showed peak ALT values >5-10xULN, for whom brief narratives were submitted, but none for the 11 patients who had only slight ALT elevations >3-5xULN and none for the single patient on placebo (Indian male 35, Study 32\_1033211) with peak ALT 18.2xULN, AST 4.3xULN and TBL 3.5xULN in the potentially worrisome range but no investigation for alternative cause.

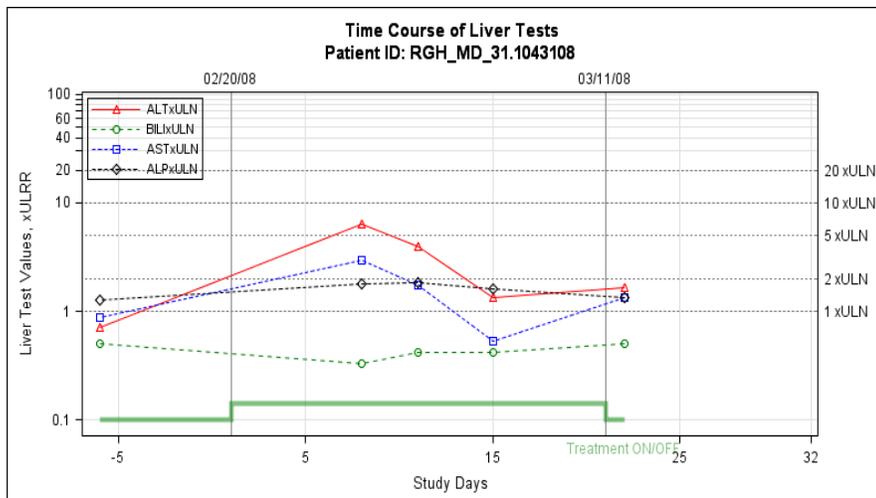


For completeness, the time courses of the 5 patients who showed the moderate ALT peak elevations without significant bilirubin increase are shown below, with short comments as obtained from the narratives (the patients profiles submitted 1 July 2013 only repeated what was already known and plotted from the study case reports.

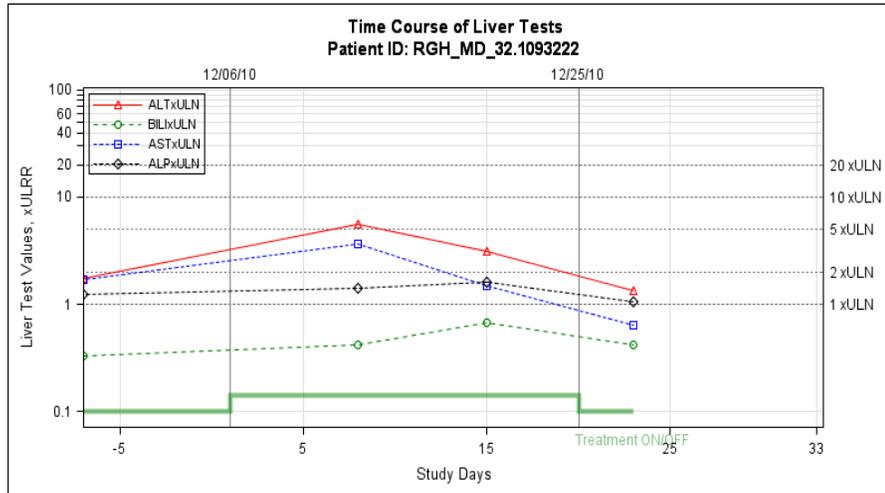
Study 32, #1123213, Indian male 37, cariprazine 12 mg/day for 21 days: The patient reported no symptoms. Serologic tests for viral hepatitis A, B, C were negative.



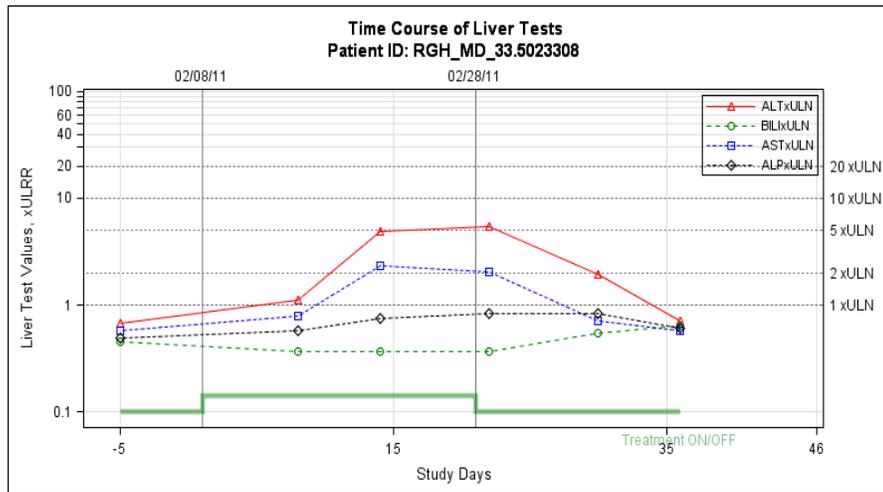
Study 31, #1043103, Indian female 55, cariprazine 9 mg/day for 21 days: mild abdominal pain, decreased appetite noted, but no nausea, vomiting, fatigue, jaundice. Elevated enzymes at day 8 decreased despite continuing drug.



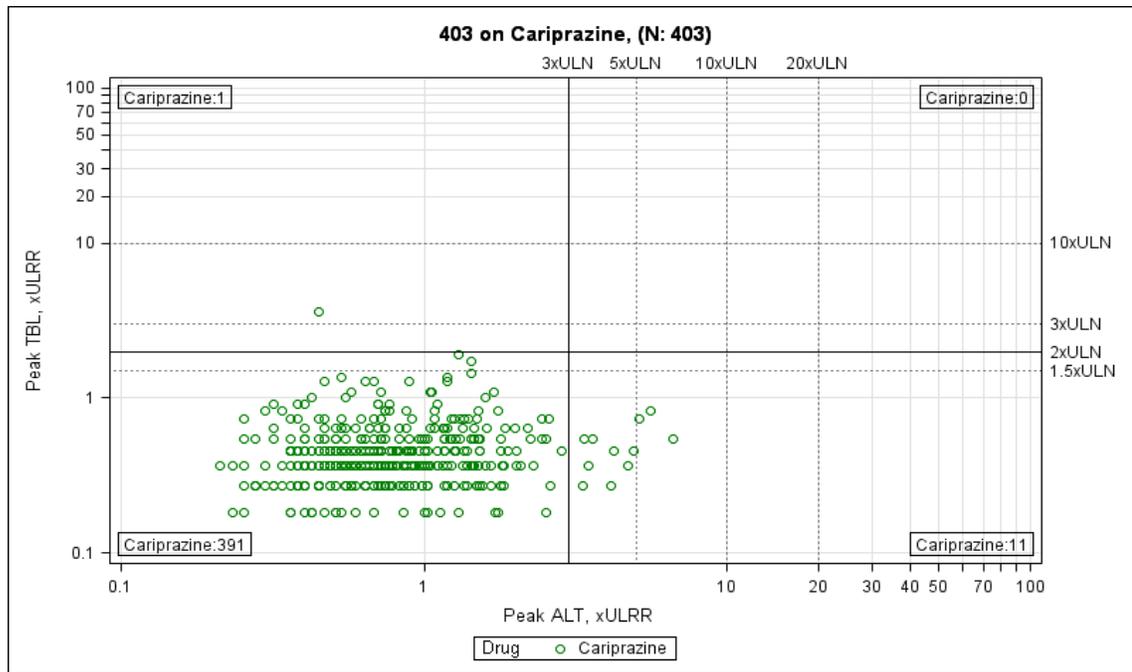
Study 32, #1093222, Indian female 24, cariprazine 12 mg/day for 20 days: the modestly elevated ALT and AST declined despite continuing cariprazine administration. She reported no symptoms suggestive of liver injury or dysfunction. Acute viral hepatitis A antibody IgM negative on days 8 and 15 after starting drug.



Study 33, #5023308 Russian female 56, cariprazine 6 mg/day for 21 days. History of chronic cholecystitis, but no symptoms during current study. Modest serum enzyme increases at 8 days declined despite continuing study drug, with no notable bilirubin increase.

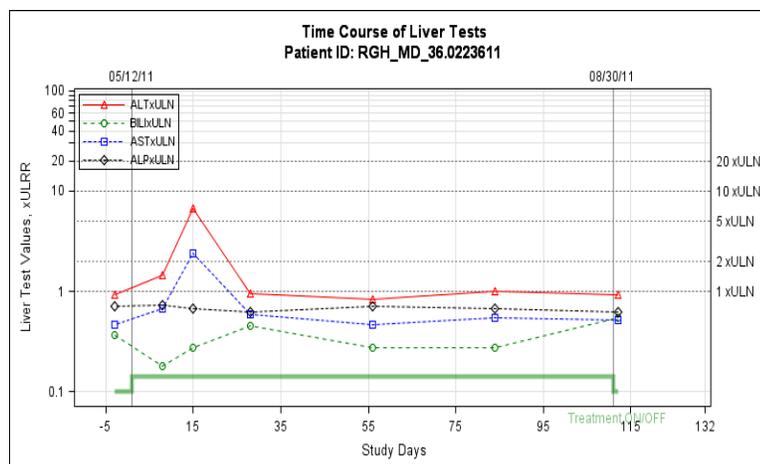


The open-label study MD-36 of bipolar mania included 403 patients whose data were sent by the sponsor for eDISH analyses:

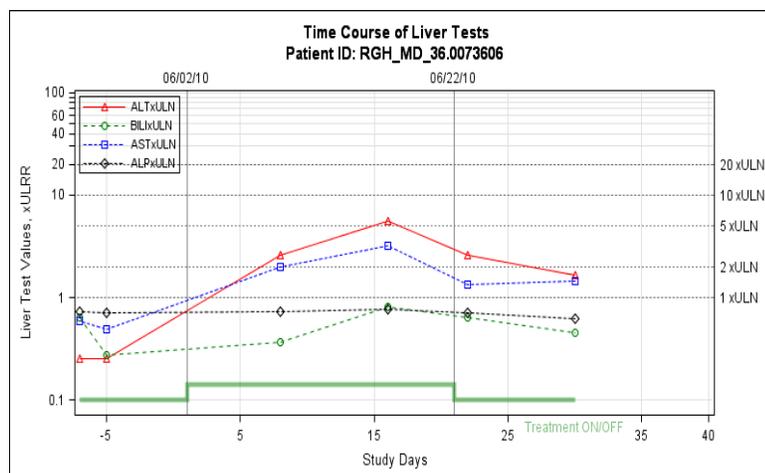


Again it may be seen that just a few ALT elevations were found, 3 with peak values >5-7xULN and 8 with minor rises >3-5xULN. No narratives were submitted for the latter group of 8 with the lesser ALT elevations. The time courses for the 3 moderate elevations indicated that the patients had no symptoms, were not clinically ill, and did not show serious liver injury or dysfunction, but recovered and appeared to adapt to the drug.

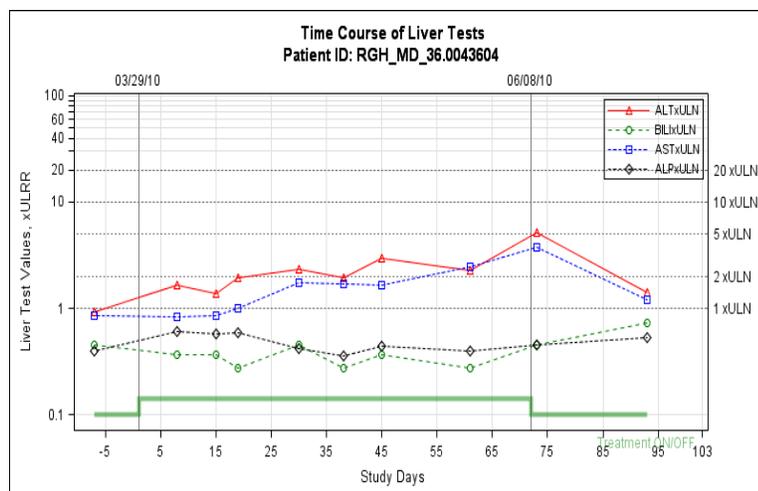
Shown below is the time course for patient #0223611, an obese white U.S. male 38 who showed a one-day rise in ALT and AST on Day 15 of cariprazine 3 mg/day, recovered and tolerated the drug for 16 weeks.



Patient # 0073606, an over weight black U.S. female 54 was only on cariprazine for 6 weeks, taking from 6 to 9 mg/day. She showed a modest rise in ALT and AST that declined after the drug was stopped. She had a history of hepatitis C the previous year.



Patient #0043604 was an obese U.S. male 39 who showed a very slowly rising level of ALT activity followed by some AST increase without rise in bilirubin over a period of about 10 weeks. He also showed some hypertriglyceridemia, and the sponsor suggested that he might have had steatohepatitis.



*Comment: The narratives provided by the sponsor apparently were prepared mainly from the MedWatch reports that had been sent by the investigators around the time of their observation of the patients studied, so were done in retrospect. Although they are somewhat better than the almost useless but bulky patient profiles sent in the massive Integrated Safety Summary sent 1 July 2013, that simply repeated what was in the study case reports and provided no diagnostic information as to the causes of the findings seen. In most of the submitted narratives they just speculate on what else other than cariprazine might be blamed for high transaminase values.*

*The time to investigate possible drug-induced liver injury is when it is happening, and not retrospectively some years later. No amount of statistical reworking of inadequate source data can overcome the lack of useful clinical information to find the most likely cause. The degree of elevation of serum enzymes is not a reliable measure of the severity of the problem, which is much more dependent on how much liver function may be lost, as shown by reduced ability to clear bilirubin from plasma or to synthesize the right amount of prothrombin to regulate nicely the bleeding-clotting balance.*

Therefore, let us conclude and turn to the questions asked:

1. The liver findings from these studies are not impressive, and reflect mostly modest and often transient elevations of serum ALT and less of AST, indicating some hepatocellular injury from this drug but no progressive damage that accumulates and leads to loss of whole-organ liver function such as increasing bilirubin concentration or rising prothrombin times (or INRs).
2. The findings do not suggest or predict a risk of serious drug-induced liver injury (DILI) with true dysfunction. It cannot be ruled out that very long-term treatment in rare people might reveal some who are susceptible, but they should be found and the drug stopped before that occurs.
3. I would not assess an approval issue here.
4. The label should report what was found, not infrequent elevation of serum transaminase activities, which are worth following to see if they reverse, or trigger investigation into the probable cause if not, preferably with consultation from knowledgeable colleagues skilled in diagnosing liver disease.
5. Additional data from the sponsor will not provide illumination, just weight of paper or overload of data memory space. The sponsor relies on massive statistical reworking of inadequate data, which cannot be fixed after the fact of inadequate investigation at the study sites all over the world. Quantity does not make up for poor quality.
6. Postmarketing studies would be fine, if done well, but it seems unlikely that they would be. It is not the central core of psychiatric training or practice to develop advanced skills in differential diagnosis of liver disease. If patient and physicians are aware that the drug often causes minor liver injury that perhaps might rarely become serious rarely, and act promptly to investigate advancing abnormalities by interrupting drug administration and investigating appropriately, with consultation if necessary, that is just good medicine.

7. Routine monitoring is burdensome, costly, much disliked by both patients and doctors, and therefore not done for long, which assures it will fail. It is a very inefficient way to discover and manage rare problems, which serious DILI nearly always is. It is not a good idea to place too much emphasis on serum enzyme activities; they do not measure any liver function and are poor indicators of severity. The important thing is to detect and prevent serious liver dysfunction that leads to disability, hospitalization, liver failure, and death or transplantation

Thank you for sending this most interesting and challenging consultation request, and also for nudging the sponsor into sending eDISH data and narratives, such as they are, to help make sense of this massive NDA submission.

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John R. Senior, M.D.

cc: OSE 2013-1842  
M. Mathis, DPP  
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/s/  
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JOHN R SENIOR  
09/30/2013



# Center for Drug Evaluation and Research

## Division of Cardiovascular and Renal Products

Consultation, NDA 204370

**DATE:** Consult requested: 28 August 2013  
Consult received: 30 August 2013  
Desired Completion date: 27 September 2013  
PDUFA Date: 11/19/13

**FROM:** Preston M. Dunmon, M.D., Medical Officer  
Division of Cardiovascular and Renal Products, HFD-110

**THROUGH:** Norman Stockbridge, M.D., Ph.D., Division Director  
Division of Cardiovascular and Renal Products, HFD-110

**TO:** Kim Updegraff, RPM / Robert Levin, CDTL  
Division of Psychiatry Products, HFD-130

**SPONSOR:** Forest Research, Inc.

**DRUG CLASS:** Central dopamine D3, D2, and 5-HT1A receptor agonist

**DRUG NAME:** Cariprazine (RGH-188)

**FORMULATION:** Oral

**APPLICATION No:** NDA 204370

**PROPOSED INDICATION:** for the treatment of schizophrenia and bipolar mania

**DOSE:**

- Schizophrenia: (b) (4)
- Mania: (b) (4)

**CONSULT QUESTIONS:** There appear to be dose-related increases in blood pressure and heart rate compared to placebo and active comparators (aripiprazole and risperidone). The review division requests that DCRP assess the blood pressure effects and CV risks of cariprazine, and answer the following questions:

1. Do the blood pressure changes appear to be dose-related?
2. Would you recommend specific risk mitigation strategies regarding hypertension and other cardiovascular risks?

3. Would you recommend including warnings and precautions in labeling for these risks?
4. Would you recommend obtaining additional data or analyses from the sponsor during the review cycle?
5. Do you recommend any specific postmarketing studies or other regulatory actions regarding blood pressure increases or other cardiovascular risks?

**DOCUMENTS AVAILABLE FOR REVIEW:**

- NDA 204370
- Additional analyses requested by DCRP from the sponsor (shift tables and time to first hypertensive event analyses for low, medium, and high dose range cariprazine with respect to JNC-7 defined categories of hypertension)

**SUBMISSION LINK:** <\\CDSESUB5\EVSPROD\NDA204370\204370.enx>

**Background**

Cariprazine is an antipsychotic proposed for the treatment of schizophrenia and bipolar mania. It has partial agonist activity at central dopamine D3, D2, and 5-HT1A receptors. There appear to be dose-related increases in blood pressure and heart rate compared to placebo and active comparators (aripiprazole and risperidone). There are greater proportions of outliers with increases in blood pressure in the cariprazine groups, compared to the placebo and active comparator groups; and there are higher proportions of subjects with adverse events reported as hypertension in the cariprazine groups compared to the other groups. Other significant dose-related effects are extrapyramidal symptoms and elevations in CPK and transaminases. In some studies, there appears to be an increase in mean creatinine. There appear to be dose-related decreases in LDL and total cholesterol.

There are important PK findings. The parent drug and active metabolites have long half-lives. The half-life of the parent is 3 to 9 days, and the half-life of the most important active metabolite is 2 to 3 weeks. This active metabolite accounts for 70% of the active moiety. The drug has a very large volume of distribution and is highly lipid soluble. There is evidence that several types of adverse events and laboratory findings (CPK and transaminase) can persist for more than a month after discontinuation of treatment.

The Review Division requests DCRP's assessment of the blood pressure findings and potential cardiovascular risks with cariprazine. Patients with schizophrenia and bipolar disorder are at significantly greater risk of serious cardiovascular events and generally have higher medical morbidity and earlier ages of death compared to the general population. They have very high rates of tobacco smoking and alcohol and other substance abuse. All antipsychotics, including cariprazine can significantly increase the risk of developing metabolic syndrome. These patients are often poorly adherent/compliant with medical care and medications.

**The Sponsor's Analysis of Integrated Vital Sign Data, NDA 204370**

There are 4 short-term (6-week), placebo-controlled studies in schizophrenia; and there are 3 short-term (3-week) placebo-controlled studies in mania. There are two uncontrolled, long-term studies in schizophrenia (48 weeks) and one uncontrolled long-term study in mania (24 weeks). Some studies used fixed doses, some have fixed ranges with flexible dosing, and some are flexible-dose studies. Two of the schizophrenia studies have active comparators. These studies (number designations and doses during the controlled trials) are as follows:

Schizophrenia Studies:

Study MD-03: Fixed-ranges/flexible dosing (cariprazine 1.5 to 4.5 mg and 6 to 12 mg)

Study MD-04: Fixed-dose (cariprazine 3 mg and 6 mg) and aripiprazole 10 mg

Study MD-05: Fixed-ranges/flexible dosing (cariprazine 3 to 6 mg and 6 to 9 mg)

Study MD-16: Fixed-dose (cariprazine 1.5, 3, 4.5 mg) and risperidone 4 mg

Studies MD-11 and MD-17 were Schizophrenia, uncontrolled, long-term extensions.

Bipolar Mania Studies:

Study MD-31 and MD-32 were flexible-dose studies (3 to 12 mg)

Study MD-32: Fixed-ranges/flexible dosing (3 to 6 mg and 6 to 12 mg)

Study MD-36 was an uncontrolled, long-term extension study in mania.

For the purposes of the integrated summary of safety (ISS), the sponsor categorized the above studies according to the following table (from the ISS, volume 1, page 113):

**Table 4.3.1–1. Grouping of Cariprazine Studies in the Integrated Summary of Safety**

<i>Group 1 Schizophrenia Studies</i>	
<b>Group 1A: Controlled Schizophrenia Studies</b>	<b>Group 1B: Long-term, Open-label Schizophrenia Studies</b>
RGH-MD-03 RGH-MD-04 <sup>a</sup> RGH-MD-05 <sup>a</sup> RGH-MD-16 <sup>a</sup>	RGH-MD-11 <sup>b</sup> (interim safety database) RGH-MD-17
<i>Group 2 Bipolar Mania Studies</i>	
<b>Group 2A: Controlled Bipolar Mania Studies</b>	<b>Group 2B: Long-term, Open-label Bipolar Mania Studies</b>
RGH-MD-31 <sup>a</sup> RGH-MD-32 <sup>a</sup> RGH-MD-33 <sup>a</sup>	RGH-MD-36

a Pivotal study.

b Ongoing.

MD = multiple-dose; PD = pharmacodynamic; PK = pharmacokinetic; SD = single-dose

Source: Statistical analysis plan (Appendix II); Individual clinical study reports in Module 5.

The sponsor maintains the nomenclature of controlled studies (Groups 1A + 2A) and long-term extension studies (Groups 1B + 2B) in all the subsequent safety tables (as well as the additional analyses that were performed at DCRP's request in the next section).

Per study 04, the protocol-defined technique for vital sign data acquisition was as follows (from the trial 04 FSR, Vol 1 pg 66):

*Supine blood pressure and radial pulse rate measurements were collected twice at every visit, once after the patient had been in the supine position for 5 minutes followed by a second supine measurement 1 minute later; the second supine measurement was entered into the eCRF. Standing blood pressure and radial pulse rate was measured twice (after the supine measurements were collected), once after the patient had been standing for 1 to 3 minutes, followed by a second standing measurement 1 minute later; the second standing measurement was entered into the eCRF. The same arm and blood pressure cuff was used for all measurements. Pulse rate was measured after blood pressure measurements.*

Overall, the mean baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) were similar between placebo and cariprazine treated patients (all doses combined) in both schizophrenia and mania studies, and the mean change from baseline in these parameters was small, as can be seen from the sponsor's ISS table 9.1-1 below (ISS volume 1 pg 313):

**Table 9.1–1. Overview of Mean Changes From Baseline to Endpoint for Vital Signs Data in the Schizophrenia and Bipolar Mania Studies—Safety Population**

<i>Parameter, Unit</i>	<i>Schizophrenia</i>			<i>Bipolar Mania</i>		
	<i>Group 1A</i>		<i>Group 1B Long-term</i>	<i>Group 2A</i>		<i>Group 2B Long-term</i>
	<b>Placebo (N = 584)</b>	<b>Cariprazine (N = 1317)</b>	<b>Cariprazine (N = 622)</b>	<b>Placebo (N = 442)</b>	<b>Cariprazine (N = 623)</b>	<b>Cariprazine (N = 402)</b>
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>Mean ± SD</i>
<b>Supine systolic blood pressure, mm Hg</b>						
Baseline	120.6 ± 11.2	120.9 ± 10.7	121.0 ± 10.1	121.8 ± 11.3	121.8 ± 10.5	121.7 ± 11.1
Change from baseline	0.9 ± 10.4	1.2 ± 10.8	0.8 ± 11.2	-0.5 ± 10.8	1.4 ± 10.3	1.4 ± 10.9
<b>Supine diastolic blood pressure, mm Hg</b>						
Baseline	76.6 ± 7.9	76.1 ± 8.2	75.8 ± 7.7	76.5 ± 7.8	76.8 ± 8.0	75.9 ± 8.5
Change from baseline	0.4 ± 8.0	1.3 ± 8.3	0.6 ± 8.8	0.9 ± 7.7	1.7 ± 8.1	1.8 ± 8.6
<b>Supine pulse rate, bpm</b>						
Baseline	76.6 ± 10.6	77.6 ± 10.4	76.4 ± 10.3	76.8 ± 10.4	77.6 ± 10.8	75.5 ± 10.2
Change from baseline	-0.1 ± 12.6	0.7 ± 11.6	-1.5 ± 11.9	-0.7 ± 11.0	2.0 ± 11.6	-0.9 ± 12.2
<b>Weight, kg</b>						
Baseline	77.89 ± 19.73	76.75 ± 18.73	78.47 ± 19.90	77.37 ± 19.13	77.29 ± 18.95	86.73 ± 17.93
Change from baseline	0.32 ± 2.99	1.07 ± 2.96	1.46 ± 5.03	0.17 ± 2.17	0.54 ± 2.07	0.92 ± 3.47
<b>Body mass index, kg/m<sup>2</sup></b>						
Baseline	26.40 ± 5.35	26.05 ± 5.26	26.68 ± 5.65	26.93 ± 5.69	26.92 ± 5.64	29.28 ± 5.35
Change from baseline	0.10 ± 0.97	0.35 ± 0.98	0.52 ± 1.71	0.06 ± 0.74	0.18 ± 0.71	0.30 ± 1.17

As defined by the sponsor, the percentage of patients experiencing potentially clinically significant vital sign shifts were small and similar between placebo and cariprazine treated patients (all doses combined) of the integrated blinded studies (though body weight tended to increase on active therapy), as seen in ISS table 9.1-2 below (ISS volume 1 pg 314):

**Table 9.1–2. Percentage of Patients With Potentially Clinically Significant Vital Sign Values and Orthostatic Hypotension in the Schizophrenia and Bipolar Mania Studies—Safety Population**

<i>PCS Criterion</i>	<i>Schizophrenia</i>			<i>Bipolar Mania</i>		
	<i>Group 1A</i>		<i>Group 1B Long-term</i>	<i>Group 2A</i>		<i>Group 2B Long-term</i>
	<b>Placebo (N = 584)</b>	<b>Cariprazine (N = 1317)</b>	<b>Cariprazine (N = 622)</b>	<b>Placebo (N = 442)</b>	<b>Cariprazine (N = 623)</b>	<b>Cariprazine (N = 402)</b>
<b>Supine systolic blood pressure</b>						
<i>Low</i> : ≤ 90 mm Hg and decrease ≥ 20 mm Hg	0.7%	0.5%	1.3%	0.7%	0.8%	0.3%
<i>High</i> : ≥ 180 mm Hg and increase ≥ 20 mm Hg	0	0.1%	0.3%	0.5%	0	0
<b>Supine diastolic blood pressure</b>						
<i>Low</i> : ≤ 50 mm Hg and decrease ≥ 15 mm Hg	0	0	0.3%	0	0.3%	0.3%
<i>High</i> : ≥ 105 mm Hg and increase ≥ 15 mm Hg	0.2%	0.5%	0.5%	0.5%	0.3%	1.3%
<b>Supine pulse rate</b>						
<i>Low</i> : ≤ 50 bpm and decrease ≥ 15 bpm	0.7%	0.2%	1.1%	0.2%	0.2%	0.8%
<i>High</i> : ≥ 120 bpm and increase ≥ 15 bpm	0	0.3%	0.3%	0.9%	0.2%	0.3%
<b>Weight</b>						
Decrease ≥ 7%	3.1%	1.5%	10.6%	1.6%	1.0%	3.5%
Increase ≥ 7%	4.7%	9.2%	25.3%	1.6%	1.9%	9.3%
<b>Orthostatic hypotension</b>						
Reduction in SBP of ≥ 20 mm Hg OR reduction in DBP of ≥ 10 mm Hg while changing from the supine to standing position	12.3%	13.4%	19.2%	13.5%	11.5%	13.7%

### Vital Signs by Dose - Controlled Schizophrenia Trials

However, a different picture begins to emerge as vital sign analyses are performed based on the dose of drug the patient was treated with. In the controlled schizophrenia studies, higher doses of drug were associated with a dose responsive change from baseline in both SBP and DBP comparing placebo to low dose cariprazine (1.5 - 6 mg) and high dose cariprazine (6 -12 mg). It is unclear if patients treated with 6 mg were counted in both low and high dose cohorts. The data from this analysis is per the sponsor's ISS table 9.2.1.1-1 below (ISS page 316:

**Table 9.2.1.1–1. Change From Baseline to the End of the Double-blind Treatment Period for Blood Pressure and Pulse Rate in Group 1A (Controlled Schizophrenia Studies)—Safety Population**

Parameter, Unit	Placebo (N = 584)		Cariprazine						Risperidone 4 mg (N = 140)		Aripiprazole 10 mg (N = 152)	
			1.5-6 mg (N = 1032)		6-12 mg (N = 285)		Overall (N = 1317)					
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
<b>Supine systolic blood pressure, mm Hg</b>												
Baseline		120.6 ± 11.2		121.0 ± 10.6		120.5 ± 11.1		120.9 ± 10.7		120.8 ± 10.5		119.8 ± 9.4
Change from baseline	574	0.9 ± 10.4	1005	0.8 ± 10.3	280	2.4 ± 12.0	1285	1.2 ± 10.8	138	-2.2 ± 10.1	150	1.7 ± 8.9
<b>Supine diastolic blood pressure, mm Hg</b>												
Baseline		76.6 ± 7.9		76.2 ± 8.0		75.6 ± 8.8		76.1 ± 8.2		77.5 ± 8.3		74.3 ± 6.7
Change from baseline	574	0.4 ± 8.0	1005	0.8 ± 7.9	280	3.4 ± 9.3	1285	1.3 ± 8.3	138	-1.6 ± 7.7	150	0.8 ± 7.4
<b>Supine pulse rate, bpm</b>												
Baseline		76.6 ± 10.6		77.5 ± 10.5		77.9 ± 10.2		77.6 ± 10.4		77.5 ± 12.3		75.2 ± 10.0
Change from baseline	574	-0.1 ± 12.6	1005	0.5 ± 11.5	280	1.5 ± 11.8	1285	0.7 ± 11.6	138	0.2 ± 12.8	150	0.0 ± 11.7

TEAEs of hypertension, blood pressure increased, blood pressure systolic increased, blood pressure immeasurable, blood pressure diastolic increased, and hypertensive crisis occurred in a dose responsive fashion as well (17/285 (6%) versus 25/1032 (2.4%) versus 6/184 (1%) for high dose, low dose, and placebo treated patients respectively), as seen from the sponsor's ISS Table 9.2.1.2-2 below (ISS page 318):

**Table 9.2.1.2–2. Number (%) of Patients With TEAEs Associated With Blood Pressure or Pulse Rate, Including Orthostasis, During the Double-blind Treatment Period in Group 1A (Controlled Schizophrenia Studies)—Safety Population**

<i>Preferred Term</i>	<i>Placebo (N = 584) n (%)</i>	<i>Cariprazine</i>			<i>Risperidone 4 mg (N = 140) n(%)</i>	<i>Aripiprazole 10 mg (N = 152) n (%)</i>
		<i>1.5-6 mg (N = 1032) n (%)</i>	<i>6-12 mg (N = 285) n (%)</i>	<i>Overall (N = 1317) n (%)</i>		
<b>TEAEs associated with blood pressure</b>						
Hypertension	2 (0.3)	17 (1.6)	5 (1.8)	22 (1.7)	0	1 (0.7)
Blood pressure increased	4 (0.7)	6 (0.6)	9 (3.2)	15 (1.1)	2 (1.4)	0
Blood pressure systolic increased	0	1 (0.1)	1 (0.4)	2 (0.2)	0	0
Blood pressure immeasurable	0	0	1 (0.4)	1 (0.1)	0	0
Blood pressure diastolic increased	0	0	1 (0.4)	1 (0.1)	0	0
Hypertensive crisis	0	1 (0.1)	0	1 (0.1)	0	0
Orthostatic hypotension	7 (1.2)	6 (0.6)	1 (0.4)	7 (0.5)	0	2 (1.3)
Postural orthostatic tachycardia syndrome	4 (0.7)	4 (0.4)	0	4 (0.3)	0	0
Hypotension	5 (0.9)	2 (0.2)	0	2 (0.2)	1 (0.7)	0
Orthostatic intolerance	2 (0.3)	0	0	0	0	0
Blood pressure decreased	1 (0.2)	0	0	0	0	0
<b>TEAEs associated with heart rate</b>						
Tachycardia	3 (0.5)	14 (1.4)	4 (1.4)	18 (1.4)	3 (2.1)	4 (2.6)
Heart rate increased	2 (0.3)	6 (0.6)	1 (0.4)	7 (0.5)	2 (1.4)	0
Bradycardia	1 (0.2)	4 (0.4)	0	4 (0.3)	0	1 (0.7)
Palpitations	0	3 (0.3)	1 (0.4)	4 (0.3)	1 (0.7)	0
Heart rate irregular	0	0	1 (0.4)	1 (0.1)	0	0

Of note, TEAEs involving hypotension were confined almost exclusively to the low dose and placebo groups, in which hypotension occurred with similar frequency. Complaints of palpitations and heart rate irregular were confined solely to the cariprazine treated patients (rhythm unknown during these episodes, though at least one episode of SVT was noted in the ISS).

Three schizophrenia patients from the controlled trials experienced either an SAE of "blood pressure increased" or discontinued participation in the trials due to TEAEs associated with blood pressure elevation. All were treated with cariprazine. A fourth cariprazine-treated patient experienced a nonserious "hypertensive crisis" (it is unclear from the details given in this case if the highest blood pressures were reported).

## Vital Signs by Dose - Controlled Mania Trials

The sponsor does not present the integration of the controlled mania data by dose administered, and defines potentially clinically significant elevations of SBP/DBP with high cutoffs ( $\geq 180/105$ , either criterion) which produce unrealistically low numbers of patients experiencing clinically significant elevations of blood pressure.

It is noted once again, however, that TEAEs of hypertension (hypertension, blood pressure increased, blood pressure diastolic increased, secondary hypertension) occurred more frequently in cariprazine treated patients (all doses) than placebo treated patients (25/623 (4.0%) versus 6/442 (1.4%) respectively), as seen in the sponsor's table 9.2.3.2-2 below (ISS page 325):

**Table 9.2.3.2-2. Number (%) of Patients With TEAEs Associated With Blood Pressure or Pulse Rate, Including Orthostasis, During the Treatment Periods in Groups 2A and 2B (Bipolar Mania Studies)—Safety Population**

<i>Preferred Term</i>	<i>Group 2A</i>		<i>Group 2B</i>
	<i>Placebo (N = 422) n (%)</i>	<i>Cariprazine (N = 623) n (%)</i>	<i>Cariprazine (N = 402) n (%)</i>
<b>TEAEs associated with blood pressure</b>			
Hypertension	4 (0.9)	13 (2.1)	17 (4.2)
Blood pressure increased	2 (0.5)	10 (1.6)	8 (2.0)
Blood pressure diastolic increased	0	1 (0.2)	1 (0.2)
Secondary hypertension	0	1 (0.2)	0
Orthostatic hypotension	2 (0.5)	6 (1.0)	3 (0.7)
Hypotension	0	4 (0.6)	3 (0.7)
Postural orthostatic tachycardia syndrome	3 (0.7)	2 (0.3)	0
Orthostatic heart rate response increased	1 (0.2)	1 (0.2)	1 (0.2)
Blood pressure decreased	1 (0.2)	0	0
<b>TEAEs associated with heart rate</b>			
Tachycardia	4 (0.9)	5 (0.8)	1 (0.2)
Heart rate increased	1 (0.2)	2 (0.3)	6 (1.5)
Palpitations	2 (0.5)	2 (0.3)	2 (0.5)
Bradycardia	1 (0.2)	0	3 (0.7)

Two patients from the controlled mania trials discontinued treatment due to hypertension, both of whom were being treated with cariprazine.

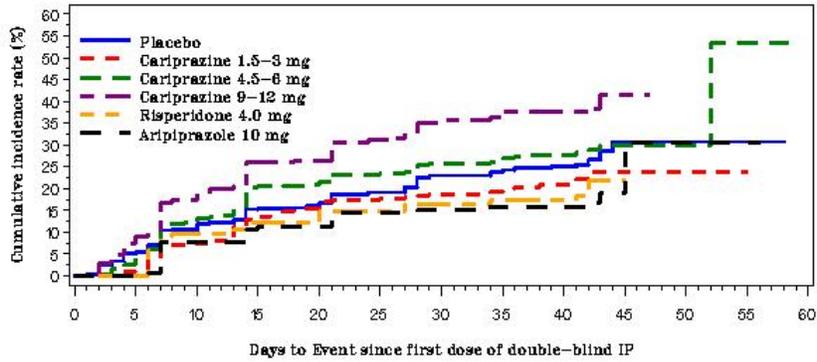
## **FDA Requested Reanalysis of the Integrated Blood Pressure Data**

Given that drug-induced hypertension in the schizophrenia and mania populations can be reasonably considered to be a drug effect and not a function of the underlying psychiatric disease, DCRP requested a complete reanalysis of the blood pressure data for cariprazine according to the following parameters:

- Integration of controlled data from the schizophrenia and mania trials
- Integration of uncontrolled data from the schizophrenia and mania trials
- Assessment of three dose groups in the integrated data sets:
  - Low dose - 1.5 and 3.0 mg doses combined
  - Intermediate dose - 4.5 and 6.0 mg doses combined
  - High dose - 9.0 and 12.0 mg doses combined
- For both the controlled and open label extension data sets so constructed, the following analyses were performed:
  - K-M time to first BP  $\geq$  140/90 (either SBP or DBP criteria)
  - K-M time to first BP  $\geq$  160/100 (either SBP or DBP criteria)
  - Shift tables assessing changes from baseline JNC-7 categories (normal, pre-hypertension, stage I, or stage II hypertension) to the highest JNC-7 category achieved during the treatment period
  - Shift tables assessing changes from baseline JNC-7 categories (normal, pre-hypertension, stage I, or stage II hypertension) to the JNC-7 category demonstrated at the end of study.

It is immediately apparent from the K-M analyses that blood pressure elevations into the stage I hypertension range are happening more frequently and more rapidly in cariprazine treated patients, in a dose related fashion, with the two highest dose ranges separating from the others (high dose > intermediate dose > placebo/low dose):

Figure 30.A.1.1.1 Kaplan-Meier Plot for Time to First Blood Pressure Event during Double-blind Treatment Period  
 Blood Pressure Event is Defined as Supine Systolic BP >=140 mmHg or Diastolic BP >=90 mmHg  
 Group 1A+2A (Controlled Schizophrenia and Bipolar Mania Studies)  
 Safety Population



At Risk	0	5	10	15	20	25	30	35	40	45	50	55	60
Placebo	1013	944	818	692	646	354	304	291	267	22	3	1	0
Cariprazine 1.5-3 mg	552	522	458	388	359	314	287	272	249	14	1	1	0
Cariprazine 4.5-6 mg	789	757	659	540	506	335	310	301	279	21	3	2	0
Cariprazine 9-12 mg	563	521	443	380	337	126	107	101	92	2	0	0	0
Risperidone 4.0 mg	138	135	118	108	106	100	90	85	84	1	0	0	0
Aripiprazole 10 mg	150	149	130	123	119	111	107	102	97	7	2	1	0

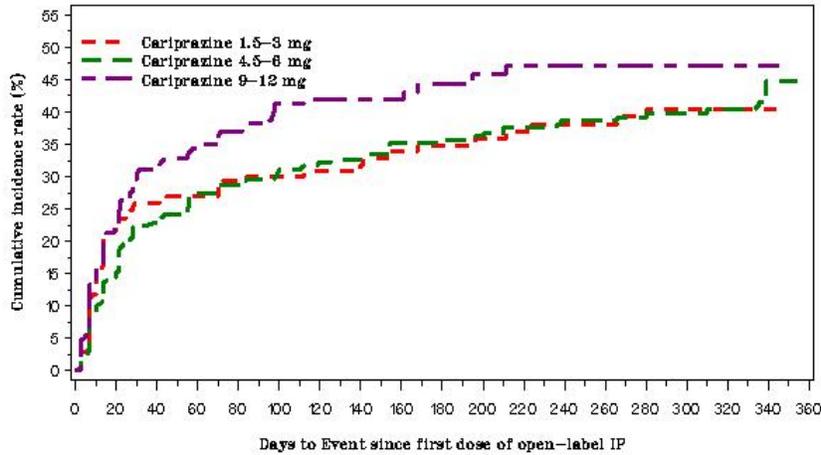
Event	0	5	10	15	20	25	30	35	40	45	50	55	60
Placebo	0	55	116	147	156	173	189	194	197	204	204	204	204
Cariprazine 1.5-3 mg	0	8	39	67	82	85	86	92	96	102	102	102	102
Cariprazine 4.5-6 mg	0	30	103	154	161	172	182	187	190	195	195	196	196
Cariprazine 9-12 mg	0	51	104	142	144	163	171	174	174	176	176	176	176
Risperidone 4.0 mg	0	0	13	16	19	19	21	22	22	24	24	24	24
Aripiprazole 10 mg	0	0	11	16	16	20	21	22	22	25	25	25	25

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This finding is corroborated for the high dose range (9 mg + 12 mg) by the analogous K-M curve for time to first BP  $\geq$  140/90 from the open label trials in which blood pressure was re-baselined at the beginning of the open label studies, as seen in the figure below:

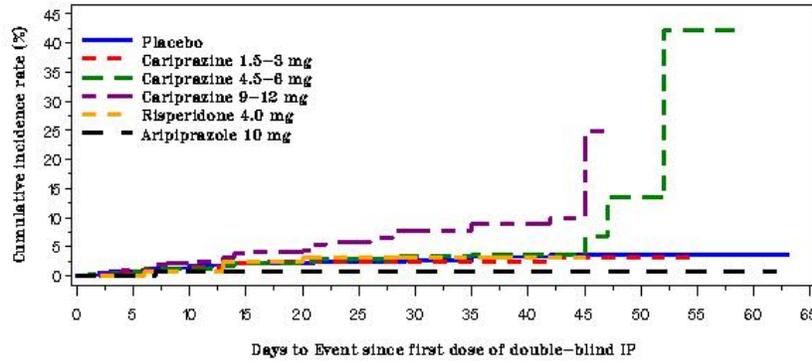
Figure 30.A.1.2.1 Kaplan-Meier Plot for Time to First Blood Pressure Event during Open-label Treatment Period  
Blood Pressure Event is Defined as Supine Systolic BP  $\geq$  140 mmHg or Diastolic BP  $\geq$  90 mmHg  
Group 1B+2B (Long-term, Open-label Schizophrenia and Bipolar Mania Studies)  
Safety Population



At Risk	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360
Cariprazine 1.5-3 mg	281	175	136	121	113	104	71	66	64	61	60	57	54	52	51	49	49	6	0
Cariprazine 4.5-6 mg	473	380	274	235	222	193	166	155	143	140	134	130	121	114	106	103	101	13	0
Cariprazine 9-12 mg	316	223	158	130	113	95	55	52	48	43	38	35	33	33	31	31	29	4	0
Event	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360
Cariprazine 1.5-3 mg	0	56	65	67	71	72	73	74	76	77	78	79	80	80	82	82	82	82	82
Cariprazine 4.5-6 mg	0	70	100	115	119	126	129	131	136	137	139	141	143	143	145	145	146	149	149
Cariprazine 9-12 mg	0	70	94	100	105	112	113	113	115	116	117	117	117	117	117	117	117	117	117

Though the shifts to stage II hypertension occurred less frequently, this identical pattern of results is seen for the high dose range of cariprazine in K-M analysis of time to first BP event  $\geq 160/100$  per the figure below:

Figure 30.A.1.1.2 Kaplan-Meier Plot for Time to First Blood Pressure Event during Double-blind Treatment Period  
Blood Pressure Event is Defined as Supine Systolic BP  $\geq 160$  mmHg or Diastolic BP  $\geq 100$  mmHg  
Group 1A+2A (Controlled Schizophrenia and Bipolar Mania Studies)  
Safety Population



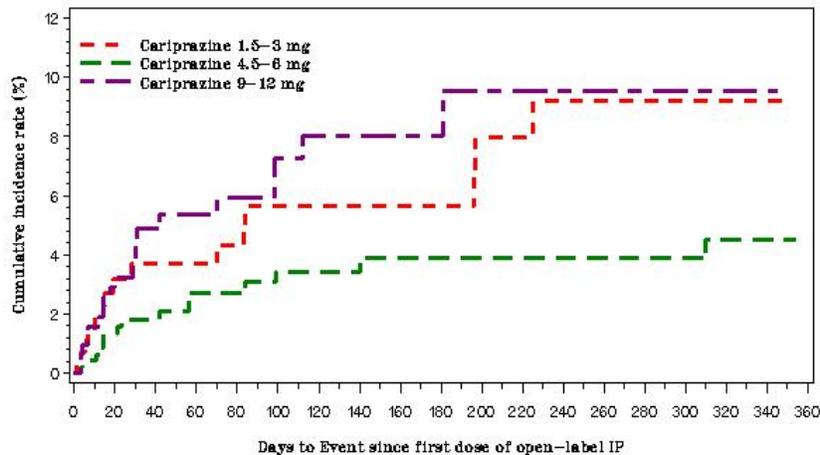
At Risk	0	5	10	15	20	25	30	35	40	45	50	55	60	65
Placebo	1013	985	898	794	743	410	368	353	327	29	6	3	1	0
Cariprazine 1.5-3 mg	552	525	483	433	407	361	336	319	299	21	1	1	0	0
Cariprazine 4.5-6 mg	789	773	738	649	605	406	366	377	358	30	4	2	0	0
Cariprazine 9-12 mg	563	557	523	458	420	159	143	136	128	6	0	0	0	0
Risperidone 4.0 mg	136	135	128	118	116	112	103	99	97	2	0	0	0	0
Aripiprazole 10 mg	150	149	140	136	133	126	124	119	114	11	4	2	1	0

Event	0	5	10	15	20	25	30	35	40	45	50	55	60	65
Placebo	0	6	16	20	20	22	23	25	25	26	26	26	26	26
Cariprazine 1.5-3 mg	0	1	7	11	12	12	12	12	12	13	13	13	13	13
Cariprazine 4.5-6 mg	0	6	9	17	18	20	22	23	23	24	25	26	26	26
Cariprazine 9-12 mg	0	5	14	22	23	26	31	33	33	35	35	35	35	35
Risperidone 4.0 mg	0	0	1	3	4	4	4	4	4	4	4	4	4	4
Aripiprazole 10 mg	0	0	1	1	1	1	1	1	1	1	1	1	1	1

Unfortunately, the open label K-M analysis also corroborates the likelihood of the high dose range to be associated with shifts to stage II hypertension, but suggests that this type of important BP elevation can happen almost as frequently with the low dose range of cariprazine, as seen in the figure below:

Figure 30.A.1.2.2 Kaplan-Meier Plot for Time to First Blood Pressure Event during Open-label Treatment Period  
Blood Pressure Event is Defined as Supine Systolic BP  $\geq$  160 mmHg or Diastolic BP  $\geq$  100 mmHg  
Group 1B+2B (Long-term, Open-label Schizophrenia and Bipolar Mania Studies)  
Safety Population



At Risk	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360
Cariprazine 1.5-3 mg	281	211	173	155	145	133	89	84	83	81	79	75	72	70	70	68	68	8	0
Cariprazine 4.5-6 mg	473	416	341	308	291	281	221	209	197	191	184	183	173	164	159	154	152	19	0
Cariprazine 9-12 mg	318	277	209	178	158	138	76	71	64	60	55	52	49	48	48	45	43	8	0
Event	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360
Cariprazine 1.5-3 mg	0	8	9	9	10	12	12	12	12	12	14	14	15	15	15	15	15	15	15
Cariprazine 4.5-6 mg	0	6	8	11	11	13	13	14	14	14	14	14	14	14	14	14	14	15	15
Cariprazine 9-12 mg	0	10	14	15	16	18	19	19	19	19	20	20	20	20	20	20	20	20	20

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For the low, intermediate, and high dose range groupings, the sponsor calculated the following relationships between dose range and BP events per patient years {events/pt-years (rate)} from the K-M event occurrences and follow-up periods (FDA Table 1):

FDA Table 1: K-M estimated BP event rates by dose range

	Placebo	1.5 - 3.0 mg	4.5 - 6.0 mg	9.0 - 12 mg
<b>DB <math>\geq</math> 140/90</b>	<b>204/64.5 (3.16)</b>	<b>102/42.0 (2.43)</b>	<b>196/55.0 (3.56)</b>	<b>176/31.4 (5.61)</b>
OL $\geq$ 140/90		82/78.6 (1.04)	149/161.3 (0.92)	117/70.8 (1.65)
<b>DB <math>\geq</math> 160/100</b>	<b>26/72.1 (0.36)</b>	<b>13/46.4 (0.28)</b>	<b>26/63.4 (0.41)</b>	<b>35/37.2 (0.94)</b>
OL $\geq$ 160/100		15/99.5 (0.15)	15/212.4 (0.07)	20/95.0 (0.21)

*Reviewer's note: dose responsive elevations of event rates for time to first occurrence of stage I and stage II blood pressure events is noted.*

Shift tables were created based on JNC-7 blood pressure categories (normal, pre-hypertension, stage I hypertension, and stage II hypertension). In FDA table 2 below, upward shifts by two JNC-7 categories (in red), and upward shifts by a single JNC-7 category (in black) were generated for the integrated controlled data, by dose range, to assess for a dose response in the occurrence of these shifts:

FDA Table 2: Upward shift of JNC-7 blood pressure groups by dose range in **controlled trials** (baseline to highest JNC-7 category recorded, n(%))

JNC-7 Category Shift	Placebo	1.5 - 3.0 mg	4.5 - 6.0 mg	9.0 - 12 mg
<b>Controlled trials</b>				
<b>Normal to Stages I or II</b>	<b>20 (5.8)</b>	<b>10 (5.1)</b>	<b>29 (10.3)</b>	<b>24 (13.9)</b>
<b>Pre-HT to Stage II</b>	<b>12 (2.1)</b>	<b>5 (1.7)</b>	<b>7 (1.6)</b>	<b>14 (4.2)</b>
Normal to pre-HT	195 (56.7)	117 (59.7)	186 (66.2)	106 (61.3)
Pre-HT to Stage I	95 (16.7)	45 (14.9)	105 (24.0)	94 (27.9)
Stage I to Stage II	10 (10.4)	6 (11.8)	11 (17.7)	13 (27.1)

*Reviewer's note - dose responsive upward shifts by two JNC-7 categories is noted involving the intermediate and high dose ranges. Single category shifts to either stage I or stage II hypertension were likewise dose responsive and occurred in more than a quarter of the patients treated with the high dose range.*

*The general trends in the controlled data are seen in the open label analysis of the occurrence of these shifts, as seen in FDA table 3 below. The relatively high incidence of the two category shifts for the low dose range below as compared to the placebo rates for these two-category shifts in the placebo arms of the controlled studies (FDA table 2 above) is concerning in that it suggests that the low dose range is capable of inducing important blood pressure shifts upward in vulnerable patients.*

FDA Table 3: Upward shift of JNC-7 blood pressure groups by dose range in open label extensions (baseline to highest JNC-7 category recorded, n(%))

JNC-7 Category Shift	1.5 - 3.0 mg	4.5 - 6.0 mg	9.0 - 12 mg
<b>Open Label Extensions</b>			
<b>Normal to Stages I or II</b>	<b>20 (17.4)</b>	<b>24 (15.2)</b>	<b>23 (23.0)</b>
<b>Pre-HT to Stage II</b>	<b>5 (3.6)</b>	<b>6 (2.1)</b>	<b>15 (7.5)</b>
Normal to pre-HT	65 (56.5)	113 (71.5)	65 (65.0)
Pre-HT to Stage I	34 (24.3)	91 (32.4)	67 (33.7)
Stage I to Stage II	7 (31.8)	7 (20.6)	2 (13.3)

## Metabolic Effects of Cariprazine

The sponsor summarizes metabolic effects of cariprazine in ISS table 8.1-2, reproduced below for convenience:

**Table 8.1–2. Overview of Changes in Metabolic Parameters During Treatment in the Schizophrenia and Bipolar Mania Programs—Safety Population**

	<i>Schizophrenia</i>			<i>Bipolar Mania</i>		
	<i>Group 1A</i>		<i>Group 1B Long-term</i>	<i>Group 2A</i>		<i>Group 2B Long-term</i>
	<b>Placebo (N = 584)</b>	<b>Cariprazine (N = 1317)</b>	<b>Cariprazine (N = 622)</b>	<b>Placebo (N = 442)</b>	<b>Cariprazine (N = 623)</b>	<b>Cariprazine (N = 402)</b>
<b>Change from baseline at endpoint, mean ± SD</b>						
<b>Total cholesterol, mg/dL: BL</b>	181.8 ± 39.2	179.7 ± 40.5	179.7 ± 41.1	182.5 ± 45.0	179.7 ± 43.4	191.1 ± 40.7
Change at endpoint	2.0 ± 32.6	–2.5 ± 31.7	–5.6 ± 29.6	3.8 ± 30.8	0.7 ± 34.1	–5.0 ± 32.8
<b>LDL cholesterol,<sup>a</sup> mg/dL: BL</b>	108.4 ± 34.3	106.2 ± 34.7	104.7 ± 34.3	107.3 ± 37.4	104.2 ± 36.0	108.8 ± 34.5
Change at endpoint	2.7 ± 28.3	–2.2 ± 26.3	–4.1 ± 25.0	5.0 ± 26.8	0.5 ± 28.6	–2.8 ± 27.4
<b>HDL cholesterol, mg/dL: BL</b>	49.8 ± 14.2	50.1 ± 15.3	49.5 ± 14.3	48.8 ± 15.1	51.3 ± 15.3	56.5 ± 17.6
Change at endpoint	–1.3 ± 10.3	–0.6 ± 10.7	–0.9 ± 11.4	–0.9 ± 10.7	–1.1 ± 10.8	–2.1 ± 10.7
<b>Triglycerides,<sup>a</sup> mg/dL: BL</b>	127.3 ± 69.0	124.6 ± 80.0	128.0 ± 81.5	133.2 ± 81.6	122.7 ± 73.9	125.4 ± 76.6
Change at endpoint	2.6 ± 63.7	–1.1 ± 71.2	2.6 ± 84.9	–4.4 ± 72.2	3.1 ± 65.7	4.8 ± 73.0
<b>Fasting glucose,<sup>a</sup> mg/dL: BL</b>	92.1 ± 15.4	91.2 ± 13.8	92.5 ± 15.4	91.3 ± 15.9	90.8 ± 14.1	92.7 ± 11.9
Change at endpoint	4.9 ± 26.8	4.9 ± 19.6	4.8 ± 21.6	1.7 ± 20.5	7.0 ± 21.5	5.5 ± 17.1
<b>Percentage of patients who met criterion for postbaseline shifts (from normal baseline values)<sup>b</sup></b>						
Total cholesterol ≥ 240 mg/dL	4.7%	3.8%	4.4%	5.5%	4.8%	6.0%
LDL cholesterol ≥ 160 mg/dL <sup>a</sup>	1.8%	1.4%	1.4%	4.4%	1.5%	0
HDL cholesterol < 40 mg/dL	23.8%	17.5%	33.7%	19.7%	17.9%	14.0%
Triglycerides ≥ 200 mg/dL <sup>a</sup>	8.3%	7.6%	18.6%	11.9%	12.0%	16.3%
Fasting glucose ≥ 126 mg/dL <sup>a</sup>	6.7%	7.7%	14.3%	3.7%	6.9%	12.7%

a Fasting (data are summarized for samples obtained in the fasting state only).

b Shifts from normal at baseline to high during the treatment period (normal to low for HDL cholesterol).

*Reviewer's note: Changes in cholesterol parameters are unimpressive during the short controlled trials, but a trend to higher fasting blood sugars is noted during the controlled studies.*

*In longer- term follow-up studies, blood sugar and triglycerides increased; as did HgA1c (seven percent (7%) of patients in the long-term schizophrenia studies had shifts in glycosylated hemoglobin above the clinically significant level of 6.1%). The triglyceride changes may have been related/secondary to the blood sugar elevations. From the controlled schizophrenia studies, greater elevation of serum insulin levels in the cariprazine-treated patients as compared to the placebo-treated patients (13.5 pmol/L with placebo and 41.2 pmol/L with cariprazine) suggests drug-induced insulin resistance.*

There was no clear association of overall hyperlipidemia-related or hyperglycemia-related TEAEs with drug therapy, and none of the adverse events reported in either of these two adverse event categories were SAEs. TEAEs of hyperlipidemia and hyperglycemia are shown in the two ISS tables below:

**Table 8.3.1.2–1. Number (%) of Patients With Hyperlipidemia TEAEs During the Double-blind Treatment Period in Group 1A (Controlled Schizophrenia Studies)—Safety Population**

<i>Preferred Term</i>	<i>Placebo (N = 584) n (%)</i>	<i>Cariprazine</i>			<i>Risperidone 4 mg (N = 140) n (%)</i>	<i>Aripiprazole 10 mg (N = 152) n (%)</i>
		<i>1.5-6 mg (N = 1032) n (%)</i>	<i>6-12 mg (N = 285) n (%)</i>	<i>Overall (N = 1317) n (%)</i>		
<b>Patients with ≥ 1 hyperlipidemia TEAE</b>	<b>3 (0.5)</b>	<b>7 (0.7)</b>	<b>4 (1.4)</b>	<b>11 (0.8)</b>	<b>1 (0.7)</b>	<b>1 (0.7)</b>
Blood triglycerides increased	0	5 (0.5)	2 (0.7)	7 (0.5)	0	0
Blood cholesterol increased	1 (0.2)	1 (0.1)	1 (0.4)	2 (0.2)	0	0
Dyslipidaemia	0	1 (0.1)	0	1 (0.1)	0	0
Hypercholesterolaemia	0	1 (0.1)	0	1 (0.1)	0	0
Hypertriglyceridaemia	2 (0.3)	0	1 (0.4)	1 (0.1)	0	0
Hyperlipidaemia	0	0	0	0	1 (0.7)	1 (0.7)

**Table 8.3.1.2–2. Number (%) of Patients With Hyperglycemia and Diabetes Mellitus TEAEs During the Double-blind Treatment Period in Group 1A (Controlled Schizophrenia Studies)—Safety Population**

<i>Preferred Term</i>	<i>Placebo</i> ( <i>N</i> = 584) <i>n</i> (%)	<i>Cariprazine</i>			<i>Risperidone</i> 4 mg ( <i>N</i> = 140) <i>n</i> (%)	<i>Aripiprazole</i> 10 mg ( <i>N</i> = 152) <i>n</i> (%)
		1.5-6 mg ( <i>N</i> = 1032) <i>n</i> (%)	6-12 mg ( <i>N</i> = 285) <i>n</i> (%)	<i>Overall</i> ( <i>N</i> = 1317) <i>n</i> (%)		
<b>Patients with ≥ 1 TEAE</b>	<b>6 (1.0)</b>	<b>3 (0.3)</b>	<b>1 (0.4)</b>	<b>4 (0.3)</b>	<b>1 (0.7)</b>	<b>0</b>
Blood glucose increased	5 (0.9)	2 (0.2)	1 (0.4)	3 (0.2)	0	0
Glycosuria	0	0	1 (0.4)	1 (0.1)	0	0
Hyperglycaemia	0	1 (0.1)	0	1 (0.1)	0	0
Diabetes mellitus	1 (0.2)	0	0	0	0	0
Urine ketone body present	0	0	0	0	1 (0.7)	0

## Answers to Questions

1. Do the blood pressure changes appear to be dose-related?

Yes. Overall, the intermediate and high dose ranges in the controlled trials are associated with notably higher shift rates to higher JNC-7 blood pressure categories. Some of these shifts are profound (two JNC-7 category shifts) (FDA table 2). K-M estimated BP event rates by dose range corroborate the dose-responsive nature of first occurrence of BP  $\geq$  140/90 and BP  $\geq$  160/100 events. (FDA table 1). While the lower dose range generally appears to mimic placebo event rates in the controlled trials, it is noted that the time to first occurrence of BP  $\geq$  160/100 events is similar between the low dose range and the high dose range (sponsor figure 30.A.1.1.2 above), and the low dose range group demonstrates the highest frequency of stage I to stage II blood pressure shifting in the open label extensions. This suggests that the low doses of this drug are capable of elevating blood pressure in vulnerable patients with pre-existing hypertension.

We think that the blood pressure findings are at least as bad as what is seen in the above tables, as it appears that BP ascertainment had no relationship to  $C_{max}/T_{max}$  of the drug. Blood pressures at peak exposures may have been higher.

We note that these conclusions are at variance with the sponsor's assessment of minimal/unimportant blood pressure effects of this drug, which were arrived at using a cutoff of BP  $\geq$  180/105 mmHg (either criterion).

2. Would you recommend specific risk mitigation strategies regarding hypertension and other cardiovascular risks?

Yes. This drug, if approved, should carry a warning for blood pressure elevation with a recommendation for weekly or biweekly blood pressure evaluations for the first

month of therapy, monthly thereafter for three months, and then periodically while on therapy.

It is concerning to consider that these patients tend to have more limited access to medical care than patients not suffering from schizophrenia and/or mania, and so their follow-up for their blood pressures may be difficult.

3. Would you recommend including warnings and precautions in labeling for these risks?

Yes. See answer to question 2.

4. Would you recommend obtaining additional data or analyses from the sponsor during the review cycle?

Yes. At DCRP's request, the Review Division has requested that the sponsor provide data regarding the number (%) of patients who started on new antihypertensive therapy during the controlled trials (beta blockers, calcium channel blockers, diuretics, ACE inhibitors, ARBs, and vasodilators), what their BP was before starting the new antihypertensive medication, and what their follow-up blood pressures were. The issue here is whether these cariprazine-induced blood pressure elevations, some of which are impressive, are reasonably responsive to antihypertensive therapy (understanding that this additional medication adds further complexity to the medical management of patients who may have compliance challenges for a variety of reasons).

This is not a theoretical concern. DCRP notes that in table 6.2.2-1 of the ISS showing con-meds used by  $\geq 10\%$  of the controlled and extension populations, there is a remarkable increase in the use of beta blockers (from 4.3% of the placebo population to 10.8% of the controlled treatment population to 23.6% of the open-label extension population), which may be indicative of an attempt to manage drug-induced blood pressure elevations during these studies.

The OCP reviewer is in the process of generating mountain plot analyses (modified cumulative function plots) of change from baseline of SBP and DBP, by dose, for all doses of this drug (not the combined dose ranges that were generated by the sponsor for this consult), so that we can get a better picture of what is happening to the entire population of patients on the various doses.

5. Do you recommend any specific postmarketing studies or other regulatory actions regarding blood pressure increases or other cardiovascular risks?

The approval decision for this drug will take into consideration the risk of BP elevation, as well as other risks that the Review Division is evaluating. We think the overall CV risk is modest, and hopefully the sponsor can provide the data described in our answer to Question 4 with respect to the medical manageability of treatment

emergent hypertension. If a registry were to be required as a condition of this drug's approval for other reasons, it would be reasonable for the sponsor to include blood pressure assessments, need for medical therapy, and response to therapy data as part of that registry.

The elevations in blood sugar, HgA1C, and serum triglycerides are noted in the uncontrolled follow-up data, but these were not accompanied by an important imbalance in hyperlipidemia-related or hyperglycemia-related TEAEs. If this drug is approved, labeling should include a recommendation for monitoring of these parameters periodically, in a way that is appropriate to patients' baseline metabolic states (i.e., known diabetics will need more intensive follow-up of blood glucose and triglycerides than will be required for non-diabetic patients).

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PRESTON M DUNNMON  
09/30/2013

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09/30/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
CONSULTATION**

**Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**DATE:** Sept 10, 2013

**FROM:** Smita B. Abraham, MD, Medical Officer  
Division of Metabolism and Endocrinology Products (DMEP)

**THROUGH:** Dragos Roman, MD, Team Leader, DMEP  
Jean-Marc Guettier, MD, Acting Director, DMEP

**TO:** Kim Updegraff, RPh, MS, RAC, Regulatory Project Manager, Division of  
Psychiatry Products (DPP)  
Francis Becker MD, Primary reviewer, DPP  
Elzbieta Chalecka-Franaszek, PhD, Nonclinical reviewer, DPP

**SUBJECT: Cariprazine and adrenal toxicity in humans**

**I. Background and basis for consult**

On 11/19/2012, Forest Pharmaceutical Research Institute submitted an NDA (204370) to the Division of Psychiatry Products (DPP) for cariprazine (RGH-188). Cariprazine is a new molecular entity (NME) and is intended to be used orally as a daily treatment at doses of [REDACTED] <sup>(b) (4)</sup>. Cariprazine acts via the central dopamine D<sub>3</sub>, D<sub>2</sub> and 5-HT<sub>1A</sub> receptors for which it has partial agonist activity. Of note, its major active metabolite has a half-life of 2-3 weeks.

FDA's review of cariprazine's toxicology/pharmacology program identified evidence of adrenal gland toxicity in more than one species (rats, dogs and mice). Adrenal function, however, was not investigated in cariprazine's Phase III human clinical trials. Given the safety signal of adrenocortical toxicity noted in animals, DPP is requesting DMEP to comment on the potential relevance of this finding in humans, to provide guidance on how adrenal dysfunction should be analyzed in the existing cariprazine Phase III studies, and whether additional hypothalamic-pituitary-axis (HPA) evaluation should be done in the cariprazine clinical program, particularly if the drug were to be approved.

**II. Materials reviewed for consult**

1. DPP's consult request and an abbreviated version of the non-clinical review provided by Dr. Chalecka-Franaszek.
2. Clinical review by Dr. Francis Becker in DARRTS dated July 22, 2013.
3. Applicant's Response to Late Cycle Meeting Background Package: Potential for Adrenal Toxicity.

4. Several direct communications with clinical and non-clinical reviewers assigned to this NDA.
5. Literature: See bibliography at end of consult.

### III. DMEP responses to DPP's questions

*DPP Question: "Please evaluate for and comment on the potential of cariprazine to cause adrenal toxicity in humans."*

Review of the information forwarded by the DPP reviewers indicates that the applicant did not evaluate adrenal function in human studies of cariprazine. The only available evidence to date that cariprazine adversely affects the adrenal gland comes from animal studies, which indicate that the adrenal gland is a target organ of cariprazine toxicity. Below is summary of such observations derived from the non-clinical review provided by Dr. Chalecka-Franaszek.

#### Findings in rats:

- Adrenal cortex: hypertrophy, with necrotic cells, and hemorrhages (observed in a 14 day study in female rats at a dose of 50 mg/kg/day); multifocal cystic degeneration, diffuse dilated sinusoids, and cell vacuolation (observed in a 28 day study at a dose of 50 mg/kg/day).
- The NOEL for animal death and changes in adrenal cortex was 12.5 mg/kg/day, which is approximately 14 times the MRHD [REDACTED] <sup>(b) (4)</sup> based on mg/m<sup>2</sup> and approximately 10 times human exposure at this MRHD.
- There is no information available on the reversibility of adrenocortical changes in the rats.

#### Findings in dogs:

- Phospholipidosis (PLD) of zona fasciculata cells was observed by transmission electron microscopy in a 13 week study in dogs. The NOEL for PLD could not be determined in male dogs, while for female dogs the NOEL was 1 mg/kg/day, which is 3.6 times the MRHD [REDACTED] <sup>(b) (4)</sup> based on mg/m<sup>2</sup> and 1.3-1.7 times human exposure expected at the MRHD [REDACTED] <sup>(b) (4)</sup> based on the combined AUC for cariprazine, DCAR, and DDCAR (active pharmacologic metabolites of cariprazine).
- The adrenal glands were noted to be enlarged and increased in absolute weight at the 4 and 6 mg/kg/day in both males and females in a 1 year study. PLD without observation of inflammation or hemorrhage was noted at all dose levels except 1 mg/kg/day in male dogs and did not resolve at the end of a 2-month recovery period.
- Zona fasciculata and glomerulosa cell hypertrophy/hyperplasia and vesiculation/vacuolization were observed at 4 and 6 mg/kg/day and were absent at

the end of the recovery period. It is not clear if they are related to the presence of PLD or not. The NOEL for PLD-like changes within the adrenal could not be determined and is less than 1 mg/kg/day indicating no margin of safety for human dosing. The NOEL for hypertrophy/hyperplasia and vesiculation/vacuolization of the adrenal cortex is 2 mg/kg, which is 7 times the MRHD [REDACTED] (b) (4) based on mg/m<sup>2</sup> and 2.8-3.8 times human exposure expected at the MRHD [REDACTED] (b) (4) on the combined AUC for cariprazine, DCAR and DDCAR.

#### Findings in mice:

- Enlarged adrenal glands with evidence of hypertrophy (6 week study).
- Lipofuscin pigment deposition (lipofuscinosis), which can be part of PLD, was noted at the corticomedullary interface in a 28-week carcinogenicity study.

Given the nonclinical information summarized above, we agree with DPP that it is reasonable to be concerned about potential adrenal toxicity in association with cariprazine use in humans. Because there was no evidence of adrenomedullary toxicity, this discussion will address only adrenocortical function.

It has been noted that adrenocortical activity was not formally evaluated in the Phase III program. Specifically, the applicant did not measure biomarkers of adrenocortical function such as cortisol levels or cortisol response to ACTH stimulation. Signs and symptoms suggestive of adrenal insufficiency, such as nausea, fatigue, circulatory collapse, etc., were not pre-specified or prospectively assessed. As such, any conclusions regarding adrenal failure are based on standard analyses of adverse events conducted by FDA reviewers and on an additional analysis that the sponsor conducted at the request of the FDA, entitled: Response to FDA Late Cycle Meeting Background Package: Potential for Adrenal Toxicity. None of these analyses identified a clear adrenal insufficiency safety signal in the human cariprazine Phase III program.

Although a clear safety signal was not identified in the standard or additional analyses reviewed, one must acknowledge the limitation of these analyses, in particular the absence of biochemical testing. Furthermore, one must also consider that approximately 90% of the adrenal cortex has to be destroyed before a complete clinical picture of primary adrenal insufficiency becomes apparent. An early or partial picture of adrenal hypofunction is hard to diagnose without biochemical testing. The signs and symptoms of mild adrenocortical hypofunction include nausea, vomiting, hyperkalemia, eosinophilia and hypotension, all of which, by themselves, are non-specific and relatively common findings. Not surprisingly, all of them were identified in the aforementioned report, but were not attributed to adrenal hypofunction.

Part of the challenge in assessing the significance of the cariprazine-associated animal findings to humans is that the changes observed were histopathological only. The significance of changes such vacuolization/vesiculization, hypertrophy and hyperplasia is not clear as they do not have a clear clinical corollary. In addition to the uncertainty of whether these histopathological changes will occur in humans, and what their significance

could be, it is not clear how to evaluate such potential changes other than assessing adrenal cortical function with accepted biochemical testing (cortisol in particular).

There is uncertainty around the findings of phospholipidosis, as it is not known if the entity is progressive or reversible. Such uncertainty has implications on whether the absence of a clear signal of adrenal insufficiency in the clinical trials should be interpreted as reassuring or as a false sense of security. If phospholipidosis is a slowly progressive process, evidence of adrenal insufficiency may not be seen for a long time, after prolonged treatment. If the process causes irreversible damage to the adrenal cortex, the patient is subject to lifelong glucocorticoid and mineralocorticoid replacement and increased mortality risk. Therefore, based on the limited data provided, we cannot provide a definite answer to the question of what is the significance of the preclinical findings of phospholipidosis to humans. DPP will have to weigh this residual uncertainty in the overall risk-to-benefit analysis and approvability decision.

*Question: What specific recommendations, if any, do you have for analysis of the existing clinical database for cases of potential adrenal insufficiency/toxicity (e.g. adverse events, laboratory parameters, blood pressure changes, etc.)?*

DMEP does not have any additional recommendations at this time. DPP has already requested and reviewed an analysis of adverse events specifically aimed at identifying evidence of adrenal hypofunction. We reviewed the data provided by the sponsor as well. As discussed in the response to Question 1, and keeping in mind the limitations of this analysis, these data did not reveal a convincing signal for adrenal hypofunction.

*Question: DPP is considering requesting a postmarketing commitment to conduct endocrine assessments such as cortisol or HPA stimulation testing or other relevant assessments:*

*a) Is this a reasonable approach?*

We agree that given the lack of evaluation of adrenal function in the cariprazine Phase III program, a postmarketing evaluation of the potential preclinical signal is reasonable, should the drug be approved. If DPP makes a final determination in favor of approval, we recommend that the division consider labeling the possibility of adrenal hypofunction so that practitioners are made aware of this potential risk. In addition, consideration should be given to postmarketing enhanced pharmacovigilance of adrenal insufficiency.

*b) In a post-marketing study, what type of assessments for adrenal insufficiency and toxicity would you recommend?*

If the drug is intended for long-term use, we recommend baseline and periodic on-treatment adrenal function evaluations (see paragraph below for specifics). The baseline evaluation is aimed at demonstrating adrenal sufficiency prior to initiating cariprazine; subsequent evaluations are aimed at assessing preservation of adrenal function. In the absence of specific information related to the timing adrenal dysfunction in humans,

selecting a duration of monitoring is largely arbitrary and should take into consideration the anticipated duration of treatment with cariprazine.

Patients starting cariprazine should have vital signs measured, specifically including blood pressure measurement. In an ideal situation, the test of choice for baseline biochemical evaluation of adrenocortical function consists of a 250 mcg ACTH stimulation test along with a morning, fasting ACTH level, electrolyte panel and plasma renin activity in all patients. It may not be feasible to require performance of dynamic testing in all patients starting the drug in a large trial. Therefore, checking a morning fasting cortisol level instead of conducting an ACTH stimulation test is another option. In this scenario the result of the morning, fasting, cortisol level determines the need for additional testing. All participants with a morning, fasting, cortisol level of  $\leq 3$  mcg/dl should undergo a 250 mcg ACTH stimulation test to confirm a diagnosis of adrenal insufficiency. Participants with a morning, fasting, cortisol level of  $\geq 18$  mcg/dl are adrenally sufficient and do not need to undergo a 250 mcg ACTH stimulation test. Participants with morning, fasting, cortisol levels  $>3$  but  $\leq 18$  mcg/dl are considered to have 'indeterminate' adrenal function status (Grinspoon). In these patients the need for testing should be based on the pre-test probability of adrenal insufficiency (e.g., baseline symptoms consistent with adrenal insufficiency).

After starting cariprazine, we recommend periodic evaluation (e.g. every 6 months) of vital signs including blood pressure and blood draw for fasting ACTH, cortisol, electrolyte panel and plasma renin activity. Concerning laboratory patterns over time would be increasing ACTH or plasma renin activity levels, decreasing cortisol levels, decreasing sodium levels and increasing potassium levels. A cortisol level  $\leq 3$  mcg/dl at any point in time warrants a repeat 250 mcg ACTH stimulation test.

In addition, we recommend educating the patient and caregivers about the signs/symptoms of primary adrenal insufficiency, which include but are not limited to new onset fatigue, nausea, vomiting, hyperpigmentation, lightheadedness, postural dizziness, unexplained fever, salt craving (e.g., asking specifically about foods like potato chips, olives, pickle juice), memory loss or cognitive decline.

*c) In a post-marketing study, what type of specific study design would you recommend (e.g. targeted adrenal study)?*

A controlled study is highly desirable. For instance one could consider a trial that compares patients on cariprazine to a group of patients with a similar diagnosis who are treated with non-cariprazine anti-psychotic or anti-depression medications. There are, however, challenges to designing such a study.

Given the rarity of adrenal insufficiency, a single cohort, long-term (e.g. 3-5 years) study could be designed. Each case of adrenal insufficiency identified would be evaluated by endocrinologists with expertise in adrenal diseases in order to determine whether the adrenal failure is primary and, if so, the etiology.

*d) Do you recommend studying the intended population (patients with schizophrenia or bipolar disorder) or healthy controls?*

Assuming that the nonclinical signal of adrenal toxicity is relevant to humans and given that adrenal impairment can develop later in the course of treatment, we do not see how studying the drug short-term in healthy volunteers would be informative. However, a short-term study with drug at steady state in healthy volunteers may provide useful information if you believed cariprazine has an immediate pharmacodynamic effect on adrenal function. At this point there are data to support or refute this. Such a study would not replace the need for a long-term study for the reason mentioned above (i.e., delayed latency). The long-term study should be conducted in patients and reflect real-world use of the product.

*Would you recommend conducting endocrine assessments in the ongoing depression program?*

Although there is uncertainty concerning the relevance of the nonclinical data to humans, the safety signal is of reasonable concern and therefore, we recommend conducting endocrine assessments in the ongoing depression program. Specific recommendations should be tailored to the specific phase of development (See our responses above with regards to type of assessments).

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- 3) Grinspoon SK, Biller, BMK. Clinical Review 62: Laboratory Assessment of Adrenal Insufficiency. *J Clin Endocrinol Metab.* 1994;79:923

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/s/  
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SMITA B ABRAHAM  
09/10/2013

JEAN-MARC P GUETTIER  
09/10/2013

I concur with Drs. Roman and Abraham's recommendations.

Medical Officer's Review of NDA 204-370  
Ophthalmology Consultant

Original NDA Submission Date: 11/19/12  
Safety Update with Ophthalmic Data Submission Date: 3/20/13  
Review completed: 8/16/13

Name: Cariprazine (RGH-188)

Applicant: Forest Research Institute, Inc.

Requested: We would appreciate your assessment of the ocular safety issues for NDA 204370. The indications are Cariprazine for the treatment of Schizophrenia and Bipolar Mania. During the review of the IND 71958, there have been concerns about nonclinical ocular toxicity: cataracts in dogs (bilateral subcapsular); retinal degeneration and melanin binding in rat retina. Your division has previously provided consultation regarding these findings and has recommended clinical ophthalmologic exams in all patients and OCT in a subset of patients exposed long-term to cariprazine.

There are potential clinical concerns in the NDA. There are a number of cases of new cataract or worsening cataract, opacity, opalescence, drusen, retinal/macular degeneration, separation of retinal layers, retinal/macular thickening and thinning, visual impairment, reduced visual acuity, abnormal color vision, and retinal/macular pigmentation. Some of studies were relatively short-term controlled trials. Much of the data derives from a long-term (12 months) open label study (Study RGH-MD-11). Please note that at the baseline visit before entering the long-term (12-month) open-label study, patients had already been exposed to cariprazine in controlled trials.

We requested narratives for cases of reported ocular adverse events. Below is a preliminary list of narratives of potential clinical concern. We will also request narratives for cases that did not have ocular AEs but that contain specific ocular-related terms of interest.

Subject ID for cases of potential clinical concern:

- 0010017
- 0250318
- 0350301
- 0480308
- 0010413
- 0020412
- 0040418
- 0040432
- 0410535
- 0450501
- 00480510
- 5040509
- 0040442
- 1080402

- 033333
- 0023604
- 0023626
- 0043654
- 0043678

The submission is electronic and can be found via:

- Global Review Submit: \\CDSESUB5\EVSPROD\NDA204370\204370.enx
- EDR Location: <http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8340308>
- Eroom link to materials: [http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0\\_b6d64](http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_b6d64)

The ISS, Volume one contains the narratives and the ocular summary. The sponsor has provided OCTs and other data. Some of the relevant nonclinical data submitted to the NDA is from ERG

Study RGH-TX-49: "3-month Electroretinography Study of Cariprazine (RGH-188) Following Daily Oral Capsule Administration in Beagle Dogs with a 2-Month Recovery" - Sponsor study No. RGH-TX-49 (ERG study), submitted to the NDA 204370.

We appreciate your assessment of the ocular findings. We would like to invite you to the filing on January 10, 2013.

Specific questions:

- 1) Has the sponsor provided adequate ocular data for your review?
- 2) Would you suggest requesting any additional information?
- 3) What is your assessment of the risk of cataract?
- 4) What is your assessment of the risk of retinal toxicity?
- 5) We recognize that it is early in the review cycle, but do you think it would be necessary or useful to have an AC meeting to discuss the ocular findings?

If you need additional information, please contact the clinical reviewer, Dr. Frank Becker at 301-796-2288, [francis.becker@fda.hhs.gov](mailto:francis.becker@fda.hhs.gov); or the clinical team leader, Dr. Robert Levin at 301-796-1110, [robert.levin@fda.hhs.gov](mailto:robert.levin@fda.hhs.gov). Thank you for all of your help with the NDA and IND.

## **Nonclinical Ocular Findings**

### ***Cataract***

Cataract formation was noted in 13-week and 1-year toxicity studies in dogs. The no-observed-effect levels (NOELs) for cataract formation in dogs (3 mg/kg/day and 2 mg/kg/day, respectively) provide approximately 6- and 4-fold exposure margins (cariprazine AUC) at the maximum recommended human dose (MRHD) (b) (4).

**Reviewer's Comments:** *The finding of cataract development in dogs appears to be reproducible. The clinical significance in humans is unknown without at least a two year study in humans.*

### ***Melanin Binding***

<sup>14</sup>[C]-cariprazine and/or its metabolites bind to the melanin-rich choroid layer of the eyes of pigmented rats with an elimination half-life of approximately 28 days.

### ***Retinal Degeneration/Atrophy in Rats***

Retinal degeneration/atrophy was noted in albino rats in the 2-year rat carcinogenicity study. While this finding may occur in aging albino rats, and was present in all groups including controls, it was more prominent in cariprazine-treated rats. Retinal degeneration/atrophy was not observed in any other studies in rats, or in long-term studies with pigmented mice and dogs providing cariprazine exposures (AUC) up to 29 and 12 times the MRHD, respectively. The relevance of this finding to human risk is unknown.

### **Study RGH-TX-49: "3-month Electroretinography Study of Cariprazine (RGH-188) Following Daily Oral Capsule Administration in Beagle Dogs with a 2-Month Recovery"**

Male and female purebred beagles were assigned to four groups (0, 1, 3 and 8 mg/kg/day), and doses were administered orally via gelatin capsule carrier once daily. There were 6 male and 6 female animals per group. Animals in Groups 3 and 4 underwent a 2- or 4-week dose-adaptation period, respectively, prior to Day 1 of the dosing phase. Assessment of toxicity was based on mortality, clinical signs, food consumption, body weight, ophthalmic examinations, and electroretinography (ERG) evaluation. Blood samples were collected for toxicokinetic evaluations for cariprazine and two metabolites (desmethyl cariprazine and didesmethyl cariprazine).

Exposure to cariprazine and its metabolites, desmethyl cariprazine and didesmethyl cariprazine, increased with the increase in dose level from 1 to 8 mg/kg/day. The increases in mean  $C_{max}$  and  $AUC_{0-24}$  were roughly dose proportional for cariprazine and desmethyl cariprazine while the increases for didesmethyl cariprazine were inconsistently dose proportional. For all three analytes, males generally had higher  $C_{max}$  and  $AUC_{0-24}$  values than females, but sex differences were less than 2-fold. Little to no accumulation of cariprazine and desmethyl cariprazine was observed after multiple dosing in dogs while potential accumulation was noted for didesmethyl cariprazine.

The most notable test article-related observations related to behavioral and neurological effects, consistent with anti-psychotic exaggerated pharmacology. Convulsions were sporadically reported (however it is likely that the convulsions reported by the technical staff in this study were actually extrapyramidal signs due to the pharmacology of the test article and not true convulsions), and more frequently, tremors. Observations of lost teeth, swelling, broken skin, red skin, and scabs at various regions of the anatomy were likely the result of injury during aggressive interactions. Aggressive behavior (snapping/biting, growling/snarling, hyperactivity, and lunging) was noted in the test article-treated groups. Clear ocular discharge was observed in a few animals given 3 or 8 mg/kg/day. Some of the behavioral effects persisted into the recovery phase. Hyperactivity and snapping/biting behaviors were observed in all test article-treated groups; however, snapping/biting was not observed in females.

### Results of Statistical Analysis of Electroretinography Data (Model 1) - Separated Sexes

Sex	Parameter	Treatment p-value	Time p-value	Treatment x Time p-value	Covariate p-value
<b>Oscillatory Potentials</b>					
M	Amplitude <sup>a</sup>	0.0009**	<0.0001**	0.0005**	0.2519
F	Amplitude	0.9297	0.0005**	0.1233	0.0004**
<b>Photopic 30 Hz</b>					
M	Amplitude <sup>a</sup>	0.0043**	<0.0001**	<0.0001**	0.5557
F	Amplitude	0.3113	0.0381*	0.1160	0.1682
<b>Photopic Single White</b>					
M	A Wave Amplitude <sup>a</sup>	0.0027**	<0.0001**	<0.0001**	0.1279
F	A Wave Amplitude	0.4085	0.0705	0.6240	0.1010
M	B Wave Latency (ms)	0.0409*	0.0027**	0.2130	0.5780
Across the time points: Grand means: Group 1 – 26.9; Group 2 – 25.3; Group 3: 24.4; Group 4 – 23.5 Treatment comparisons: Group 4 vs. Group 1: p – 0.0177-.*					
F	B Wave Latency (ms) <sup>a</sup>	0.0451*	0.0324*	0.0040**	0.0076**
<b>Scotopic Single Dim</b>					
M	A Wave Latency (ms)	0.2783	0.1760	0.3796	0.6753
F	A Wave Latency (ms)	0.0132*	0.1207	0.9192	0.0126*
Across the time points: Grand means: Group 1 – 18.1; Group 2 – 16.4; Group 3: 17.2; Group 4 – 18.1 Treatment comparisons: Group 2 vs. Group 1: p – 0.0113-.*					
M	B Wave Amplitude	0.9666	0.0385*	0.2180	0.7582
F	B Wave Amplitude <sup>a</sup>	0.9550	0.0090**	0.0412*	0.1218
M	B Wave Latency (ms) <sup>a</sup>	<0.0001**	<0.0001**	0.0313*	0.0265*
F	B Wave Latency (ms)	0.5290	0.0069**	0.5181	0.2624

\* – Significant at 5% level; \*\* – Significant at 1% level; - – Effect in the decreased direction.

a See Table 4 for reduced model (Model 2).

### Results of Statistical Analysis of Electroretinography Data (Model 1) - Separated Sexes

Sex	Parameter	Treatment p-value	Time p-value	Treatment x Time p-value	Covariate p-value
<b>Scotopic Single Med</b>					
M	A Wave Latency (ms)	0.0012**	0.0002**	0.0514	0.0587
Across the time points: Grand means: Group 1 – 7.7; Group 2 – 9.5; Group 3: 10.0; Group 4 – 10.0 Treatment comparisons: Group 2 vs. Group 1: p – 0.0121+*; Group 3 vs. Group 1: p – 0.0015+**; Group 4 vs. Group 1: p – 0.0015+**					
F	A Wave Latency (ms)	0.1548	<0.0001**	0.2510	0.4138
<b>Scotopic Single White</b>					
M	A Wave Amplitude <sup>a</sup>	0.0099**	<0.0001**	0.0017**	0.3435
F	A Wave Amplitude	0.9465	0.0003**	0.4772	0.0171*
M	A Wave Latency (ms)	0.0113*	0.0007**	0.2226	0.0260*
Across the time points: Grand means: Group 1 – 10.7; Group 2 – 11.9; Group 3: 10.5; Group 4 – 11.1 Treatment comparisons: Group 2 vs. Group 1: p – 0.0179+*					
F	A Wave Latency (ms)	0.7766	0.7881	0.1684	0.0061**
M	B Wave Latency (ms) <sup>a</sup>	0.0135*	0.1279	0.0092**	0.1139
F	B Wave Latency (ms)	0.3194	0.0193*	0.4479	0.0004**

\* – Significant at 5% level; \*\* – Significant at 1% level; + – Effect in the increased direction.

a See Table 4 for reduced model (Model 2).

## Scotopic Single Med

B Wave Amplitude ( $\mu\text{V}$ )										
Dosing Phase			Recovery Phase							
Number	Sex	Group	Item	Predose	Week 4	Week 8	Week 13	Week 4	Week 8	
H02920	M	3	Value	126.9	140.9	248.1	207.4	224.6	221.4	
H02921	M	3	Value	207.3	177.6	223.8	258.5	294.5	166.1	
H02922	M	3	Value	156.9	210.2	273.9	288.7	435.1	453.3	
H02923	M	3	Value	151.3	144.6	278.1	1393.6	253.9	225.1	
H02924	M	3	Value	187.1	167.2	286.1	389.3	356.3	406.0	
H02925	M	3	Value	293.0	201.8	278.0	282.3	226.8	260.6	
H02944	F	3	Value	384.2	342.3	394.6	333.7	365.4	448.6	
H02945	F	3	Value	159.1	167.8	165.5	260.2	223.5	329.4	
H02946	F	3	Value	305.0	272.7	242.2	247.4	244.6	382.7	
H02947	F	3	Value	176.0	193.1	138.5	186.3	418.8	141.6	
H02948	F	3	Value	245.7	154.8	225.4	232.0	213.8	222.9	
H02949	F	3	Value	376.0	223.3	190.7	310.0	421.7	265.1	

## Scotopic Single Med

A Wave Amplitude ( $\mu\text{V}$ )										
Dosing Phase			Recovery Phase							
Number	Sex	Group	Item	Predose	Week 4	Week 8	Week 13	Week 4	Week 8	
H02920	M	3	Value	-3.6	-4.5	-11.3	-11.7	-11.2	-8.4	
H02921	M	3	Value	-3.4	-11.7	-7.7	-16.8	-3.4	-2.8	
H02922	M	3	Value	-10.5	-2.0	-6.8	-8.6	-1.1	-1.7	
H02923	M	3	Value	-3.8	-1.9	-7.5	-632.9	-4.2	-2.7	
H02924	M	3	Value	-8.2	-8.6	-12.2	-12.8	-4.0	-7.8	
H02925	M	3	Value	-9.3	-9.8	-6.2	-12.3	-9.2	-4.8	
H02944	F	3	Value	-8.4	-5.7	-8.4	-13.7	-3.0	-8.7	
H02945	F	3	Value	-4.8	-3.7	-3.9	-21.3	-0.3	-2.3	
H02946	F	3	Value	-2.8	-13.9	-9.3	-7.1	-2.0	-7.9	
H02947	F	3	Value	-1.6	-14.1	-2.5	-12.4	-8.1	-5.4	
H02948	F	3	Value	-12.8	-6.8	-7.7	-15.5	-4.8	-9.2	
H02949	F	3	Value	-5.3	-9.4	-3.3	-6.6	-6.5	-1.1	

**Reviewer's Comments:** *The A and B Wave amplitudes for dog H02923 at Week 13 appear to be incorrect. It is not clear whether this was a typographical error or an error with the recording, but the values should have been discarded as not being physiological.*

**Slit Lamp Results**

	<b>Males</b>			
mg/kg/day	0	1	3	8
Posterior Subcapsular Cataract- Left eye	0/6	0/6	1/6	5/6
Posterior Subcapsular Cataract- Right eye	0/6	0/6	1/6	5/6

	<b>Females</b>			
mg/kg/day	0	1	3	8
Posterior Subcapsular Cataract- Left eye	0/6	0/6	0/6	3/6
Posterior Subcapsular Cataract- Right eye	0/6	0/6	0/6	3/6

**Reviewer's Conclusions of Non-clinical Results:**

*Ophthalmic examination abnormalities consisted of posterior capsular to posterior cortical cataracts in one male given 3 mg/kg/day, and in five males and three females given 8 mg/kg/day. These findings are consistent with other studies in dogs. There were no other notable examination findings.*

*Due to the large variability observed in the data, there were few statistically significant effects were observed in the ERG parameters. There were no consistent trends in the direction of a deleterious effect. The observed effects were consistent with random variation. There were two non-physiologic values which should have been discarded.*

**Ophthalmologic Monitoring in the Clinical Program**

Forest Research Institute, Inc., initially included ophthalmologic testing at 5 study centers in Study RGH-MD-03. After consultation with FDA, ophthalmologic monitoring was expanded. Ophthalmology testing was performed in 8 of the cariprazine clinical studies included in this application (RGH-MD-01, -03, -04, -05, -11, -17, -18, and -36). Ophthalmology parameters included BCVA; color discrimination; IOP; LOCS III grades for nuclear opalescence, nuclear color, and cortical and posterior subcapsular opacities; and slit-lamp biomicroscopy and dilated examination of each eye. OCT scans were performed in long-term schizophrenia Study RGH-MD-11. Statistical methods for analyzing the ophthalmology data are provided in the SAP.

Three independent, consultant ophthalmologists ( (b) (4) ) reviewed the clinical AE and ophthalmology data (summary statistics for changes and shifts from baseline, by-patient data listings, and ocular AE narratives). (b) (4) prepared a report based on the review of the ophthalmology data. The panel concluded that based on ophthalmologic testing in the cariprazine clinical development program there was no evidence for retinal toxicity or lenticular changes of clinical significance.

**Overall Summary of Ocular Adverse Events in 3 or more Patients in Any Treatment Group (Groups 1 through 3) in Cariprazine Clinical Studies— Safety Population**

	<i>Group 1A+1B+2A+2B</i>	<i>Controlled Studies Group 1A+2A</i>		<i>Group 3A</i>		<i>Group 3B</i>	
	<i>Cariprazine (N = 2718)</i>	<i>Placebo (N = 1026)</i>	<i>Cariprazine (N = 1940)</i>	<i>Placebo (N = 23)</i>	<i>Cariprazine (N = 191)</i>	<i>Placebo (N = 91)</i>	<i>Cariprazine (N = 144)</i>
<b>Any Ocular TEAE, n (%)</b>	<b>152 (5.59)</b>	<b>23 (2.2)</b>	<b>86 (4.4)</b>	<b>3 (13.0)</b>	<b>7 (3.7)</b>	<b>6 (6.6)</b>	<b>14 (9.7)</b>
Blurred vision	64 (2.4)	7 (0.7)	42 (2.2)	0	4 (2.1)	2 (2.2)	9 (6.3)
Dry eye	20 (0.74)	2 (0.2)	7 (0.4)	0	1 (0.5)	2 (2.2)	1 (0.7)
Conjunctivitis	7 (0.26)	4 (0.4)	2 (0.1)	0	0	0	0
Eye irritation	6 (0.22)	3 (0.3)	4 (0.2)	2 (8.7)	1 (0.5)	1 (1.1)	0
Photophobia	5 (0.18)	1 (0.1)	3 (0.2)	0	1 (0.5)	0	1 (0.7)
Diplopia	4 (0.15)	0	3 (0.2)	0	0	0	0
Eye pain	4 (0.15)	1 (0.1)	3 (0.2)	0	0	0	0
Eye swelling	4 (0.15)	0	3 (0.2)	0	0	0	0
Ocular hyperaemia	4 (0.15)	1 (0.1)	3 (0.2)	0	0	0	0
Oculogyric crisis	4 (0.15)	1 (0.1)	3 (0.2)	0	0	0	1 (0.7)

Note: TEAEs include those reported during the respective treatment periods in each Group. Group 1A = controlled schizophrenia studies; Group 1B = long-term, open-label schizophrenia studies; Group 2A = controlled bipolar mania studies; Group 2B = long-term, open-label bipolar mania studies; Group 3A = clinical PK and PK/PD studies in healthy subjects; Group 3B = clinical PK and PK/PD studies in patients with schizophrenia. n = number of patients who had the event; PD = pharmacodynamic; PK = pharmacokinetic; TEAE = treatment-emergent adverse event.

Source: ISS Appendix X, Tables 5.1.6, 5.1.7, 5.1.8, 5.1.9.

**Reviewer's Comments:** *There is consistent reporting of blurred vision being more common in the cariprazine group than in the placebo group in each of the study populations.*

**Common Treatment-Emergent Adverse Events With an Incidence of  $\geq 2\%$  and Greater Than Placebo in the Overall Cariprazine Group During the Double-blind Treatment Period in Group 2A (Controlled Bipolar Mania Studies)**

	<i>Placebo (N = 442) n (%)</i>	<i>Cariprazine (N = 623) n (%)</i>
<b>Patients with at least 1 TEAE</b>	<b>296 (67.0)</b>	<b>496 (79.6)</b>
Vision blurred	5 (1.1)	22 (3.5)

Treatment-Emergent Adverse Events in Schizophrenia Trials occurred in less than 2% of patients in controlled trials.

### Change From Baseline to Endpoint for Mean BCVA: Group 1A (Controlled Schizophrenia Studies)—Safety Population

<i>Parameter</i>	<i>Placebo (N = 304)</i>		<i>Overall Cariprazine (N = 619)</i>		<i>Aripiprazole 10 mg (N = 152)</i>	
	<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>
<b>Visual acuity, right eye</b>						
Baseline	248	0.084 ± 0.229	485	0.085 ± 0.217	129	0.135 ± 0.291
Change from baseline to endpoint	248	-0.019 ± 0.157	485	-0.005 ± 0.167	129	-0.014 ± 0.170
<b>Visual acuity, left eye</b>						
Baseline	248	0.085 ± 0.222	484	0.093 ± 0.232	129	0.147 ± 0.305
Change from baseline to endpoint	248	-0.017 ± 0.161	484	-0.008 ± 0.168	129	-0.020 ± 0.178

Note: Includes data from Studies RGH-MD-04 and RGH-MD-05.

BCVA = best-corrected visual acuity; n = number of patients with an available value at baseline and endpoint (end of the double-blind treatment period); SD = standard deviation.

Source: ISS Appendix X, Table 13.4.1.

### Change From Baseline to Endpoint for Mean BCVA: Group 1B (Long-term, Open-label Schizophrenia Studies)

<i>Parameter</i>		<i>Cariprazine (N = 622)</i>			
		<i>Right Eye</i>		<i>Left Eye</i>	
		<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>
<b>Visual acuity</b>	Baseline	383	0.084 ± 0.219	382	0.094 ± 0.233
	Change at endpoint	383	-0.020 ± 0.206	382	-0.020 ± 0.209

Source: ISS Appendix X, Table 13.4.2.

### Change From Baseline to Endpoint for Mean BCVA: Group 2B (Long-term, Open-label Bipolar Mania Studies)

<i>Parameter</i>		<i>Cariprazine (N = 402)</i>			
		<i>Right Eye</i>		<i>Left Eye</i>	
		<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>
<b>Visual acuity</b>	Baseline	293	0.029 ± 0.173	293	0.037 ± 0.150
	Change at endpoint	293	0.006 ± 0.119	293	-0.005 ± 0.128

Source: RGH-MD-36, Table 14.5.9.1A.

The data for patients whose BCVA changed by  $\geq 0.3$  at any time point was examined. In Group 1A, 6 of 304 placebo-treated patients, 2 of 152 aripiprazole-treated patients, and 13 of 619 cariprazine-treated patients had changes of  $\geq 0.3$  in BCVA (ISS Appendix X, Table 13.8.4.1). In Group 1B, 26 of 622 patients had changes of  $\geq 0.3$  in BCVA, and in Group 2B, 7 of 402 patients had changes of  $\geq 0.3$  in BCVA (ISS Appendix X, Tables 13.8.4.2 and 13.8.4.3). The majority of patients had normal ocular exams and no reported TEAEs. A few patients had the following TEAEs: blepharitis, photopsia, oculogyric crisis, or worsening of diabetic retinopathy. No TEAE of vision loss was reported in any of these patients. The majority of patients appeared to have either transcription errors (1.0 instead of 0.1), or an abnormally high baseline, or returned to normal after a high recording, and occasionally an incorrect baseline value was recorded. One patient had keratoconus (PID 0051615) and another patient had worsening diabetic retinopathy, in both eyes (PID 0841117).

**Reviewer's Comments:** *Agree with assessment. The majority of decreases of  $\geq 0.3 \log \text{MAR}$  units appear to be due to transcription errors or questionable baseline values, including some which are well outside a normal value.*

## From Sponsor's Ophthalmic Consultant Report

### Lens: LOCS III

Assessment for cataract formation was performed in all studies in which ophthalmologic assessments were done. The LOCS III system for nuclear opalescence, nuclear color, cortical cataract, and posterior subcapsular cataract was used for each eye. The largest positive change from baseline for each patient was evaluated.

The definitions of positive lenticular shifts Class I, II, III were:

- Class I: increase from baseline in LOCS III grade of  $\geq 0.5$  (nuclear opalescence), or  $\geq 0.8$  (cortical), or  $\geq 0.5$  (posterior subcapsular)
- Class II: increase from baseline in LOCS III grade of  $\geq 0.9$  (nuclear opalescence),  $\geq 1.5$  (cortical), or  $\geq 0.9$  (posterior subcapsular)
- Class III: LOCS III grade of  $\geq 2.0$  for any type of opacity (nuclear opalescence, cortical, or posterior subcapsular) and increase from baseline in LOCS III grade of  $\geq 0.9$  (nuclear opalescence),  $\geq 1.5$  (cortical), or  $\geq 0.9$  (posterior subcapsular), or cataract surgery since baseline

### Change From Baseline for LOCS III Results: Group 1A (Controlled Schizophrenia Studies)

<i>Parameter, Unit</i>	<i>Placebo (N = 304)</i>		<i>Overall Cariprazine (N = 619)</i>		<i>Aripiprazole 10 mg (N = 152)</i>	
	<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>	<i>n</i>	<i>Mean ± SD</i>
<b>Cortical, right eye</b>						
Baseline	250	0.24 ± 0.36	486	0.26 ± 0.44	128	0.21 ± 0.32
Change from baseline to endpoint	250	0.03 ± 0.29	486	-0.00 ± 0.18	128	0.02 ± 0.07
<b>Cortical, left eye</b>						
Baseline	250	0.24 ± 0.40	487	0.27 ± 0.44	128	0.21 ± 0.31
Change from baseline to endpoint	250	0.02 ± 0.26	487	-0.01 ± 0.23	128	0.02 ± 0.10
<b>Posterior subcapsular, right eye</b>						
Baseline	250	0.13 ± 0.10	486	0.5 ± 0.21	128	0.12 ± 0.08
Change from baseline to endpoint	250	0.00 ± 0.07	486	0.00 ± 0.14	128	0.00 ± 0.03
<b>Posterior subcapsular, left eye</b>						
Baseline	250	0.15 ± 0.22	487	0.15 ± 0.19	128	0.12 ± 0.08
Change from baseline to endpoint	250	0.00 ± 0.05	487	-0.00 ± 0.13	128	0.00 ± 0.03

n = number of patients with an available value at baseline and endpoint (end of the double-blind treatment period). Source: ISS Appendix X, Table 13.5.1.

**Number (%) of Patients With Lenticular Shifts in Group 1B (Long-term, Open-label Schizophrenia Studies)**

	<i>Cariprazine (N = 622)</i> <i>n/N1 (%)</i>		
	<i>Class I</i>	<i>Class II</i>	<i>Class III</i>
<b>Positive lenticular shifts</b>			
End of Study	20/404 (5.0)	13/404 (3.2)	6/404 (1.5)
Overall (at any time of study)	24/404 (5.9)	14/404 (3.5)	8/404 (2.0)
<b>Negative lenticular shifts</b>			
End of Study	34/404 (8.4)	9/404 (2.2)	3/404 (0.7)
Overall	37/404 (9.2)	13/404 (3.2)	3/404 (0.7)

N1 = number of patients with non-missing baseline and at least one postbaseline LOCS III assessment or with cataract surgery.  
Source: ISS Appendix X, Tables 13.6.1 and 13.6.1.2.

**Number (%) of Patients With Lenticular Shifts in Group 2B (Long-term, Open-label Bipolar Mania Studies)**

	<i>Cariprazine (N = 402)</i> <i>n/N1 (%)</i>		
	<i>Class I</i>	<i>Class II</i>	<i>Class III</i>
<b>Positive lenticular shifts</b>			
End of Study	11/309 (3.6)	4/309 (1.3)	5/309 (1.6)
Overall	17/309 (5.5)	8/309 (2.6)	5/309 (1.6)
<b>Negative lenticular shifts</b>			
End of Study	10/309 (3.2)	6/309 (1.9)	3/309 (1.0)
Overall	17/309 (5.5)	10/309 (3.2)	3/309 (1.0)

N1 = number of patients with non-missing baseline and at least one postbaseline LOCS III assessment or with cataract surgery.  
Source: RGH-MD-36, Tables 14.5.9.2A and 14.5.9.3A.

In Group 1B and Group 2B long-term studies, almost equivalent numbers of patients had positive and negative changes in LOCS III, pointing to the inherent variability of the testing procedure, especially where the examiners varied. Of the patients with positive lenticular changes, 6 of 39 in Group 1B and 5 of 20 in Group 2B had Class III changes. Detailed examination of patient listings indicated no major AE or test abnormalities associated with lenticular changes in any of these patients. The majority of patients had totally normal examinations, including no change in BCVA, with only the LOCS III assessments being abnormal. These Class III changes lacked the signature of bilaterality and regional consistency of drug-induced changes, indicating test-retest ascertainment variability commonly experienced with the assessment instrument and variability induced by different examiners, and not with a true finding.

**Reviewer's Comments:** *Agree in part. Cataract development does not have to be bilateral to have been caused by a systemically administered drug product. Cataract changes are highly unlikely to reverse and therefore reported decreases are likely to be errors in grading or recording by the investigators. The cases of Class III have been individually reviewed below because there are more positive changes than negative changes and because they represent a greater change.*

**Summary of Patients With Class III Positive Lenticular Shifts in Groups 1B (Long-term, Open-label Schizophrenia Studies) and 2B (Long-term, Open-label Bipolar Mania Study)**

<i>PID, Treatment</i>	<i>Nuclear Opalescence</i>	<i>Nuclear Color</i>	<i>Cortical Cataract</i>	<i>Posterior Subcapsular Cataract</i>	<i>BCVA</i>	<i>Ocular AE</i>
<b>Group 1B: Long-Term, Open-Label Schizophrenia Studies</b>						
0060419, cariprazine	0.5/ 0.7 TO 1.2/ 1.6	Not CS	Not CS	Not CS	Not CS	None
0120416, cariprazine	2.1/ 2.1 TO 3.1/ 3.1	Not CS	Not CS	Not CS	Not CS	None
0400506, cariprazine	0.6/ 2.2 TO 1.2/ 2.6	Not CS	Not CS	Not CS	Not CS	None
5100502, cariprazine	Not CS	Not CS	Not CS	0.2/ 0.2 TO 2.1/ 2.1	Not CS	None
0871120, cariprazine	Not CS	Not CS	Not CS	0.1/ 0.1 TO 1.2/ 0.3	Not CS	None
0191616, cariprazine			0.1/ 0.1 TO 2.7/ 3.2		Not CS	
<b>Group 2B: Long-Term, Open-Label Bipolar Mania Study</b>						
0043628, cariprazine	1.1/ 0.9 TO 2.8/ 2.7	1.3/ 1.4 TO 2.1/ 2.1	Not CS	Not CS	Not CS	Mild blurred vision
0023654, cariprazine	0.7/ 0.8 TO 2.7/ 2.7	Not CS	Not CS	Not CS	Not CS	None
0043644, cariprazine	2.0/ 1.8 TO 3.1/ 2.7	1.4/ 1.2 TO 2.6/ 2.2	Not CS	Not CS	Not CS	None
0043645, cariprazine	1.3/ 1.6 TO 2.1/ 1.9 TO 2.5/ 2.2	Not CS	0.1/ 0.1 TO 0.1/ 0.1 TO 1.2/ 1.0	Not CS	Not CS	Mild dry eye
0183601, cariprazine	Not CS	Not CS	0.1/ 0.2 TO 2.3/ 1.8	2.4/ 1.8 TO 0.1/0.3	Not CS	None

Numbers reflect LOCS III grading at baseline and end of study in right eye/left eye, respectively.

**Reviewer's Comments concerning Cataracts:** *Nuclear opalescence and nuclear color are of minimal concern since they have a minimal effect on visual function. While there are individual cases of increasing lens opacification, there are relatively few cases. It remains possible that the follow-up period was not long enough to detect lens changes. It is recommended that cataract development be listed in the adverse reaction section of the labeling.*

**Intraocular pressure (IOP):** Mean changes from baseline to the end of treatment in IOP were negligible in both short- and long-term studies, and in controlled studies changes were similar across treatment groups. Only 4 patients had IOP readings of > 25 mm Hg, and based on normal ocular examination findings, 3 of these 4 patients are likely to be ocular hypertensive. The remaining patient, who had a report of increased cup disc ratio, is likely to have had undiagnosed chronic open-angle glaucoma.

**Reviewer's Comments:** *Concur with consultant's findings.*

**Retina:** Dilated examination of the eyes, including the posterior segment, revealed no significant ocular changes from baseline in either the short- or long-term cariprazine studies.

OCT scans were performed in long-term study RGH MD-11. Approximately 172 cariprazine-treated patients had OCT performed and about 85 of these patients received cariprazine therapy for 1 year. Three independent ophthalmologists assessed the OCT scans separately. Although a number of abnormalities were observed, some of which were artifact, abnormalities such as drusen or a pseudo-macular hole were also noted. Only 1 patient was noted to have macula edema. The patient had a known history of diabetes, was on insulin therapy, and was noted to have diabetic retinopathy at baseline. Therefore, based on OCT, no abnormality of note related to separation of the retinal layers or in the retinal pigment epithelium was seen in patients receiving long-term cariprazine treatment.

**Reviewer's Comments:** *Concur with consultant's findings.*

The following case report forms were reviewed for their reported ocular events:

0831118
0831125
2030415
5130501
6020511
6040505
0020412
0450501
0480510
0040442
0070411
0140410
0180410
0430502
0731121
0741113
0741119
0801106
0831172
0841117
0841155
0871111
0871112
0871120
0871127
0871133
0871136
1030401
1080402
2030404
2030407
2030415
6020511
6040505
6050520
2041614
1051621
0011801
0011828
0011852
0033333

0160409
0180410
0721101
0731121
0831172
0841155
0871120
0871124
0871127
0871133
0871136
0871137
1080402
2030415
3010408
6010512
6020511
6040505

**Reviewer's Comments:** *The findings in these case reports varied. Many of the reports were either normal anatomical variations, clinically insignificant findings, changes which do not represent a change from baseline, or changes which represented an improvement from baseline. There was no recognizable pattern to the events or high frequency of any particular type of event.*

**Questions from Division:**

1) Has the sponsor provided adequate ocular data for your review?

**Reviewer Response:** *Yes. The applicant has used currently available methodologies to investigate the potential for cariprazine to cause ocular events.*

*While there was no evidence of rapid cataract development in humans as observed in studies with dogs, a less rapid increase in cataract development (such as caused by corticosteroid use) cannot be ruled out without studies of at least 3 years duration.*

2) Would you suggest requesting any additional information?

**Reviewer Response:** *Not at this time.*

3) What is your assessment of the risk of cataract?

**Reviewer's Response:** *The number of reported cases of cataract development in the clinical trials is low. Unlike the risk to dogs, the long term risk of cataract development can neither attributed to use of cariprazine, nor ruled out, but there does not appear to be signs of rapid cataract progression attributable to cariprazine.*

4) What is your assessment of the risk of retinal toxicity?

**Reviewer's Response:** *The applicant has used currently available methodologies to investigate the potential for cariprazine to cause ocular events. Limitations exist in the number of patients available (85 patients) for one year follow-up in study MD-11. Due to the limited number of patients studied, adverse events at frequencies less than 4% may not have been detected, however, retinal degeneration in a manner similar to that seen in rats was not observed in human clinical trials.*

5) We recognize that it is early in the review cycle, but do you think it would be necessary or useful to have an AC meeting to discuss the ocular findings?

**Reviewer's Response:** *With the absence of clear signals in humans of ocular toxicity, it does not appear to be the best use of resources to engage an advisory committee in a discussion of the few clinically significant ocular findings presented in this application.*

**Summary:**

1. Animal data demonstrated a risk to dogs of developing cataracts following administration of cariprazine and a risk to rats of developing retinal degeneration following administration of cariprazine.
2. The review of potential cataract development was confounded by apparent errors in assessment, grading and/or recording of lens scores during the clinical trials, but no evidence of rapid cataract development or high frequencies of cataract development were observed in the human clinical trials. The findings in humans are therefore not consistent with the findings in dogs. Long term development or low frequencies of cataract development cannot be ruled out without carefully monitoring in clinical trials or practice over a period of at least 3 years.
3. Limitations exist in the number of patients available (85 patients) for one year follow-up with macular OCT testing, and limitations exist in the methods available to detect early peripheral retina changes. With the technology currently available, there was no signal of retinal degeneration in human studies similar to that seen in rat studies. Due to the limited number of patients studied, adverse events at frequencies less than 4% may not have been detected.
4. Ocular adverse reactions were reported in 5-6% of patients. The most frequently reported ocular adverse reaction was blurred vision which accounted for approximately half of the reported ocular adverse reactions. The physiologic cause of the blurred vision was not identified in the clinical trials.

**Additional Comments:**

1. It is unclear why the applicant's review of the data from Study RGH-TX-49 did not detect two apparently non-physiologic high values when abnormal low values were appropriately discarded, but correcting these values is unlikely to have a significant effect on the conclusions of the study.
2. The applicant's review of the cataract data notes errors in the assessment, grading and/or recording of cataracts as a reason for signals of cataract development in patients treated with cariprazine. It would have been better to have included monitoring in the study which reviewed these abnormal observations in a timeframe which allowed re-checking of the clinical findings. Future trials should include this type of monitoring.

**Recommendations:**

There is no objection to the approval of NDA 204-370 for cariprazine from an ophthalmologic prospective. If the application is approved, it is recommended that the labeling include information on the potential for cariprazine to cause cataracts in dogs and retinal degeneration in rats. It is also recommended that the adverse reactions section of the labeling include blurred vision as an event which was observed in clinical trials in 2-3% of patients, and cataract development as a rare event.

Wiley A. Chambers, M.D.  
Supervisory Medical Officer, Ophthalmology

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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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WILEY A CHAMBERS  
08/27/2013

**DIVISION OF PULMONARY, ALLERGY AND RHEUMATOLOGY**  
**PRODUCTS (DPARP) MEDICAL OFFICER CONSULTATION**

Date: August 23, 2013  
To: Kim Updegraff, RPM, DPP  
Francis Becker, MD, Medical Officer, DPP  
From: Sally Seymour, MD, Deputy Director for Safety, DPARP  
Through: Badrul A. Chowdhury, MD, PhD., Division Director, DPARP  
Subject: Cariprazine

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**General Information**

NDA/IND#: NDA# 204370  
Sponsor: Forest Pharmaceuticals  
Drug Product: Cariprazine  
Request From: Kim Updegraff, RPM, DPP  
Date of Request: August 8, 2013  
Date Received: August 9, 2013  
Materials: Clinical and pharm/tox reviews for NDA# 204370, Clinical  
Reviewed: Summary, ISS for NDA# 204370  
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**I. Executive Summary**

This is a Medical Officer Consultation intended to respond to the request for consultation by the Division of Psychiatry Products (DPP), regarding NDA# 204370 for cariprazine. Cariprazine is a dopamine D<sub>2</sub>/D<sub>3</sub> receptor partial agonist and serotonin 5-hydroxytryptamine (5-HT) 1A agonist proposed for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder. The NDA for cariprazine is currently under review with a PDUFA date of November 19, 2013. Although cariprazine is an NME, an advisory committee meeting is not planned.

In the non-clinical program, phospholipidosis (PLD) in the lungs was observed in rats, dogs, and mice with no safety margin. The PLD was associated with subchronic/chronic inflammation observed in the lungs in both rats and dogs. Lung fibrosis was observed in dogs following long-term (52 week) cariprazine administration and reversibility was not demonstrated in the 2 month recovery period. PLD was also observed in other organs, such as the adrenal glands and cataracts were also noted in the dog toxicology studies.

In the clinical programs in patients with bipolar disorder and schizophrenia, no specific assessment of pulmonary safety was included in the safety monitoring. A review of spontaneous adverse event reports does not reveal a pulmonary safety signal with the exception of some pulmonary infection SAEs. Cariprazine and its active metabolites have a long terminal half-life (4-7 days cariprazine, 2-4 days for DCAR and 4-10 weeks for DDCAR). It is extensively distributed into tissues.

In DPARP's experience, PLD in the lungs is a common finding in rats, especially with inhaled drugs, but PLD in the lungs in dogs is not as common. We generally do not consider the finding of foamy alveolar macrophages (AM) alone adverse unless there is evidence of progression, such as histological changes (e.g. inflammation, hemorrhage, fibrosis accompanying findings of foamy AMs). When we see PLD associated with these progressive changes, we generally determine a NOAEL (e.g., no evidence of foamy AMs given concerns that macrophages are mediating the lung damage) and limit clinical dosing to ensure an adequate safety margin for PLD. We do not consider these microscopic changes monitorable in patients as bronchoscopy, HRCT, or PFTs are unlikely to detect these types of changes unless there is considerable progression. Therefore, it is important to have an adequate safety margin based upon the non-clinical studies.

In the cariprazine program, the toxicology studies show that PLD is associated with inflammation and fibrosis in the lung in rats and dogs. The fact that the findings were in more than one species raises concern. The PLD findings in the rats did not seem to progress with longer exposure as the nonclinical review did not note inflammation in the 6 month rat study. However, in the dog toxicity studies, inflammation and fibrosis in the lungs were noted that were not completely reversible in the 1 year study. The findings appear to be dose related. If aware of these findings in the IND stage, depending upon the indication, we would not let clinical studies proceed until the sponsor identified a NOAEL and a safety margin could be identified to select a supported dose for clinical studies.

In this case, clinical studies with caraprazine have already been completed. While no pulmonary safety signal was identified, as noted above, we don't consider these histological changes monitorable. Therefore, the lack of a signal in the clinical program does not assure that cariprazine does not have adverse effects on the lungs. The effects of inflammation and fibrosis in the lungs could take years to manifest clinically. Adverse events in humans that would have been seen histologically may take many years to manifest with clinical signs and symptoms.

Based upon the non-clinical findings, there is potential risk for adverse effects on the lungs in patients exposed to cariprazine. We cannot predict the likelihood of serious and/or irreversible pulmonary injury in humans. Additional clinical data at the proposed doses (e.g. post-marketing safety trial) is not likely to be informative, as the nonclinical findings would not be detected clinically unless there was significant progression. (b) (4)

However, since no NOAEL was identified, an acceptable dose with regards to the pulmonary findings cannot be identified. To determine a dose supported by the nonclinical studies, the sponsor would need to conduct another long-term dog toxicity study with lower doses of cariprazine to identify a NOAEL with respect to the adverse lung findings. Unless the benefits of cariprazine outweigh the potential risk of pulmonary injury, a complete response action should be considered to determine a dose of cariprazine supported by non-clinical data.

In the consult request, DPP requests feedback on the following questions. DPARP's responses are provided below.

**Question 1. Based on the data available, what is the potential risk or likelihood of serious and/or irreversible pulmonary injury (e.g. fibrosis) in cariprazine-treated patients?**

DPARP Response:

*There is concern for potential risk for serious pulmonary injury based upon the non-clinical studies. However, we cannot predict the likelihood of serious and/or irreversible pulmonary injury in cariprazine-treated patients. Unless the benefits of cariprazine outweigh the potential risk of pulmonary injury, a complete response action should be considered to determine a dose of cariprazine supported by non-clinical data.*

**Question 2. DPP is considering [REDACTED] (b) (4). Considering the long half-life of the active moiety, would [REDACTED] (b) (4) provide acceptable reassurance of pulmonary safety?**

DPARP Response:

[REDACTED] (b) (4)  
*a NOAEL was not identified, we cannot identify a dose of cariprazine that assures pulmonary safety. To determine a dose supported by the nonclinical studies, the sponsor would need to conduct another long-term dog toxicity study with lower doses of cariprazine to identify a NOAEL (e.g., no evidence of foamy AM or consistent with concurrent control) with respect to the adverse lung findings.*

**Question 3. What recommendations, if any, would you have for monitoring cariprazine-treated patients for pulmonary toxicity if the NDA is approved?**

DPARP Response:

*As the pulmonary findings in the non-clinical studies are not monitorable, unless there is significant progression, there is no specific recommendation for clinical monitoring.*

**Question 4. DPP is considering requesting a postmarketing commitment to conduct a long-term maintenance study. What recommendations, if any, would you have for further evaluating pulmonary safety during this study?**

DPARP Response:

*As noted above, the pulmonary findings are not considered monitorable. If you require a long term safety trial, collection of pulmonary SAEs would be of interest, but could not assure pulmonary safety.*

### **Background**

Cariprazine is a dopamine D<sub>2</sub>/D<sub>3</sub> receptor partial agonist with preferential binding to D<sub>3</sub> receptors and partial agonism at serotonin 5-hydroxytryptamine (5-HT) 1A receptors. It is a new molecular entity. Cariprazine is being developed by Forest Research Institute and Gideon Richter for the treatment of schizophrenia, bipolar disorder, and major depressive disorder and by Mitsubishi Tanabe Pharma Corporation for the treatment of schizophrenia in Japan. The proposed dosing ranges from [REDACTED] (b) (4) once daily. Cariprazine is not currently marketed anywhere in the world. NDA# 204370 was submitted on November 19, 2012. The PDUFA date is November 19, 2013.

Cariprazine has a terminal half-life between 4 to 7 days and the Tmax is between 3-6 hours for cariprazine. It is extensively distributed into tissues. There are at least two major metabolites (DCAR and DDCAR) with activity. The terminal half-life for DCAR and DDCAR is 2 to 4 days and 4 to 10 weeks, respectively.

### Nonclinical Findings

Toxicology studies with cariprazine showed that the target organs of toxicity are the eyes (cataracts), adrenal glands (increased weight, vacuolation), male and female reproductive system, and lungs. Per Dr. Chalecka-Franaszek’s nonclinical review, “drug-related findings in the lungs in animals included discoloration, presence of alveolar macrophages with foamy cytoplasm, increased alveolar inflammation and hemorrhages, histiocytic multifocal infiltration, and subacute/chronic inflammation/fibrosis. These changes increased in incidence and severity in a dose-dependent manner and were not reversible during recovery periods. In general, a NOAEL for PLD could not be determined in the pivotal studies; therefore, for this adverse effect, there is no margin of safety for cariprazine administration to humans at the MRHD (b) (4).” The pulmonary nonclinical findings as described in Dr. Chalecka-Franaszek’s review are briefly summarized below.

### Rat Studies

The Applicant conducted a 28 day oral gavage toxicity study in rats with a 2 week recovery and doses of 0, 0.5, 2.5, 12.5, and 50mg/kg/day of cariprazine. Deaths were observed at higher doses and no NOAEL was identified because of reproductive findings. This study showed an increased incidence and severity of alveolar macrophage foci and increased alveolar inflammation in animals at 12.5 and 50mg/kg. Following the 2 week recovery period, alveolar macrophage foci in the lungs were observed in HD males.

Lungs: Alveolar macrophage foci were seen at increased incidences and severity in groups administered the highMD and HD. This effect was accompanied by increased alveolar inflammation. The results are presented in the following reviewer’s table:

Lungs: Alveolar macrophage foci										
	Males (10/group)					Females (10/group)				
Cariprazine mg/kg/day	0	0.5	2.5	12.5	50	0	0.5	2.5	12.5	50
minimal	0	0	0	1	0	0	1	0	2	0
slight	1	0	0	4	0	0	0	2	3	0
moderate	0	0	0	1	9	0	0	0	2	9
severe	0	0	0	0	0	0	0	0	0	1
total	1	0	0	6	9	0	1	2	7	10

Lungs: Alveolar inflammation										
	Males (10/group)					Females (10/group)				
Cariprazine mg/kg/day	0	0.5	2.5	12.5	50	0	0.5	2.5	12.5	50
minimal	1	2	0	2	4	1	1	2	4	1
slight	1	1	0	5	5	0	0	0	3	7
moderate	0	0	0	0	0	0	0	0	0	2
total	2	3	0	7	9	1	1	2	7	10

A 13 week oral gavage toxicology study was conducted in rats with doses of 0, 1, 3, and 10-12.5 mg/kg/day of cariprazine. This study showed an increased incidence of discolored tan foci observed in lungs at 12.5 mg/kg and increased incidence alveolar/intraalveolar

macrophages and foamy cytoplasm with and without inflammatory cell infiltration observed in lungs of males at the 12.5 mg/kg and in females at all dose levels. This finding was associated with pulmonary hemorrhage and attributed to PLD. There was only a partial recovery in the LDF and MDF groups after the 4-week recovery period, and no recovery in the HD groups. The NOAEL could not be determined and there is no margin of safety due to the PLD in female rats.

**Table 3.10.2.1 Lung - Foamy Cytoplasm in Alveolar/Intraalveolar Macrophages**

		Incidence and Severity								
Males						Females				
Dose (mg/kg/day)		0	1	3	12.5	Dose (mg/kg/day)				
		0	1	3	12.5	0	1	3	12.5	
<b>Term</b>	N	10	10	10	10	N	10	10	10	10
	Minimal	2	3	3	3	Minimal	1	4	4	2
	Slight	0	0	0	6	Slight	0	0	2	7
	Moderate	0	0	0	1	Moderate	0	0	0	1
	<b>Total</b>	<b>2</b>	<b>3</b>	<b>3</b>	<b>10</b>	<b>Total</b>	<b>1</b>	<b>4</b>	<b>6</b>	<b>10</b>
<b>Recovery</b>	N	5	5	5	5	N	5	5	5	5
	Minimal	0	2	1	3	Minimal	1	1	2	3
	Slight	0	0	0	1	Slight	0	0	0	1
	Moderate	0	0	0	1	Moderate	0	0	0	1
	<b>Total</b>	<b>0</b>	<b>2</b>	<b>1</b>	<b>5</b>	<b>Total</b>	<b>1</b>	<b>1</b>	<b>2</b>	<b>5</b>

A 6 month oral gavage toxicology study was conducted in rats with doses of 0, 1, 3, or 10-12.5 mg/kg/day of cariprazine. This study showed an increased incidence and severity of alveolar/intra-alveolar macrophages with foamy cytoplasm observed in the lungs in males at 10 mg/kg/day and in females at all dose levels, attributed to PLD and not reversible during the recovery period. Presence of lysosomal concentric lamellar bodies within the cytoplasm of type 2 pneumocytes and macrophages, typical of those seen with pulmonary PLD, was observed in TEM examination. The findings were not completely reversible after the 4-week recovery period, and no recovery in the HD groups. The NOAEL could not be determined and there is no margin of safety for the MRHD (b) (4) due to the PLD in the lungs and degeneration of the sciatic nerve.

Incidence and severity of alveolar/intraalveolar foamy macrophages in the lungs

Sex	Males				Females			
Dose (mg/kg/day)	0	1	3	10	0	1	3	12.5
Termination	10	10	10	10	10	10	10aa	10
Number examined								
Minimal	4	3	5	5	2	4	4	0
Slight	0	0	0	2	0	0	3	9
Moderate	0	0	0	0	0	0	0	1
Total	4	3	5	7	2	4	7	10
% animals affected	40%			70%	20%		70%	100%
Recovery	5	5	5	5	5	5	5	5
Number examined								
Minimal	0	1	1	1	0	2	1	0
Slight	1	1	1	4	0	1	2	5
Moderate	0	0	0	0	0	0	0	0
Total	1	2	2	5	0	3	3	5
% animals affected				100%				100%

aa - includes descendent

Congestion and hemorrhage in the lungs was noted by the reviewer; however, this finding was also noted in controls and was not dose related or reversible. The reviewer concluded the findings may be from gavage administration. The reviewer also noted that there was some increase in the incidence of alveolar/intra-alveolar inflammatory cell infiltrate at termination

in some dosed females, but not in Controls (2/10, 1/9, and 2/10 in the LDF, MDF, and HDF groups, respectively), which may be test article-related but unlikely adverse. Based on these considerations, there was no indication of any significant concurrent lung toxicity despite presence of PLD.

*Reviewer’s comment: The findings of PLD in the rat study are consistent and dose related and do not completely reverse during the recovery period. While the table in the 6 month study does not show inflammation and progression in the lungs, the reviewer did note some inflammation in the lungs at termination in the cariprazine groups and not in the controls.*

**Dog Studies**

The Applicant conducted a 13 week oral toxicity study in dogs with doses of 0, 1, 3, and 8mg/kg/day of cariprazine. Findings consistent with PLD were observed in the lungs (increased incidence of accumulation of foamy alveolar macrophages) in 3/4 females dosed at 8 mg/kg/day. The findings in the lungs were reversible.

The Applicant conducted a 1 year oral toxicity study in dogs with doses of 0, 1, 2, 4, and 6 mg/kg/day of cariprazine. Lung findings including discoloration generally at 4 or 6 mg/kg/day and microscopic PLD-like changes of alveolar/intraalveolar foamy macrophages accompanied by subacute/chronic inflammation/fibrosis observed in all cariprazine-dosed groups at the end of the dosing phase (except the low dose females).

At the end of dosing, alveolar/intra-alveolar foamy macrophages with or without “cholesterol clefts” consistent with PLD and accompanied by subacute/chronic inflammation/fibrosis were noted in all 4/4 M and 4/4 F at MD and HD, in 2/4 M and 2/4 F at MD, and in 2/4 M at LD. Severity of both findings ranged from minimal to moderate and was dose-related. At the end of 2-month recovery period, these findings in the lungs were minimal to slight and were present in 1/2 M and 1/2 M at MD, and in 2/2 M and 2/2 F at HD. The decrease in the incidence and severity indicated incomplete reversibility of PLD in the lungs during the recovery period. The findings are shown in the following tables.

**Table 3.10.2-2: Test Article-Related Microscopic Findings - Lungs**

Group	1		2		3		4		5	
	0		1		2		4		6	
Sex	M	F	M	F	M	F	M	F	M	F
<b>Dosing Phase (number/group)</b>	4	4	4	4	4	4	4	4	4	4
Alveolar/intraalveolar foamy macrophages	0	0	2	0	2	2	4	4	4	4
Subacute/chronic inflammation	0	0	2	0	2	2	4	4	4	4
<b>Recovery Phase (number/group)</b>	2	2	2	2	2	2	2	2	2	2
Alveolar/intraalveolar foamy macrophages	0	0	0	0	0	0	1	1	2	2
Subacute/chronic inflammation	0	0	0	0	0	0	1	1	2	2

RGH-188 HCl: A One-Year Oral (Capsule) Toxicity Study  
in Dogs with a Two Month Recovery Period

Incidence Summary of Microscopic Findings with Severity Levels  
Terminal Sacrifice

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	-- Animals					Affected --				
		-- Males --					-- Females --				
		Ctls	2	3	4	5	Ctls	2	3	4	5
Controls from group(s): 1		4	4	4	4	4	4	4	4	4	4
Lungs	Number examined:	4	4	4	4	4	4	4	4	4	4
CONGESTION	->	1	2	0	2	0	0	0	0	2	0
	2>	3	2	4	2	4	4	4	4	2	4
	Total Incidence of Finding Observed:	3	2	4	2	4	4	4	4	2	4
HEMORRHAGE(S)	->	2	3	4	2	3	4	4	4	2	4
	1>	1	1	0	2	1	0	0	0	1	0
	2>	1	0	0	0	0	0	0	0	1	0
	Total Incidence of Finding Observed:	2	1	0	2	1	0	0	0	2	0
ALVEOLAR/INTRAALVEOLAR FOAMY MACROPHAGES (WITH/WITHOUT "CHOLESTEROL" CLEFTS)	->	4	2	2	0	0	4	4	2	0	0
	1>	0	2	1	2	0	0	0	2	2	0
	2>	0	0	1	1	1	0	0	0	1	1
	3>	0	0	0	1	3	0	0	0	1	3
	Total Incidence of Finding Observed:	0	2	2	4	4	0	0	2	4	4
LYMPHOID CELL AGGREGATE(S)	->	4	3	4	3	4	4	3	3	4	3
	1>	0	1	0	1	0	0	1	1	0	1
	Total Incidence of Finding Observed:	0	1	0	1	0	0	1	1	0	1
SUBACUTE (CHRONIC ACTIVE)/CHRONIC INFLAMMATION/FIBROSIS	->	4	2	2	0	0	4	4	2	0	0
	1>	0	2	1	2	0	0	0	2	2	0
	2>	0	0	1	1	1	0	0	0	1	1
	3>	0	0	0	1	3	0	0	0	1	3
	Total Incidence of Finding Observed:	0	2	2	4	4	0	0	2	4	4

All Diagnoses; Phases: P4; Death types: All; Date of death range: 07-Dec-06 To 21-Dec-06

*Reviewer's Comment: The finding of PLD along with other histologic changes (inflammation, congestion, hemorrhage, fibrosis) in the lungs in the dog studies is of concern. The findings appear to be dose related and not completely reversible. Foamy alveolar macrophages (AM) are more than likely mediating the findings of lung injury that included inflammation, congestion, hemorrhage, and fibrosis. A NOAEL (defined as no evidence of foamy AM or consistent with concurrent control) was not identified.*

The following table shows the safety margins based upon NOAELs, using AUC and assumed MRHD (b) (4) as determined by the non-clinical reviewer (Dr. Elzbieta Chalecka-Francaszek's review, page 212).

Toxicity	Species	NOAEL (mg/kg) M/F	Safety Margin Based on AUC*
Cataracts	Beagle dog 13-week ERG study	1 mg/kg/day M	1.7
		3 mg/kg/day F	4.7
Cataracts, lens fibers swollen, degenerated, fragmented with vacuoles, clefts and eosinophilic granular material, irregular shaped/collapsed lens	Beagle dog 1-year study	2 mg/kg/day M	3.8
		2 mg/kg/day F	2.8
Cystic degeneration of the retina	Beagle dog 1-year study	2 mg/kg/day M	3.8
		4 mg/kg/day F	
Lens fiber swelling	Beagle dog 1-year study	not determined	none
Retinal degeneration/ atrophy	Wistar rat 2-year carcinogenicity study	0.25 mg/kg/day M	0.1
		F: not determined	none
Adrenal cortex: hypertrophy/hyperplasia, vesiculation/vacuolation	Beagle dog 1-year study	2 mg/kg/day M	3.8
		2 mg/kg/day F	2.8
Phospholipidosis in adrenals and lungs	Beagle dog (multiple studies)	not determined	none
Phospholipidosis in lungs	Wistar rat (multiple studies)	not determined	none

\*AUC in human: 1626 ng.hr/ml (b) (4) (combined AUC values for cariprazine, DCAR, and DDCAR)

### Phospholipidosis (PLD)

The following summary on PLD is based upon an April 2010, FDA Pharmaceutical Sciences Advisory Committee meeting in which PLD was discussed.<sup>1</sup> PLD is the excessive accumulation of phospholipid within cells. Drug-induced phospholipidosis has been observed in a variety of tissues in animal toxicity studies and the significance of the finding in humans is unknown. PLD can be identified by the appearance of foamy macrophages or cytoplasmic vacuoles in cells. By TEM, PLD appears as lamellar inclusions or multilamellar bodies. There are many pharmacological classes of drugs that induce PLD and antipsychotics are included in the list. Many of the drugs are amphiphilic drugs, meaning they possess both hydrophilic and hydrophobic properties. Some product labels include mention of the PLD findings but note that the significance in humans is unknown. PLD may be an adaptive response to the presence of a drug and may be reversible after discontinuation of the drug. While the toxicological significance of PLD is unclear, lung tissue damage has been observed with PLD in the present case. The lung injury is not a common finding observed with amphiphilic drugs and is considered adverse and unmonitorable in a clinical setting.

### Clinical Program

The Applicant conducted multiple phase 3 clinical trials in patients with schizophrenia and patients with bipolar disorder. Trials in patients with bipolar and major depressive disorder (MDD) trials are ongoing. Clinical trials were primarily randomized, double-blind, placebo-controlled, parallel group in design and ranged from 3 weeks (bipolar disorder) to 6 weeks (schizophrenia). Long term, open-label, safety and tolerability studies ranged from 16 weeks (bipolar disorder) up to 48 weeks (schizophrenia). Doses of cariprazine ranged from 1.5 to 12 mg/day with flexible dosing allowed in many trials.

<sup>1</sup> April 14, 2010 FDA Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee Meeting <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm>

According to Dr. Becker’s clinical review, in the pivotal trials in patients with schizophrenia and in the trials in patients with bipolar disorder, there was a statistically and clinically significant improvement with cariprazine compared to placebo for primary and secondary efficacy parameters. A dose response was noted in the schizophrenia trials, but not in the bipolar trials.

In terms of safety, the following is a table for the overall exposure in patients with schizophrenia and bipolar mania trials. Overall, there were over 2700 patients treated with at least one dose of cariprazine in the pivotal clinical trials. There were 239 patients exposed to cariprazine for > 48 weeks.

**Table 93: Summary of Overall Exposure in Schizophrenia and Bipolar Mania Trials (Groups 1 and 2) – Safety Population**

Exposure	Group 1A+1B+ 2A+2B <sup>a</sup> (N = 2758)	Schizophrenia			Bipolar Mania		
		Group 1A		Group 1B Long-term	Group 2A		Group 2B Long-term
		Placebo (N = 584)	Cariprazine (N = 1317)	Cariprazine (N = 679)	Placebo (N = 442)	Cariprazine (N = 623)	Cariprazine (N = 402)
<b>Treatment duration, n</b>							
≥ 1 day	2758	584	1317	679	442	623	402
≥ 3 weeks	2050	435	994	592	280	408	293
≥ 6 weeks	1224	284	676	511	—	—	206
≥ 12 weeks	619	—	—	449	—	—	150
≥ 24 weeks	364	—	—	346	—	—	—
≥ 48 weeks	239	—	—	211	—	—	—
<b>Patient-years of exposure</b>	<b>566.5</b>	<b>50.7</b>	<b>117.9</b>	<b>350.3</b>	<b>21.1</b>	<b>30.4</b>	<b>63.5</b>

a Treatment duration for cariprazine-treated patients in Group 1A+1B+2A+2B was calculated as the number of days from the date of first dose of cariprazine taken to the date of last dose of cariprazine taken (inclusive of the gap in dosing between lead-in and extension studies for patients who took cariprazine in both). Source: 5.3.5.3 ISS, Table 5.1-1, page 128; 120-Day Safety Update, Tables 5.1-1, page 31, 2.1.3, page 1162, and 2.1.6, page 1172

The following table shows dose and duration of exposure. Overall, there is limited long term experience with doses greater than 6mg. The Applicant has proposed dosing up to <sup>(b)</sup><sub>(4)</sub> mg/day of cariprazine.

**Table 97: Cariprazine Mean Daily Dose by Treatment Duration in Group 1A – Safety Population**

Treatment Duration	Overall Mean Daily Dose of Cariprazine				Any Dose of Cariprazine (N = 1317) N1
	< 3.0 mg (N = 295) n (%)	3.0-6.0 mg (N = 814) n (%)	6.1-9.0 mg (N = 125) n (%)	> 9.0 mg (N = 83) n (%)	
1-7 days	63 (75.0)	21 (25.0)	0	0	84
8-21 days	83 (31.3)	150 (56.6)	27 (10.2)	5 (1.9)	265
22-42 days	121 (15.2)	516 (64.7)	90 (11.3)	70 (8.8)	797
> 42 days	28 (16.4)	127 (74.3)	8 (4.7)	8 (4.7)	171
<b>Any duration</b>	<b>295 (22.4)</b>	<b>814 (61.8)</b>	<b>125 (9.5)</b>	<b>83 (6.3)</b>	<b>1317</b>

N = number of patients in the Safety Population for the specific mean daily dose category; n = number of patients with specific dose and duration of treatment; N1 = number of patients taking any dose of cariprazine for the specified treatment duration; Percentage is calculated as n/N1×100.  
Electronically copied and reproduced from sponsor’s submission: 5.3.5.3 ISS, Table 5.2.1.2-2, page 133

In terms of safety, specific assessments of the pulmonary system were not included in safety monitoring. Therefore the pulmonary safety database is based upon the adverse event reports. The relevant findings are summarized below.

There were 6 deaths in patients who received cariprazine. The primary cause of death was suicide in addition to one pulmonary embolism, one cardiac arrest, and one acute myocardial infarction/ischemic stroke. The SAE data were reviewed and potential pulmonary SAEs are listed in the table below. No obvious pulmonary safety signal was noted.

<b>Pulmonary Serious Adverse Events in Cariprazine Clinical Program</b>						
Group 1A	Placebo	Cariprazine 1.5-6mg	Cariprazine 6-12mg	Cariprazine Overall	Risperidone 4mg	Aripiprazole 10mg
	N= 584	N=1032	N=285	N=1317	N=140	N=152
Bronchitis	0	0	1 (0.4)	1 (0.1)	0	1 (0.7)
Pneumonia	2 (0.3)	1 (0.1)	0	1 (0.1)	0	0
COPD exacerbation- infection	1 (0.2)	0	0	0	0	0
Pneumonia – viral	1 (0.2)	0	0	0	0	0
URTI	1 (0.2)	0	0	0	0	0
Group 1B				N=622		
Bronchitis/ tracheobronchitis				2 (0.3)		
Asthma				1 (0.2)		
COPD				1 (0.2)		
Dyspnea				1 (0.2)		
Group 2A	N=422			N=623		
Pneumonia	0			1 (0.2)		
Pulmonary Embolism	0			1 (0.2)		
Group 2B				N=402		
Asthma				1 (0.2)		
COPD				1 (0.2)		
Group 1A – Controlled schizophrenia Group 1B – Long term open label schizophrenia Group 2A – Controlled bipolar mania Group 2B – Long term open label bipolar mania						

In terms of AEs leading to discontinuation, there were a handful of respiratory AEs that led to discontinuation: COPD exacerbation, pneumonia, hiccups, nasal discomfort, throat irritation, dyspnea, pulmonary TB, respiratory tract infection, URTI. These were generally only in a single patient.

Overall, review of the clinical data did not identify a pulmonary safety signal. However, given the nature of the non-clinical findings, the clinical database cannot assure pulmonary safety.

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/s/  
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SALLY M SEYMOUR  
08/23/2013

BADRUL A CHOWDHURY  
08/23/2013  
I concur



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** August 13, 2013

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** Evaluation of Rat Self-Administration Studies  
Cariprazine  
NDA 204370  
Indication: Treatment of Psychosis and Bipolar Disorder  
Dosage: (b) (4) mg/day (oral)  
Sponsor: Forest Pharmaceutical Research Institute  
PDUFA Goal Date: November 19, 2013

**Materials reviewed:** “Assessment of the Relapse Preventing Potential of Cariprazine in a Cue-Induced Reinstatement of Cocaine-Seeking Paradigm” (11/19/12), “Pharmacology/Toxicology NDA/BLA Review and Evaluation” (E. Chalecka-Fransz, 7/22/13)

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## **1 Background**

This memorandum responds to a consult request by the Division of Psychiatry Products to evaluate the abuse potential of cariprazine, based on receptor binding data and two self-administration studies conducted in rats with cariprazine. Cariprazine (RGH-188) has very high affinity for dopamine receptors (D3 has  $K_i = 0.085$  nM and D2 has  $K_i = 0.49$  to  $0.69$  nM) as partial agonists, and high affinity for serotonin receptors (5-HT2B has  $K_i = 0.58$  nM, 5-HT1A has  $K_i = 3$  nM as a partial agonist, 5-HT2A has  $K_i = 19$  nM as a full antagonist, and 5-HT2C has  $K_i = 134$  nM). The atypical antipsychotic, aripiprazole, a drug with no known abuse potential, has a similar but slightly different binding profile, with highest affinity for dopamine D2 and 5-HT2B receptors, with lesser affinity for histamine H1, dopamine D3, and 5-HT1A receptors (Citrome, 2013).

Cariprazine is being developed for the treatment of schizophrenia and bipolar disorder. The Sponsor for NDA 204370 is Forest Pharmaceutical Research Institute. Cariprazine is not marketed in any country.

### **Conclusions (to be conveyed to Sponsor):**

- 1) The receptor binding studies show that cariprazine has high affinity for dopamine D2 and D3 receptor subtypes and the serotonin 5HT1A and 5HT2A receptor subtypes. Functional studies show cariprazine acts as a partial agonist at the D2, D3 and 5HT1A sites and as an antagonist at the 5HT2A site. These mechanisms of action are not associated with abuse potential.
- 2) The self-administration studies conducted with cariprazine do not evaluate whether cariprazine produces rewarding properties indicative of abuse potential. Instead, these studies evaluate whether cariprazine can block self-administration of cocaine and reinstatement of cocaine self-administration after an abstinence (extinction) procedure. These two studies show that cariprazine, a dopamine partial agonist, acts as a dopamine antagonist at higher doses in both a cocaine self-administration paradigm and in a cocaine self-administration reinstatement paradigm.
- 3) Although the receptor binding studies and self-administration studies provide information about the preclinical effects of cariprazine, they are not designed to evaluate the drug for abuse potential. Thus, CSS can make no conclusions regarding the abuse potential of cariprazine.
- 4) Given that the Sponsor's cover letter and proposed drug label do not propose label claims for any indication related to the treatment of drug abuse (such as anti-addiction properties or relapse-preventing properties), the self-administration studies conducted with cariprazine are not submitted to the NDA in service of indications beyond the currently proposed indications of schizophrenia or bipolar disorder.

### **3 Recommendation (to be conveyed to Sponsor):**

The receptor binding studies and the self-administration studies with cariprazine may be described accurately in the drug label if desired, but they should not be used to conclude that the drug has been evaluated for abuse potential.

### **4. Discussion:**

#### **4.1 Pharmacology of drug substance**

The summary statements in the sections below are derived from the Pharmacology/ Toxicology review by Dr. Elzbieta Chalecka-Franaszek (placed into DARRTS on 7/22/13):

##### **4.1.1 In vitro studies**

###### **4.1.1.1 Receptor Binding Studies**

Cariprazine has high affinity for dopamine D3 receptors ( $K_i = 0.085$  nM), dopamine D2 receptors ( $K_i = 0.49$  and  $0.69$  nM for D2L and D2S, respectively), serotonin 5-HT1A ( $K_i = 2.6$  nM) receptors and serotonin 5-HT2A receptors ( $K_i = 18.8$  nM)

Cariprazine does not exhibit appreciable binding affinity ( $IC_{50} > 1$   $\mu$ M) for any other receptors, transporters, or ion channels tested, including adenosine A1, A2 and A3, adrenergic  $\alpha_2A$  and  $\beta$ , cannabinoid CB1 and CB2, dopamine D1, D4 and D5, GABA A and GABA B, glutamate AMPA, kainate and NMDA, serotonin 5-HT3, 5-HT4, 5-HT5A and 5-HT6, muscarinic M1, M2, M3, M4 and M5, nicotinic, opiate  $\delta$ ,  $\kappa$  and  $\mu$ , and sigma  $\sigma_2$  receptors; transporters for adenosine, choline, DA, 5-HT and noradrenaline; or calcium, potassium and sodium channels.

###### **4.1.1.2 Functional Studies**

Cariprazine displayed antagonism at both D2 and D3 receptors in [ $^{35}$ S]GTP $\gamma$ S binding assays [antagonist potency ( $K_b$  value): D3 =  $0.32$  nM; D2 =  $0.88$  nM]. In cell based assays, cariprazine demonstrated partial agonist activity at both D2 and D3 receptors, with varying degrees of intrinsic activities: it inhibited cAMP accumulation ( $EC_{50} = 4.8$  nM) of 7-OH-DPAT, it potently antagonized 7-OH-DPAT-induced suppression of cAMP formation ( $K_b = 0.27$  nM), it stimulated inositol phosphate (IP) production ( $EC_{50} = 3.2$  nM) and it antagonized quinpirole-induced IP accumulation ( $K_b = 0.6$  nM).

Cariprazine displayed partial agonist activity for native rat hippocampal 5-HT1A receptors, when tested in the [ $^{35}$ S]GTP $\gamma$ S binding assay ( $EC_{50}$  values:  $50-90$  nM). In the in vitro functional assays using CHO cells expressing human 5-HT2A receptors, cariprazine displayed antagonist activities, inhibiting the DOI-induced IP formation with an  $IC_{50}$  value of  $403$  nM.

## 4.1.2 Animal Behavioral Studies

### 4.1.2.1 Self-Administration studies

CSS evaluated two rat studies were submitted that evaluated the effect of cariprazine on cocaine self-administration and on the reinstatement of cocaine self-administration following extinction. These studies do not evaluate the self-administration of cariprazine itself.

#### 4.1.2.1.1

**Study Title:** “Effect of Cariprazine on Cocaine Self-Administration in Rats”

**Objectives:** The objective of this study was to determine whether cariprazine, a dopamine agonist, antagonist and partial agonist, alter the rate of self-administration of cocaine in rats.

**Methodology:** Rats were trained to self-administer cocaine (0.25 mg/0.1 ml/injection, i.v.) through lever pressing, using a fixed ratio of one (FR1). Prior to each session, a priming infusion of cocaine (0.5 mg) was given to each rat. Infusions were paired with the sound of the minipump and flashing house lights lasting 6 seconds, followed by a 10 second period of darkness. Typically, after 14 days of training, cocaine self-administration was considered to be stable when animals would self-administer at least 10 times/session for at least 3 consecutive days.

To determine if other drugs would affect cocaine self-administration, challenge sessions were conducted in which the dopamine antagonist, haloperidol (0.25 mg/kg), the dopamine agonist, 7-OH-DPAT (0.1 mg/kg), and the dopamine partial agonists, aripiprazole (0.3, 1.0, 3.0 mg/kg) and cariprazine (0.03, 0.10, 0.17, 0.30, 1.0 mg/kg) were administered orally 30 minutes prior to animal placement in the test cage. The protocol does not state whether a priming dose of cocaine was given before challenge sessions began.

**Results:** The results of the various study treatments are shown below in Table 1. Vehicle treatment did not alter self-administration. However, the dopamine antagonist, haloperidol (0.25 mg/kg) significantly increased cocaine self-administration while the dopamine agonist, 7-OH-DPAT (0.1 mg/kg) reduced cocaine self-administration. The dopamine partial agonists, aripiprazole (1.0, 3.0 mg/kg) and cariprazine (0.17, 0.30, 1.0 mg/kg) both increased self-administration of cocaine, suggesting they were acting as full antagonists in this test. The number of lever presses in Table 1 were estimated from the graphs provided in the study report.

**Table 1: Effect of vehicle, 7-OH-DPAT, haloperidol, aripiprazole and cariprazine on cocaine self-administration**

Pretreatment Compound	Dose (mg/kg, p.o.)	Lever-Presses for Cocaine
Vehicle	0	~20-21
7-OH-DPAT (agonist)	0.1	~12*
Haloperidol (antagonist)	0.25	~26*
Aripiprazole	0.3	~20
(partial agonist)	1.0	~26*
	3.0	~26*
Cariprazine	0.03	~20
(partial agonist)	0.10	~20
	0.17	~25*
	0.30	~28*
	1.00	~29*

**Sponsor Conclusions:** Cariprazine increases self-administration in rats, similar to the effects of a full dopamine antagonist (haloperidol) and a partial dopamine agonist (aripiprazole). Thus, cariprazine itself does not have abuse potential.

**CSS Conclusions:** In rats that have a stable history of cocaine self-administration and thus expect that lever-pressing will lead to cocaine receipt, administration of a drug with full or partial dopamine antagonist properties will block the effects of cocaine and therefore increase lever-pressing in an attempt to receive cocaine. This would be similar to the effects of increasing the FR schedule of reinforcement.

#### 4.1.2.1.2

**Study Title:** “Assessment of the Relapse Preventing Potential of Cariprazine in a Cue-Induced Reinstatement of Cocaine-Seeking Paradigm”

**Objectives:** The objective of this study was to determine whether the introduction of an abstinence period following stable self-administration of cocaine in rats would alter the effects of cariprazine or another dopamine partial agonist (aripiprazole) on cocaine self-administration.

**Methodology:** Rats were trained to self-administer cocaine (0.25 mg/0.1 ml/injection, i.v.) through lever pressing on a cocaine-associated lever, using a fixed ratio of one (FR1) in daily 2 hour sessions (4-6 times per week). A second lever in the cage did not produce a cocaine infusion when pressed. Prior to each session, a priming infusion of cocaine (0.5 mg) was given to each rat. Infusions were paired with the sound of the minipump and flashing house lights lasting 6 seconds, followed by a 10 second period of darkness. Typically, after 14 days of training, cocaine self-administration was considered to be stable when animals would self-administer at least 10 times/session for at least 3

consecutive days, infusions were equally distributed during the sessions and there was no more than 15% variation between sessions.

When cocaine self-administration was stable, self-administration sessions were suspended for 14-16 days so rats would undergo an abstinence period (to induce behavioral extinction). Rats were placed in a room different from the one used for training so there were no environmental cues associated with cocaine during the abstinence period. No data were provided regarding whether the abstinence procedures produced a significant reduction in cocaine self-administration in all animals used for the challenge sessions.

After 14-16 days of cocaine abstinence, rats were placed into the test chamber again for 30 minute challenge sessions (reinstatement paradigm) in which animals were pretreated orally with vehicle, aripiprazole (1, 3, 10 mg/kg) and cariprazine (0.1, 0.17, 0.30 mg/kg) 60 minutes before the animals were placed in the test cage. According to the study report, “all the conditions were the same as in the acquisition phase except that lever presses were not paired with cocaine infusions”. This suggests that although lever-pressing did not produce a cocaine reward, the animals still received a priming dose of cocaine prior to placement in the test cage, but this is not confirmed specifically. More importantly, if cocaine priming occurred, it is unclear if the dopamine partial agonists were administered before or after cocaine priming. This timing may affect the outcome of this study.

**Results:** As shown in Table 2 (below), both drugs (aripiprazole at 3 and 10 mg/kg, and cariprazine at 0.3 mg/kg) produced a significant reduction in lever-pressing on the cocaine-associated lever compared to placebo.

**Table 2: Effect of vehicle, aripiprazole and cariprazine on lever-pressing on cocaine-associated lever (no cocaine provided following abstinence)**

Pretreatment Compound	Dose (mg/kg, p.o.)	Lever-Presses on Cocaine-Associated Lever (no cocaine )
Vehicle	0	33.7
Aripiprazole	1.0	36.9
(partial agonist)	3.0	12.6*
	10.0	11.3*
Cariprazine	0.10	34.4
(partial agonist)	0.17	22.2*

**Sponsor Conclusions:** The Sponsor concludes that cariprazine is “able to attenuate cue-induced relapse to cocaine-seeking behavior in abstinent rats”. The Sponsor suggests that since schizophrenia and drug abuse are often comorbid, use of cariprazine could also prevent relapse in cocaine abusers who also have psychosis.

**CSS Conclusions:** As expected, a priming dose of cocaine is able to reinstate attempts at cocaine self-administration in rats that had undergone an abstinence (extinction) procedure, even though lever-pressing did not produce cocaine administration. However, pretreatment with dopamine partial agonists can block the effects of the cocaine priming dose, but only when the partial agonists are given at higher doses and are thus acting as antagonist against cocaine as a dopamine agonist. The study does not address whether cariprazine is self-administered itself or whether the drug blocks the inclination of a rat to self-administer cocaine when there is no priming dose but when lever-pressing does produce cocaine receipt. Thus, this study shows that cariprazine at higher doses acts as an antagonists against a cocaine challenge.

Notably, the reason that cariprazine increased lever-pressing for cocaine in the previous study but the same doses decreased it in this study has to do with the differences in the study procedures. Specifically, in the previous study, rats were still receiving cocaine in response to lever-pressing, while in the present study, they were not. Additionally, in the present study, the rats had undergone an extinction procedure.

### **Reference**

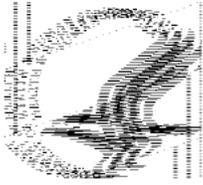
Citrome, L. Cariprazine: chemistry, pharmacodynamics, pharmacokinetics, and metabolism, clinical efficacy, safety, and tolerability, *Expert Opinion on Drug Metabolism & Toxicology* Feb 2013, Vol. 9, No. 2, Pages 193-206

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/s/  
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KATHERINE R BONSON  
08/13/2013

SILVIA N CALDERON  
08/13/2013



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**MEMORANDUM TO FILE**

**Date:** August 9, 2013

**From:** Amy M. Taylor, MD, MHS Medical Officer  
Pediatric and Maternal Health Staff

**Through:** Hari Cheryl Sachs, MD Acting OND Associate Director  
Pediatric and Maternal Health Staff

**NDA Number:** 204-370

**Sponsor:** Forest Research Institute

**Drug:** cariprazine

**Dosage form and route of administration:** capsule, oral

**Proposed Adult Indications:**

- Treatment of schizophrenia
- Treatment of manic or mixed episodes associated with bipolar I disorder

**Consult request:** The Division of Psychiatry Products requested PMHS' input on "all relevant section of the label."

**Background**

The applicant's NDA 204-370 is currently under review by the Division of Psychiatry Products for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. DPP request PMHS' assistance with the labeling language for subsection 8.4 Pediatric Use. The product has not been studied in pediatric patients.

**Current labeling (August 1, 2013)**

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

*Reviewer comment: The Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (Pediatric Labeling Guidance) states that:*

*“When substantial evidence does **not** exist to support an indication in **any** pediatric population, or the drug has not been studied in any pediatric population, the following statement (or a reasonable alternative) must be included (21 CFR 201.57(c)(9)(iv)(F)): “Safety and effectiveness in pediatric patients have not been established.” The basis for this statement should be provided (e.g., stating that studies have not been conducted or providing an explanation of why the available evidence does not support a pediatric approval).”*

*A statement should be added that the drug hasn’t been studied. The Division should confirm with the sponsor that there are no studies in pediatric patients that have not been reported. In addition, subsection 8.1 Pregnancy discusses neonatal withdrawal symptoms. The current labeling states:*

*Fetal/Neonatal Adverse Reactions*

*Monitor neonates (b) (4) extrapyramidal or withdrawal symptoms. (b) (4) agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in neonates exposed to antipsychotic drugs during the third trimester of pregnancy. These (b) (4) have varied in severity; (b) (4) prolonged hospitalization.*

*A brief statement on this topic should be included in the Pediatric Use subsection referring the reader to section 8.1 since the providers caring for the neonate will be pediatric providers.*

**Recommendations**

Subsection 8.4 Pediatric Use should contain the following language:

Safety and effectiveness in pediatric patients have not been established since pediatric studies of TRADENAME have not been conducted. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery [see *Use in Specific Populations (8.1)*]

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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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AMY M TAYLOR  
08/09/2013

HARI C SACHS  
08/12/2013

I am signing on behalf of Lynne P. Yao, Associate Director, Pediatric and Maternal Health Staff

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

**Label, Labeling and Packaging Review**

Date: July 30, 2013

Reviewer: Loretta Holmes, BSN, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Vraylar (Cariprazine Hydrochloride) Capsules  
1.5 mg, 3 mg, 4.5 mg, 6 mg (b) (4)

Application Type/Number: NDA 204370

Applicant: Forest Laboratories, Inc.

OSE RCM #: 2013-146

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

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# 1 INTRODUCTION

This review evaluates the proposed labels, labeling, and packaging for Vraylar (Cariprazine Hydrochloride), for areas of vulnerability that can lead to medication errors.

## 1.1 PRODUCT INFORMATION

Cariprazine Hydrochloride is a new molecular entity (NME). The following product information was provided in the November 19, 2012 submission.

- Active Ingredient: Cariprazine Hydrochloride
- Indication of Use: Treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder
- Route of Administration: Oral
- Dosage Form: Capsules
- Strengths: 1.5 mg, 3 mg, 4.5 mg, 6 mg (b) (4)
- Dose and Frequency of Administration:

**Schizophrenia:** The recommended dose range is (b) (4) once daily. Start with 1.5 mg (b) (4). Depending upon clinical response and tolerability, dose adjustments can be made upward or downward in 1.5 mg or 3 mg increments.

**Manic or Mixed Episodes Associated with Bipolar I Disorder:** The recommended dose range is (b) (4) once daily. Start with 1.5 mg on Day 1 and increase to 3 mg on Day 2. Depending upon clinical response and tolerability, dose adjustments can be made upward or downward in 1.5 mg or 3 mg increments.

**Dosage recommendation for patients initiating a strong CYP3A4 inhibitor when on a stable dose of Vraylar:** Dose should be reduced to one-half of the current dose. For patients taking 4.5 mg/day, the dose should be reduced to 1.5 mg or 3 mg/day. For patients taking 1.5 mg/day, the dosing regimen should be adjusted to every other day. When the CYP3A4 inhibitor is withdrawn, the Vraylar dose should then be increased. All dose modifications should be based on individual response and tolerability

**Dosage recommendation for patients initiating Vraylar therapy when already on a strong CYP3A4 inhibitor:** Patients should be administered 1.5 mg of Vraylar on Day 1 and on Day 3 with no dose administered on Day 2. From Day 4, depending upon clinical response and tolerability, the dose can be either maintained at 1.5 mg daily or increased by 1.5 mg/day up to a maximum daily dose of (b) (4). Some patients may require a dose of 1.5 mg every other day. When the CYP3A4 inhibitor is withdrawn, Vraylar dose should be reassessed, and subsequently modified based on individual response and tolerability

- How Supplied: See Table 1 and Table 2
- Storage: Store at 25°C (77°F); excursions permitted to 15°C and 30°C (to 59°F and 86°F)

- Container and Closure System: The 30-count and 90-count bottles have closures (b) (4).

<b>Table 1: Retail Packaging Configurations</b>	
<b>Capsule Strength</b>	<b>Package Configuration</b>
1.5 mg	Bottle of 30
	Bottle of 90
	Box of 100 (Hospital Unit Dose)
3 mg	Bottle of 30
	Bottle of 90
	Box of 100 (Hospital Unit Dose)
4.5 mg	Bottle of 30
	Bottle of 90
	Box of 100 (Hospital Unit Dose)
6 mg	Bottle of 30
	Bottle of 90
	Box of 100 (Hospital Unit Dose)

(b) (4)

<b>Table 2: Professional Sample Packaging Configurations</b>	
<b>Capsule Strength(s)</b>	<b>Package Configuration</b>
(1 x 1.5 mg) and (6 x 3 mg)	Carton containing one 7-count blister
1.5 mg	Carton containing one 7-count blister
3 mg	Carton containing one 7-count blister
4.5 mg	Carton containing one 7-count blister
6 mg	Carton containing one 7-count blister

(b) (4)

(b) (4)

## 2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following items submitted on November 19, 2012:

- Bottle labels, 30-count and 90-count (Appendix A)
- Hospital Unit Dose (HUD) blisters (Appendix B)
- Hospital Unit Dose carton labeling for HUD 100-count blisters (Appendix C)
- Professional sample blister cards, 7-count (Appendix D)
- Professional sample carton labeling for 7-count blister (Appendix E)
- [REDACTED] (b) (4) (Appendix F)
- [REDACTED] (b) (4) (Appendix G)
- Insert labeling submitted November 19, 2012 (no image)
- Actual samples of the product packaging received in February 2013

## 3 MEDICATION ERROR RISK ASSESSMENT

Our risk assessment of the Vraylar labels, labeling, and packaging is discussed in the following sections.

### 3.1 RISK ANALYSIS OF [REDACTED] (b) (4)

The Applicant initially proposed [REDACTED] (b) (4) (see Table 1 and Table 2).

In a labeling meeting with the Division of Psychiatry Products (DPP) and other disciplines held on April 19, 2013, we discussed our concerns regarding the [REDACTED] (b) (4) and questioned their necessity given the proposed dosage and administration of this product. Our safety concerns were as follows:

The Applicant proposed [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

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

(b) (4)

An information request (IR) was sent to the Applicant on May 17, 2013, requesting they provide the rationale for having (b) (4). According to the response from the Applicant, they will withdraw all of the (b) (4)

The following rationale was provided by the Applicant:

(b) (4)

We are concerned that the manner in which the Applicant proposes the (b) (4)

approval of this (b) (4). Therefore, DMEPA does not recommend approval of this (b) (4). Physicians will still have the ability (b) (4) dose for a patient by utilizing the 7-count professional sample blisters or providing the patient with a prescription.

### 3.2 RISK ANALYSIS OF LABELS AND LABELING

Our review of the labels and labeling determined they can be improved to increase the readability and prominence of important information as well as provide more clarity to promote the safe use of Vraylar.

## 4 CONCLUSIONS AND RECOMMENDATIONS

Our review of the labels and labeling has determined they can be improved to increase the readability and prominence of important information as well as provide more clarity to promote the safe use of the product. We do not recommend approval of the (b) (4)

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

### 4.1 COMMENTS TO THE DIVISION

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

A. (b) (4)

(b) (4)  
Therefore, we do not recommend its approval.

#### 4.2 COMMENTS TO THE APPLICANT

We advise the following recommendations are implemented prior to approval of this application.

##### A. All Bottle Labels, (b) (4) and Carton Labeling

1. The word “Tradename” is used as a placeholder in the proposed proprietary name location. Revise all labels and labeling to reflect the conditionally approved name for this product, Vraylar. Ensure the name is presented in title case.
2. The graphic located at the end of the proprietary name is too prominent and too close to the proprietary name. Minimize and relocate or remove the graphic so it does not compete with the proprietary name, established name, or strength.
3. Debold the “Rx Only” statement.
4. Debold the company (b) (4) name. Ensure the company (b) (4) name do not compete for attention with the proprietary name, established name, and strength.
5. (b) (4)

##### B. Retail Bottle Labels

Debold the net quantity statement and relocate it away from the center portion of the principal display panel (PDP). Consider locating the statement lower on the PDP and either left or right justified to ensure the net quantity statement does not compete for attention with the statement of strength. In addition, decrease the size of the net quantity statement on the 90-count bottles. Ensure the statement is not larger than the statement of strength.

##### C. Hospital Unit Dose Blisters

1. The established name is difficult to read because of the (b) (4). Use a (b) (4) to improve the readability of the established name.
2. There is inadequate strength differentiation between the various strengths of blisters. Utilize boxing, color, or other means to ensure adequate strength differentiation.

##### D. Hospital Unit Dose Carton Labeling

The net quantity statement lacks clarity. Revise the statement to read:  
100 capsules (10 x 10-count blister cards)

##### E. Professional Sample 7-count Blister Cards

The blister cards lack instructions for capsule removal. Consider adding instructions for capsule removal on the blister cards.

F. Professional Sample Carton Labeling (for the 7-count blister cards)

1. The statement of strength on the carton labeling for the 7-count (1 x 1.5 mg capsule and 6 x 3 mg capsules) blisters is confusing because the strengths are placed directly adjacent to one another. Revise the statement of strength to read “1.5 mg and 3 mg” ( (b) (4) ) to help minimize the potential for confusion.
2. The 7-count (1 x 1.5 mg capsule and 6 x 3 mg capsules) blister carton does not contain instructions for use (i.e. which capsule to start with first). This information should be added. The staggered layout of the tablet rows is also confusing. Consider realigning the tablets in straight rows in order to facilitate correct selection of the first 1.5 mg dose.
3. The 7-count 1.5 mg, 3 mg, 4.5 mg, and 6 mg blisters do not state “per capsule” in the statement of strength. Revise the statement of strength to read “XX mg per capsule”.
4. The net quantity statement (i.e., “7 capsules”) and product website address (i.e., “visit [www.tradename.com](http://www.tradename.com)”) are too prominent. Debold the net quantity statement and the website address.

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

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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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LORETTA HOLMES  
07/30/2013

IRENE Z CHAN  
07/31/2013

SCOTT M DALLAS  
08/01/2013

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: July 23, 2013

TO: Kimberly Updegraff, Regulatory Project Manager  
Francis Becker, M.D., Medical Officer  
Robert Levin, M.D., Clinical Team Leader  
Division of Psychiatry Products

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

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader  
Kassa Ayalew, M.D., Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 204-370

APPLICANT: Forest Laboratories, Inc.

DRUG: Cariprazine (RGH-188, no trade name)

NME: Yes

INDICATION: Treatment of schizophrenia or acute mania associated with bipolar disorder

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: December 21, 2012

INSPECTION SUMMARY GOAL DATE: July 31, 2013

REGULATORY ACTION GOAL DATE: November 19, 2013

PDUFA DUE DATE: November 19, 2013

## I. BACKGROUND

This original NDA for cariprazine supports two separate indications for cariprazine: schizophrenia and bipolar I disorder in manic or mixed episode (bipolar mania). Each indication is supported by three pivotal phase 3 studies: RGH-MD-04, RGH-MD-05, and RGH-MD-16 for schizophrenia; and RGH-MD-31, RGH-MD-32, and RGH-MD-33 for bipolar mania. Cariprazine was developed under IND 71958 (2005 filing) for schizophrenia, and under IND 77726 (2007 filing) for bipolar mania. Cariprazine is a potent orally active dopamine agonist with high selective affinity for the D3 receptor, making it a promising agent for either psychiatric indication (enhanced cognition, improved negative symptoms, and mood stabilization) with relatively few cardiovascular or metabolic adverse effects.

### Two Indications for Use

*Schizophrenia* is a lifelong, disabling disorder with a worldwide prevalence of 1%. The disorder usually manifests during adolescence or in young adulthood. Its major symptoms fall into three groups: positive symptoms (delusions and hallucinations), negative symptoms (lack of drive and social withdrawal), and cognitive symptoms (problems with attention and memory). Patients are also at increased risk for physical comorbidities, including diabetes, metabolic syndromes, and cardiovascular disease. Currently, atypical antipsychotics (aripiprazole, risperidone, olanzapine, quetiapine, ziprasidone, and paliperidone) are typically used as first-line agents, but their use has been limited by frequent adverse effects and/or treatment resistance. Cariprazine may be more effective than currently available agents; in pivotal studies, its efficacy in schizophrenia is supported by a decrease in Positive and Negative Syndrome Scale (**PANSS**) score by 2-9 points after 6 weeks of once daily oral dosing at 1.5-12 mg.

*Bipolar disorder* is thought to result from dysregulation of dopamine neurotransmission. According to one model, increased dopaminergic signaling induces bipolar mania, and decreased signaling (and compensatory up-regulation of D3 receptors) induces bipolar depression. In humans, stimulants that increase dopamine production (amphetamine, methylphenidate, and cocaine) induce hyperactivity and other clinical effects that closely resemble bipolar mania. Mesolimbic dopaminergic pathways are believed to control motivation and reward behaviors, and hypofunction of this system is implicated in the loss of motivation and anhedonia (core symptoms of depression). Cariprazine appears to be safe and effective in treating bipolar mania; in pivotal studies, its efficacy is supported by a decrease in Young Mania Rating Scale (**YMRS**) score by 1-5 points after three weeks of once daily oral dosing at 1.5-12 mg.

*Cariprazine safety profile* in clinical trials to date has been comparable with that of atypical antipsychotics. No major safety concerns have been identified, including concerns about QT prolongation, prolactin elevation, or increased sedation. Increased aminotransferase levels were transient and other laboratory tests were minimally abnormal. Elevated creatine phosphokinase (CPK), a commonly seen laboratory abnormality for cariprazine (and other antipsychotic medications), typically has not been clinically significant. Asian recipients may be exposed to increased levels of cariprazine and its metabolites (25% higher  $C_{max}$  and  $AUC_{0-24}$ ), an observation currently thought not to be clinically important. Akathisia and extrapyramidal symptoms (**EPS**) were common but have been readily manageable. At present, modest weight gain with increased glucose and lipids seen in longer-term (> 6 weeks) studies appears to be the only significant long-term safety concern. In support of this NDA review, five cariprazine pivotal studies were identified for good clinical practice (**GCP**) inspection (three for schizophrenia, two for bipolar mania).

### Major Pivotal Studies in Schizophrenia

The three pivotal schizophrenia Studies RGH-MD-04, RGH-MD-05, and RGH-MD-16 shared the same study objective and the overall study design. All were phase 3, randomized, controlled, double-blind studies with the same subject selection criteria and major study endpoints. Specifically:

- The primary study objective was to evaluate the efficacy, safety, and tolerability of cariprazine relative to placebo in patients with acute exacerbation of schizophrenia.

- All were 9-week studies consisting of three study periods: (1) washout and screening ( $\leq 7$  days), (2) double-blind treatment (6 weeks), and (3) safety follow-up (2 weeks).
- Subjects were hospitalized for screening and for at least the first 4 weeks of the double-blind treatment, after which eligible subjects could be discharged.
- Subjects completing 6 weeks of double-blind treatment were eligible to enter the open-label extension study (Study RGH-MD-11).

### Subject Selection

- Men or women (age 18-60 years) with schizophrenia, screening evaluation by Structured Clinical Interview (**SCI**) and confirmation of:
  - DSM-IV-TR criteria for schizophrenia
  - PANSS score  $\geq 80$  and  $\leq 120$
- At screening and at baseline evaluations (Visits 1 and 2): Rating score  $\geq 4$  (moderate) on  $\geq 2$  of the following 4 PANSS positive symptoms: delusions, hallucinatory behavior, conceptual disorganization, and suspiciousness/persecution

### Major Endpoints

- Efficacy: Change from baseline to Week 6 in PANSS total score (primary) and Global Impressions-Severity (**CGI-S**) score (major secondary)
- Safety: Adverse event (**AE**) monitoring, laboratory tests (hematology, chemistry, urinalysis, and prolactin), vital signs, electrocardiograms (**ECG**), physical (including ophthalmologic) examinations, and safety scales
- Safety scales: Columbia–Suicide Severity Rating Scale (**C-SSRS**), EPS, Barnes Akathisia Rating Scale (**BARS**), Abnormal Involuntary Movement Scale (**AIMS**), and Simpson Angus Scale (**SAS**)

The study title and other study features not common to the three pivotal schizophrenia studies are described further below, separately for each study.

#### Study RGH-MD-04

*A Double-blind, Placebo and Active-Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia*

This was a randomized, double-blind, active and placebo-controlled fixed-dose study conducted over 20 months (Apr 2010 to Dec 2011) in 153 adult subjects at 58 international study sites: US (20), Romania (12), Russia (14), and Ukraine (12).

### Treatment Groups

Subjects were randomized in equal ratio to 4 groups (once daily oral dosing): (1) placebo, (2) cariprazine 3 mg, (3) cariprazine 6 mg, or (4) aripiprazole 10 mg.

### Major Findings

- For baseline to Week 6, statistically significant improvements were seen for both cariprazine treatment groups (relative to placebo) for PANSS and CGI-S scores. The efficacy effect size was greater for cariprazine 6 mg than for cariprazine 3 mg.
- Cariprazine was generally well tolerated. However, AEs appeared to be increased for cariprazine, particularly at the higher (6 mg) dose. Serious AEs (**SAEs**) were more common for cariprazine 6 mg and aripiprazole (3% each) than for cariprazine 3 mg or placebo (1% each).

- Increased CPK was more common for cariprazine (3 mg, 18%; 6 mg, 22%) and aripiprazole (18%) than for placebo (10%).
- Increased incidence of akathisia was more common for cariprazine (3 mg, 7%; 6 mg, 15%) and aripiprazole (7%) than for placebo (5%).
- There were two deaths, both in cariprazine 6 mg group: completed suicide and cardiac arrest following ischemic stroke. Both deaths were classified as being unlikely to be related to the study medication (without good rationale for this classification).

#### Study RGH-MD-05

#### *A Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia*

This was a randomized, double-blind, placebo-controlled, fixed and flexible-dose study conducted over 20 months (April 2010 - Dec 2011, in parallel with Study RGH-MD-04) in 147 adult subjects at 41 international study sites: US (15), Colombia (4), India (19), and South Africa (3).

#### **Treatment Groups**

Subjects were randomized in equal ratio to three groups (once daily oral dosing): (1) placebo, (2) cariprazine 3-6 mg, or (3) cariprazine 6-9 mg.

- Dosing will begin at randomization (Visit 2, at bedtime, option to switch to morning dosing per subject and/or investigator discretion) at the low margin of the assigned dose range.
- At Visit 4 (after 2 weeks of treatment), the dose will be increased to the high margin for inadequate responders (< 20% improvement in PANSS total score and CGI-S score  $\geq$  4): additional 1.5 mg (one capsule) for 2 days (Days 14 and 15), followed by additional 3 mg (two capsules) thereafter (final dose level, high margin of dose range).
- The dose will be fixed after 3 weeks of treatment, except for temporarily holding the drug for a period of one to 3 days for tolerability as part of AE management.
- Lorazepam may be given as concomitant medication, provided that the dose does not exceed (total per day) 6 mg during washout through Day 7, 4 mg from Days 8 through 14, and 2 mg thereafter.

#### **Major Findings**

- For baseline to Week 6, statistically significant improvements were seen for both cariprazine treatment groups (relative to placebo) for PANSS and CGI-S scores.
- The efficacy of cariprazine treatment appeared to be dose-dependent. Greater efficacy effect was seen for cariprazine 6 mg than for cariprazine 3 mg.
- Cariprazine was generally well tolerated. However, AEs appeared to be increased for cariprazine, particularly at the higher (6-9 mg) dose:
  - Laboratory: (1) increased CPK levels were seen more commonly for cariprazine (3-6 mg, 22%; 6-9 mg, 23%) than for placebo (9%), and (2) greater mean increase in alanine aminotransferase (**ALT**) was seen for cariprazine (5.0 U/L, 3-6 mg; 13.5 U/L, 6-9 mg) than for placebo (1.3 U/L). Greater mean increase in aspartate aminotransferase (**AST**) was seen for cariprazine (2.8 U/L, 3-6 mg; 4.6 U/L, 6-9 mg) than for placebo (0.7 U/L).
  - Clinical: (1) increased incidence of akathisia was more common for cariprazine (3-6 mg, 16%; 6-9 mg, 17%) than for placebo (3%), and (2) increased incidence of EPS was also more common for cariprazine (3-6 mg, 5%; 6-9 mg, 10%) than for placebo (2%).

### Study RGH-MD-16

#### *Evaluation of the safety and efficacy of RGH-188 in the acute exacerbation of schizophrenia*

This was a randomized, double-blind, placebo-controlled, fixed and flexible-dose study conducted over 14 months (Jun 2008 - Aug 2009) in 147 adult subjects at 65 international centers: US (18), India (16), Russia (15), Ukraine (11), and Malaysia (5).

#### **Treatment Groups**

Subjects were randomized in equal ratio to three groups (once daily oral dosing): (1) placebo, (2) cariprazine 3-6 mg, or (3) cariprazine 6-9 mg.

- Dosing will begin at randomization (Visit 2, at bedtime, option to switch to morning dosing per subject and/or investigator discretion) at the low margin of the assigned dose range.
- At Visit 4 (after 2 weeks of treatment), the dose will be increased to the high margin for inadequate responders (< 20% improvement in PANSS total score and CGI-S score  $\geq$  4):
  - Additional 1.5 mg (one capsule) for 2 days (Days 14 and 15), followed by
  - Additional 3 mg (two capsules) thereafter (final dose level, high margin of dose range).
- The dose will be fixed after 3 weeks of treatment, except for temporarily holding the drug for a period of one to 3 days for tolerability as part of AE management.

#### **Major Findings**

- From baseline to Week 6, statistically significant improvements were seen for all cariprazine and risperidone treatment groups (relative to placebo) for PANSS and CGI-S scores.
- Cariprazine was generally well tolerated. AEs appeared to be increased for cariprazine and risperidone.
  - Mean changes were small and similar among treatment groups.
  - Relative to placebo, a slightly greater increase in ALT, insulin, and CPK was observed in the cariprazine treatment groups.
  - For ALT and CPK, the increase was larger for higher dosages of cariprazine.
  - Increased incidence of akathisia was more common for cariprazine and risperidone (each ~9%) than for placebo (~5%).
  - Increased incidence of EPS was also more common for cariprazine and risperidone (each ~12%) than for placebo (~5%).

#### Major Pivotal Studies in Bipolar Mania

The two pivotal bipolar mania Studies RGH-MD-32 and RGH-MD-33 shared the same study objective and the overall study design. Both were phase 3, randomized, controlled, double-blind studies with the same subject selection criteria and major study endpoints.

- The primary objective was to evaluate the efficacy, safety, and tolerability of cariprazine monotherapy versus placebo for the treatment of acute mania or mixed episodes associated with bipolar I disorder.
- The 6-week studies consisted of three study periods: washout and screening ( $\leq$  7 days), double-blind treatment (3 weeks), and safety follow-up (2 weeks).
- Subjects were hospitalized for screening and for at least the first two weeks of double-blind treatment, after which eligible subjects were discharged (and rehospitalized) as clinically appropriate.

## Subject Selection

- Men or women with bipolar I disorder, manic/mixed phase, per DSM-IV-TR criteria: Study RGH-MD-32, age 18-60 years; Study RGH-MD-33, age 18-65 years
- YMRS score  $\geq 20$  and a score of at least 4 on two of the following YMRS items: irritability, speech, content, and disruptive/aggressive behavior.

## Major Endpoints

- Efficacy: Change from baseline to Week 3 in YMRS (primary) and CGI-S (major secondary) scores
- Safety: AE monitoring, laboratory tests (hematology, chemistry, urinalysis, prolactin), vital signs and physical examinations, ECG, C-SSRS, EPS, BARS, AIMS, and SAS

The study title and other study features not common between the two pivotal bipolar mania studies are described further below, separately for each study.

### Study RGH-MD-32

*A Double-blind, Placebo-controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients with Acute Mania Associated with Bipolar I Disorder*

This is a randomized, double-blind, placebo-controlled, flexible-dose study conducted over 17 months (Feb 2010 - Jul 2011) in 312 subjects at 28 study sites, 10 in US and 18 in India.

## Treatment Groups

Subjects were randomized in equal ratio to two groups (once daily oral dosing): (1) placebo, or (2) cariprazine 3-12 mg.

- Dosing will begin at randomization (Visit 2, at bedtime, option to switch to morning dosing per subject and/or investigator discretion) at the low margin of the assigned dose range.
- When switching from evening to morning dosing, at least 24 hours should elapse between successive doses; frequent switching is discouraged. For inadequate response:
  - On Day 2: The dose may be increased (based on investigator judgment about treatment response) by 3 mg (one capsule) to 6 mg for 2 days.
  - At Visit 3 (Day 4): For  $< 50\%$  improvement in YMRS from Visit 2 to 3, the dose may be increased again to either 6 or 9 mg (depending on previous dose level).
  - Similarly, at Visits 4, 5, and 6: For  $< 50\%$  improvement in YMRS total score, the dose may be increased again to 6, 9, or 12 mg (depending on previous dose level).
- The dose may be decreased to the previous level at anytime for tolerability in decrements of 3 mg. The dose may also be temporarily held for one to 3 days.
- Dose adjustment is not permitted after Visit 6 (Day 14), except for temporarily holding the drug for one to 3 days for tolerability.

## Major Findings

- For baseline to Week 3, statistically significant improvements were seen for cariprazine (relative to placebo) in YMRS score ( $p = 0.0004$ ) and in CGI-S score ( $p = 0.0027$ )
- AEs appeared to be increased for cariprazine.
  - Akathisia and EPS were more common for cariprazine (22 and 15%, respectively) than for placebo (5 and 2%, respectively).

- Mean changes in laboratory values were small and similar among treatment groups.
- Relative to placebo, a slightly greater increase in ALT and fasting glucose were observed for cariprazine.
- ECGs were similar for both groups. Mean ventricular rate in the cariprazine group increased 7 bpm, compared with two bpm for placebo. One subject in the placebo group had a potentially clinically significant increase in QTcB interval (> 500 msec).

### Study RGH-MD-33

#### *A Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients with Acute Mania Associated with Bipolar I Disorder*

This was a randomized, double-blind, placebo-controlled, fixed and flexible-dose study conducted over 22 months (Feb 2010 - Dec 2011) in 497 subjects at 65 study sites: US (23), Ukraine (14), Romania (10), Russia (9), Serbia (5), and Croatia (4).

### **Treatment Groups**

Subjects were randomized in equal ratio to three groups (once daily oral dosing): (1) placebo, (2) cariprazine 3-6 mg, and (3) cariprazine 6-12 mg.

- Dosing will begin at randomization (Visit 2, at bedtime, option to switch to morning dosing per subject and/or investigator discretion) at the low margin of the assigned dose range.
- When switching from evening to morning dosing, at least 24 hours should elapse between successive doses; frequent switching is discouraged. For inadequate response:
  - Visit 3 (Day 3): for < 50% improvement in YMRS from Visit 2 to 3, the dose may be increased to either 4.5 or 9 mg (depending on previous dose level)
  - Visits 4, 5, and 6: similarly as at Visit 3, to 4.5 mg, 9 mg, or 12 mg for < 50% improvement in YMRS total score.
- The dose may be decreased to the previous level at anytime for tolerability in decrements of 3 mg. The dose may also be temporarily held for one to 3 days.
- Dose adjustment is not permitted after Visit 6, except for temporarily holding the drug for one to 3 days for tolerability.

### **Major Findings**

- For baseline to Week 3, statistically significant improvements were seen for both cariprazine groups (relative to placebo) in YMRS and CGI-S scores ( $p < 0.001$  for both)
- Cariprazine was generally well tolerated. Subjects withdrew due to AEs (most commonly akathisia or mania) more frequently for cariprazine (9% 3-6 mg, 15% 6-12 mg) than for placebo (5%). One subject in the cariprazine 3-6 mg group died from pulmonary embolism 9 days after the last dose.
  - Rates of akathisia were 4% placebo, 17% cariprazine 3-6 mg, and 22% cariprazine 6-12 mg, and rates of EPS were 5% placebo, 10% cariprazine 3-6 mg, and 7% cariprazine 6-12 mg.
  - Mean changes in laboratory values were small and similar among treatment groups. Relative to placebo, a slightly greater increase in ALT and fasting glucose were observed for cariprazine.
  - ECGs were similar for both groups. Mean ventricular rate in the cariprazine groups increased 3-7 bpm, compared with no increase for placebo.
  - One subject in each of placebo and cariprazine 6-12mg groups had a potentially clinically significant increase in QTcB interval (> 500 msec).

## II. INSPECTIONS

Five studies were audited at 9 sites to support the review of this NDA for a new molecular entity (NME) with two clinical indications, as shown below.

- The clinical investigator (CI) sites were selected based on: (1) multiple studies at each site, (2) adequate representation of the 5 studies to be audited for both indications, (3) high subject enrollment, and (4) remote or no FDA inspection history.
- The sites in Ukraine were selected also for their large differences from US sites in the primary efficacy results (3-fold greater) to investigate and exclude biased study conduct. The efficacy response at foreign sites (> 60% of total enrollment) were about 2-fold greater than at US sites.

### Five Studies Audited at Nine Inspections for NDA 204-370

	Inspected Entity	Studies, Sites, Subject Enrollment	Inspection Outcome
1	Robert E. Litman, M.D. Rockville, MD	RGH-MD-05, Site 44, 24 subjects RGH-MD-16, Site 07, 20 subjects RGH-MD-33, Site 06, 18 subjects	January 14 - 29, 2013 NAI
2	Barbara A. Burtner, M.D. Kissimmee, FL	RGH-MD-05, Site 41, 27 subjects RGH-MD-16, Site 01, 29 subjects RGH-MD-33, Site 02, 18 subjects	February 25 - March 20, 2013 VAI
3	Franco Sicuro, M.D. Creve Coeur, MO	RGH-MD-04, Site 17, 14 subjects RGH-MD-16, Site 10, 20 subjects RGH-MD-32, Site 03, 26 subjects	January 28 - February 1 & July 1 - 3, 2013 Pending (preliminary NAI)
4	Kenneth N. Sokolski, M.D. Costa Mesa, CA	RGH-MD-05, Site 48, 28 subjects RGH-MD-16, Site 19, 15 subjects RGH-MD-33, Site 10, 27 subjects	January 24 - March 8, 2013 VAI
5	Joseph A. Kwentus, M.D. Flowood, MS	RGH-MD-04, Site 07, 16 subjects RGH-MD-16, Site 20, 24 subjects RGH-MD-32, Site 01, 15 subjects	March 4 - 18, 2013 Pending (preliminary OAI)
6	Svitlana Moroz, M.D., Ph.D. Dnipropetrovsk, Ukraine	RGH-MD-04, Site 205, 9 subjects RGH-MD-16, Site 606, 18 subjects RGH-MD-33, Site 308, 7 subjects	March 11 - 15, 2013 VAI
7	Volodymyr Abramov, M.D., Ph.D. Donetsk, Ukraine	RGH-MD-04, Site 200, 8 subjects RGH-MD-16, Site 601, 15 subjects RGH-MD-33, Site 301, 6 subjects	March 18 - 22, 2013 NAI
8	Yuliya Blazhevych, M.D. Kyiv, Ukraine	RGH-MD-04, Site 201, 18 subjects RGH-MD-16, Site 602, 13 subjects RGH-MD-33, Site 303, 4 subjects	March 4 - 8, 2013 Pending (preliminary NAI)
9	Forest Laboratories, Inc. Jersey City, NJ	RGH-MD-04, RGH-MD-05, RGH-MD-16, RGH-MD-32, and RGH-MD-33	January 22 - February 21, 2013 VAI

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

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

**1. Robert E. Litman, MD**

- a. What was inspected: Compliance with study protocols, good clinical practice (**GCP**) regulations, and standard operating procedures (**SOPs**)
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
  - Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records as follows:
    - RGH-MD-05 (Site 44): 39 subjects were screened, 24 were enrolled, and 14 completed the study. All subject records were reviewed, including complete review for 9 enrolled subjects.
    - RGH-MD 16 (Site 07): 33 subjects were screened, 20 were enrolled, and 10 completed the study. All subject records were reviewed, including complete review for 5 subjects completing study.
    - RGH-MD 33 (Site 06): 27 subjects were screened, 18 were enrolled, and 9 completed study. All subject records were reviewed, including complete review for 4 enrolled subjects.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data matched among source records, CRFs, and NDA data listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

**2. Barbara A. Burtner, MD**

- a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
  - Records review: sponsor and IRB monitoring, financial disclosures, test article accountability, and subject records. Records for all enrolled subjects were reviewed in detail.
    - RGH-MD-05 (Site 41): 38 subjects screened, 27 enrolled, and 16 completed study
    - RGH-MD 16 (Site 01): 40 subjects screened, 29 enrolled, and 21 completed study
    - RGH-MD 33 (Site 02): 32 subjects screened, 18 enrolled, and 16 completed study
- b. General observations and comments:
- A Form FDA 483 was issued for the following deficiencies:
    - Study RGH-MD-05
      - Exclusion criterion, intraocular pressure (**IOP**) > 21 mm Hg: Subject 041-0509 with IOP of 23 mm Hg in both eyes was randomized and completed the study.
      - Not reporting AEs to the sponsor (not reported on CRFs): Subject 041-0510, worsening elevated CPK levels from baseline (802 IU/L) to Visit 6 (2133 IU/L) and increased IOP at Visit 8 (30 mmHg OD and 25 mmHg OS).

- Randomization: The study protocol specifies that the first subject to be randomized at each study center is to be assigned the lowest (available) number in the randomization sequence, and each subsequent subject is to be assigned the next number. For 3 subjects, the numbers were not in ascending sequential order.
- Data entry into electronic case report files without supporting documentation (employment of responsible lead study coordinator terminated); late informed consent for CYP2D6 genotyping for 5 subjects

Study RGH-MD 16

- For two subjects, BARNES, AIMS, and SAS evaluation instruments were administered by unqualified (not certified) study personnel.
- The following AEs were not reported to the sponsor (on CRFs) and were not captured in the NDA. The IRB remained unaware of these AE reporting violations.
  - Elevated CPK levels (IU/L), three subjects, typically worsening over time:
    - Subject 0011608: 65 (baseline), 697 (Visit 6), 369 (Visit 8)
    - Subject 0011611: 156 (baseline), 1968 (Visit 4)
    - Subject 0011614: 163 (baseline), 833 (Visit 8)
  - ECG abnormal for first degree atrioventricular block, two subjects: Subject 001-1611 (Visit 4) and Subject 001-1625 (Visit 8)
  - Weight gain of ~ 20 lbs: Subjects 0011613, 0011620, and 0011631
  - Agitation, one subject: Subject 001-1632, two episodes requiring treatment with an anxiolytic (lorazepam) at doses above the protocol-specified dose limit

Study RGH-MD 33

- For 3 subjects, BARNES, AIMS, and SAS administered by uncertified staff
  - Exclusion criterion: The study protocol specifies exclusion of men for QTc  $\geq$  450 msec (Fredericia correction, screening ECG) to be excluded. Subject 0023324 with a value of 452 was randomized (completed study).
  - Elevated CPK for Subjects 0023301 and 0023322 were not reported to the sponsor (not captured as AEs in the NDA). The IRB remained unaware of the AE underreporting.
  - Other than as noted above, no significant deficiencies were observed for all three studies. All subjects signed the informed consent document. IRB oversight and study monitoring appeared adequate. Source records appeared factual and complete. Endpoint data matched among source records, CRFs, and NDA data listings. All raters were certified and evidence of unblinding was not observed. Drug accountability was well documented.
  - The clinical investigator's response to the Form FDA 483 outlined the corrective actions to be implemented (March 11, 2013 implementation date) to prevent the recurrence of the inspectional findings.
- c. Assessment of data integrity:
- Although many deficiencies were observed for all three studies conducted at this site, the deficiencies were typically minor in seriousness and appear unlikely to have significantly affected the overall study outcome. Data from this study site appear reliable.

### 3. Franco Sicuro, MD

- a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
  - Records review: sponsor and IRB monitoring, financial disclosures, and drug accountability, and subject records. All subject records were reviewed, including detailed review for all enrolled subjects and complete review for all subjects completing study.
    - RGH-MD-04 (Site 17): 27 subjects screened, 14 enrolled, and 14 completed study
    - RGH-MD 16 (Site 10): 34 subjects screened, 20 enrolled, and 8 completed study
    - RGH-MD 32 (Site 03): 42 subjects screened, 26 enrolled, and 22 completed study

- b. General observations and comments:

No significant deficiencies were observed or discussed. A Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records appeared complete and matched corresponding CRFs. Endpoint data matched among source records, CRFs, and NDA data listings.

- c. Assessment of data integrity: Data from this site appear reliable.

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

### 4. Kenneth N. Sokolski, MD

- a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
  - Records review: sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records:
    - RGH-MD-05 (Site 48): 47 subjects screened, 28 enrolled, and 15 completed study; all subject records reviewed in detail, to include complete review for 7 enrolled subjects
    - RGH-MD 16 (Site 19): 20 subjects screened, 15 enrolled, and 11 completed study; all subject records reviewed in detail, to include complete review for 5 enrolled subjects
    - RGH-MD 33 (Site 10): 50 subjects screened, 27 enrolled, and 18 completed study; all subject records were reviewed in detail, to include complete review for 7 enrolled subjects

- b. General observations and comments:

- A Form FDA 483 was issued for the following deficiencies:

Study RGH-MD-05

- Subject 048-0526, exclusion for 22 IOP  $\geq$  21 mm Hg: IOP of 21 mm HG (OS)
- Subject# 048-0529, exclusion for posterior subcapsular cataract with a severity score  $>$  0.5 using the Lens Opacities Classification System III (**LOCS III**): LOCS III of 1.9 (OS)
- For three subjects (048-0520, 048-0523, and 048-0525), the study drug dose was increased at Visit 4 despite adequate treatment response (CGI-S score 3).

- Lorazepam may be given provided that the dose does not exceed (total per day) 6 mg during washout through Day 7, 4 mg from Days 8 through 14, and 2 mg thereafter.  
Four subjects were given excessive doses after Day 14:
  - Subject 048-0505: 3 mg once
  - Subject 048-0512: 3 mg five times, 4 mg once, and 5 mg once
  - Subject 048-0531: 4 mg twice
  - Subject 048-0540: 4 mg twice
- Prohibited medications: Subject 048-507 (clonidine) and Subject 048-0515 (compazine)
- For seven subjects, PK samples were not collected according to the protocol:
  - Subjects 048-0501, 048-0503, 048-0504, 048-0510, and 048-0518):  
Visit 4 PK samples were collected later (up to 8 hours) than the time point specified in the study protocol (four hours after dosing).
  - Subjects 048-0501 and 048-0540: Visit 6 PK samples were collected earlier (up to 12 hours) than the time point specified in the study protocol (5 to 10 minutes prior to dosing).
- Data discrepancies for CGI scores between source records and CRFs:
  - Subject 048-0512, Visit 1, CGI-S: source 4 (moderately ill), CRF 5 (markedly ill)
  - Subject 048-0530, Visit 7, CGI-S: source 5 (markedly ill), CRF 4 (moderately ill)
  - Subject 048-0532, Visit 7, CGI-I: source 3 (minimally improved), CRF 4 (no change)

#### Protocol RGH-MD-16

- Lorazepam may be given provided that the dose does not exceed (total per day) 6 mg during washout through Day 7, 4 mg from Days 8 through 14, and 2 mg thereafter. After treatment Day 14, two subjects were given Lorazepam at doses above the total allowable daily limit:
  - Subject 019-1614: 3 mg once
  - Subject 019-1618: 3 mg seven times (seven different days)
- Subject 019-1614 was given prohibited medications (on the day of study drug dosing): Diflucan 150 mg, Seroquel 300 mg, and Depakote 1000 mg.

#### Protocol RGH-MD-33

- Subjects 010-3303 and 010-3305 did not meet inclusion criterion 9, which states that a body mass index (**BMI**) must be between 18 and 40.
  - Subject 010-3303: BMI measurement of 40.2 kg/m<sup>2</sup> on Visit 2
  - Subject 010-3305: BMI measurement of 41.2 kg/m<sup>2</sup> on Visit 2
- Subject 010-3319 was not excluded despite prior clonidine therapy (prohibited medication) and continued clonidine therapy during the study.
- Subject 010-3349 did not meet inclusion 4 on Visit 2, which states that the YMRS total score must be  $\geq 20$  with a score of at least 4 on two YMRS items for irritability, speech, content, and disruptive or aggressive behavior. This subject had a score of at least a 4 on only one of the protocol-specified YMRS items (speech score of 5).
- Lorazepam may be given provided that the dose does not exceed (total per day) 6 mg during washout through Day 7, 4 mg from Days 8 through 14, and 2 mg thereafter. Four subjects were given prohibited doses of Lorazepam.
  - Subject 010-3314: 3 mg twice and 4 mg twice after Day 14
  - Subject 010-3320: 5 mg on Day 9 and 4 mg/day for five consecutive days after Day 14

- Subject 010-3334: 4 mg twice and 6 mg/day for three consecutive days after Day 14
- Subject 010-3339: 5 mg on Day 12
- Four subjects were given prohibited medications:
  - Subject 010-3301: diphenhydramine 125 mg (five consecutive days)
  - Subject 010-3319: clonidine 0.1 mg (ten consecutive days)
  - Subject 010-3316: fluconazole 150 mg (once)
  - Subject 010-3347: diphenhydramine 150 mg (once)
- Data discrepancies for AEs between source records and CRFs:
  - Subject 010-3301, AE of increased agitation: source records note moderate severity, CRF notes mild severity
  - Subject 010-3323, AEs of sedation, nausea and weight gain: source records note reasonable possibility of being treatment-related, CRF notes not treatment-related
- The following deficiency observations were verbally discussed and not cited on Form FDA 483 (inspector discretion):

Study RGH-MD-05

- Subject 048-0540, AE reporting: Elevated CK values of 211 U/L (Visit 4) and 669 U/L (Visit 6) were deemed clinically not significant and were not reported as AEs
- Subject 048-0525, drug accountability: The study records showed that this subject took 70 capsules and returned 27, and did not account for 3 of the 100 capsules originally dispensed.

Study RGH-MD-33

- Subject 010-3301, Visit 1, C-SSRS: source document notes Intensity of Ideation score of 3, NDA data listing shows a score of 1, score not shown on CRF
  - Subject 010-3331, Visit 1, C-SSRS: source document notes Suicidal Behavior as "no," CRF shows "yes."
  - The following elevated CK values were deemed clinically not significant and were not reported as AEs:
    - Subject 010-3301: 592 U/L (Visit 8)
    - Subject 010-3304: 1199 U/L (Visit 8)
    - Subject 010-3313: 1054 U/L (Visit 7), 1015 U/L (Visit 8)
    - Subject 010-3325: 1083 U/L (Visit 8), 127 U/L (Visit 9)
  - Subject 010-3314, drug accountability: The study records accounted for 92 capsules (took 55 and returned 37), 10 more than the 82 capsules originally dispensed.
  - Other than as noted above, no significant deficiencies were observed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records appeared complete and drug accountability was adequate. Endpoint data matched among source records, CRFs, and NDA data listings.
  - The clinical investigator's April 1, 2013 written response to the Form FDA 483 outlined the corrective actions to be implemented to prevent the recurrence of the inspectional findings.
- c. Assessment of data integrity:

Although many deficiencies were observed for all three studies conducted at this site, the deficiencies were typically minor in seriousness and appear unlikely to have significantly affected the overall study outcome. Data from this study site appear reliable.

## 5. Joseph A. Kwentus, MD

### a. What was inspected:

- Compliance with the study protocols and applicable good clinical practice (GCP) regulations and standard operating procedures (SOPs)
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records as follows:
  - RGH-MD-04: 24 subjects were screened, 11 were enrolled, and 4 completed the study. All subject records were reviewed, including detailed review for 7 enrolled subjects.
  - RGH-MD 16: 27 subjects were screened, 14 were enrolled, and 7 completed the study. All subject records were reviewed, including detailed review for 11 enrolled subjects.
  - RGH-MD 32: 26 subjects were screened, 15 were enrolled, and 9 completed study. All subject records were reviewed, including detailed review for 9 enrolled subjects.

### b. General observations and comments:

- A Form FDA 483 was issued for deficiencies in subject eligibility determination (Study RGH-MD-32) and reporting of AEs and concomitant medication use (all three studies):
  - Subject eligibility, Study RGH-MD-32
    - Subject 001-3211:

Axis I diagnosis other than study diagnosis: Medical records showed that this subject had been hospitalized within 6 months of enrollment (July 2010) for severe recurrent MDD. The clinical investigator noted that this hospitalization diagnosis was incorrect. Bipolar I disorder was diagnosed in 2010, and the hospitalization diagnosis should have been depressive episode of bipolar I disorder, not MDD

BMI exceeding 40: Medical records showed conflicting subject height, weight, and BMI on 7/30/2010 (5' 3" height, 233 lbs weight, and BMI 41 versus 5' 4" height, 230 lbs weight, and BMI 40)

Others: Not using reliable contraception; Inadequate (incomplete) documentation of Structured Clinical Interview for DSM-IV-TR Axis I disorders
    - Subject 001-3222: Treated for alcohol dependence within 6 months
    - Subject 001-3206: ECG heart rate of 50 bpm at screening (protocol specifies subject exclusion for heart rates below 50 bpm)
    - Subject 007-0402: History of drug abuse and positive testing for cannabinoids at screening, Substance Abuse Disorders section of the Structured Clinical Interview for DSM-IV-TR Axis I disorders not completed
  - Underreporting of AEs and medication use (all three studies conducted at this site):
    - RGH-MD-16 (11 subject records reviewed):  $\geq 160$  AEs not reported for 10 subjects
    - RGH-MD-04 (7 subject records reviewed):  $\geq 3$  AEs not reported for one subject
    - RGH-MD-32 (9 subject records reviewed):  $\geq 50$  AEs not reported for 7 subjects
- Other than as noted above, no significant deficiencies were observed for all three studies. All subjects signed the informed consent document. IRB oversight appeared adequate. Source

records appeared complete. Endpoint data matched among source records, CRFs, and NDA data listings. All raters were certified and evidence of unblinding was not observed. Drug accountability was well documented.

#### Reviewer Comments

*As discussed by the sponsor at meeting with DPP (May 2, 2013): In Studies RGH-MD-16 and RGH-MD-32, a large number of AEs were not reported, along with the medications used to manage the AEs. The unreported AEs were non-serious AEs (typically headache, back pain, constipation, indigestion, nausea, and vomiting). In Study RGH-MD-04, AE underreporting was less extensive (reasons unclear). The sponsor noted that a follow up evaluation will be submitted in writing for DPP review.*

c. Assessment of data integrity:

For Study RGH-MD-04, all study data from this site appear reliable as reported in the NDA. For Studies RGH-MD-16 and RGH-MD-32, the efficacy data appear reliable, but the safety data about non-serious AEs (including elevated CPK) may not be reliable.

Note: OSI's complete review of the final inspection report remains pending as of this clinical inspection summary.

## 6. Svitlana Moroz, MD, PhD

a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs

- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
- Records review included sponsor and IRB monitoring, financial disclosures, test article disposition and accountability, and subject case records. Records for all enrolled subjects were reviewed in detail.
  - RGH-MD-04 (Site 205): 12 subjects screened, 9 enrolled, and 6 completed study
  - RGH-MD 16 (Site 606): 22 subjects screened, 18 enrolled, and 10 completed study
  - RGH-MD 33 (Site 308): 8 subjects screened, 7 enrolled, and 7 completed study

b. General observations and comments:

- A Form FDA 483 was issued for the following deficiencies:

#### Study RGH-MD-04

- Subject 2050404: The relationship between an AE of sinus tachycardia and the investigational therapy was noted as possibly related in source records (correct) and as unrelated on the corresponding CRF (incorrect, apparent transcription error).

#### Study RGH-MD-16

- Subject 6061618: The severity of flat T waves on ECG was recorded as moderate in source records (correct) and mild on CRFs (incorrect, apparent transcription error).

#### Study RGH-MD-33

- Subject 3083305, Visit 8: Unscheduled screening chemistry laboratory tests were performed at end of treatment. There was no source documentation for this visit, including no records about why the test was performed or if the results were reviewed.
- Subject 3083305, Visit 1: There was no source documentation for a positive urine drug screen (barbiturates).

- Subject 3083306, Visit 8: Urine drug screen was not obtained at hospital discharge two days before Visit 8 as specified in the study protocol (apparent oversight).
  - Other than as noted above, no significant deficiencies were observed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Source records appeared complete and drug accountability was adequate. Endpoint data matched among source records, CRFs, and NDA data listings.
- c. Assessment of data integrity: The observed deficiencies appear isolated, minor, and unlikely to have significantly affected the study outcome. Data from this site appear reliable.

## 7. Volodymyr Abramov, MD, PhD

- a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
  - Records review included sponsor and IRB monitoring, financial disclosures, test article accountability, and subject records. Records for all enrolled subjects were reviewed in detail.
    - RGH-MD-04 (Site 200): 9 subjects screened, 8 enrolled, and 6 completed study
    - RGH-MD 16 (Site 601): 17 subjects screened, 15 enrolled, and 12 completed study
    - RGH-MD 33 (Site 301): 7 subjects screened, 6 enrolled, and 5 completed study
- b. General observations and comments:
- No significant deficiencies were observed. A Form FDA 483 was not issued and no deficiency observations were verbally discussed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data matched among source records, CRFs, and NDA data listings.
- c. Assessment of data integrity: Data from this site appear reliable.

Note: For Study RGH-MD 04, the subject enrollment number reported in the inspection report (8 subjects) differs from that shown in the original consult *Request for Inspections* (15 subjects).

## 8. Yuliya Blazhevych, MD

- a. What was inspected: Compliance with study protocols, GCP regulations, and SOPs
- Data verification: subject eligibility, informed consent, randomization, major efficacy endpoints, adverse events, protocol deviations, and subject discontinuations
  - Records review included sponsor and IRB monitoring, financial disclosures, test article accountability, and subject records. Records for all enrolled subjects were reviewed in detail.
    - RGH-MD-04 (Site 201): 20 subjects screened, 18 enrolled, and 12 completed study
    - RGH-MD 16 (Site 602): 14 subjects screened, 13 enrolled, and 11 completed study
    - RGH-MD 33 (Site 303): 5 subjects screened, 4 enrolled, and 2 completed study
- b. General observations and comments:
- No significant deficiencies were observed. A Form FDA 483 was not issued and no deficiency observations were verbally discussed. IRB oversight and study monitoring appeared to be adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records appeared factual, complete, and matched corresponding CRFs. Endpoint data matched among source records, CRFs, and NDA data listings.

- c. Assessment of data integrity: Data from this site appear reliable.

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

## 9. Forest Laboratories, Inc.

- a. What was inspected: Sponsor's oversight of Studies RGH-MD-04, RGH-MD-05, RGH-MD-16, RGH-MD-32, and RGH-MD-33
- Compliance with GCP regulations and adequacy of financial disclosure, informed consent procedures, and IRB oversight
  - Adequacy of monitoring study sites and contract research organizations (**CROs**), handling of protocol deviations, AE reporting, data management, and drug accountability
- b. General observations:
- A Form FDA 483 was issued for the following deficiency observations:
    - The monitoring plans (SOPs) specific to each study were not promptly finalized (not approved by due dates specified in quality assurance SOP).
    - NDA Listing 16.2.12.6 (positive urine drug screen) was missing ten subjects in RGH-MD-04, two in RGH-MD-05, 17 in RGH-MD-16, eight in RGH-MD-32, and 13 in RGH-MD-33.
    - NDA Listing 16.2.12.4 (over one study medication dose per day) was missing three subjects in RGH-MD-04, one in RGH-MD-32, and four in RGH-MD-33.
    - NDA Listing 16.2.12.1 (eligibility criteria violations) was missing Subject 0023308 enrolled in RGH-MD-33 despite violation of exclusion 14 (previous participation in RGH-MD-33).
    - Financial disclosures were not obtained prior to study completion for some clinical investigators at the following three study sites (typically one subinvestigator per site): RGH-MD-04 Site 100, RGH-MD-32 Site 005, and RGH-MD-32 Site 119. The disclosures obtained after study completion did not indicate any financial conflicts of interest.
  - The following deficiency observations (violations of the sponsor's monitoring SOP) were verbally discussed and not cited on Form FDA 483 (inspector discretion):
    - RGH-MD-33, Site 308 (Subjects 3083301, 3083305, 3083306, 3083307, and 3083308): Not all source data were verified at study monitoring.
    - RGH-MD-05, Site 044: Some monitoring visits were outside the time window specified in the sponsor's monitoring SOP.
    - For the following five studies at three CI sites, study monitoring reports were not promptly submitted and finalized: Burtner (RGH-MD-05, Site 41), Kwentus (RGH-MD-04, Site 7; RGH-MD-32, Site 01), and Litman (RGH-MD-05, Site 44; RGH-MD-33, Site 6).
  - Other than as noted above, the sponsor's study records indicated adequate control over the audited studies. There was no evidence of unblinding or biased data collection. Drug accountability records were adequate.
- c. Assessment of data integrity:

The deficiency observations appear (typically) minor, isolated, and unlikely to have significantly affected the study outcome. The inspectional findings support adequate sponsor oversight. The study data appear reliable as reported in the NDA.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Six pivotal studies support two indications for the NME cariprazine (schizophrenia and bipolar mania), of which five were audited at nine sites: eight clinical investigator sites and the sponsor site. The clinical investigator sites were selected based on multiple studies per site (adequate representation of the five studies to be audited), high subject enrollment, and remote or no prior FDA inspection history. The sites in Ukraine were selected also for their large differences from the US sites in the primary efficacy results.

For seven clinical investigator sites and the sponsor site, the inspectional findings do not raise significant GCP concerns and the study data appear reliable as reported in the NDA. For two studies (RGH-MD-16 and RGH-MD-32) at one clinical investigator site (Kwentus), the safety data about non-serious AEs may not be reliable due to significant AE underreporting. All other study data from this site appear reliable. The difference in efficacy results between US and Ukraine sites appears unrelated to GCP. Differences in GCP between US and Ukraine sites were not observed.

**Note:** For two CI inspections (Sicuro and Blazhevych), the final inspection report has not been received from the field office and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator. For one CI inspection (Kwentus), OSI's complete review of the final inspection report remains pending as of this clinical inspection summary. An addendum to this clinical inspection summary will be forwarded to the review division if any final classification changes from the pending classification, or if additional observations of clinical or regulatory significance are discovered after completing the review of the final inspection reports.

{See appended electronic signature page}

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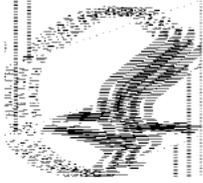
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**    Public Health Service

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**Pediatric and Maternal Health Staff Review**

**Date:** July 18, 2013

**From:** Carrie Ceresa, Pharm D, MPH  
Regulatory Reviewer, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Jeanine Best, MSN, RN, PNP  
Team Leader, Maternal Health Team  
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,  
Pediatric and Maternal Health Staff

**To:** The Division of Psychiatry Products (DPP)

**Drug:** Cariprazine capsules for oral administration

**NDA:** 204-370

**Subject:** Pregnancy and nursing mothers labeling language

**Applicant:** Forest Research Institute

**Materials Reviewed:** Package insert submitted by sponsor November 19, 2012.

**Consult Question:** NDA 204370 is the being reviewed under “The Program” and provides for the use of cariprazine, an antipsychotic, for the treatment of schizophrenia and bipolar I disorder. We would like your input on all relevant sections of the label, e.g., use in specific populations (pregnancy, labor and delivery, nursing mothers, highlights, and patient counseling.

## INTRODUCTION

On November 19, 2012, Forest Laboratories, Inc., submitted an original New Drug Application (NDA 204-370), for cariprazine capsules with the proposed indications, for the treatment of schizophrenia and for the treatment of manic or mixed episodes associated with bipolar I disorder.

The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the cariprazine labeling.

This review provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

## BACKGROUND

Cariprazine is a dopamine D3-preferring, D3/D2 receptor partial agonist, second-generation atypical antipsychotic.<sup>1</sup> The active metabolites for cariprazine are desmethyl-cariprazine and didesmethyl-cariprazine.<sup>1</sup> The mechanism of action of cariprazine is unknown; however, it is believed that cariprazine's therapeutic action is through a combination of activity on central dopamine D3/D2 and serotonin 5-HT<sub>1A</sub> receptors.<sup>2</sup> Cariprazine acts as a partial agonist at D3, D2 and 5-HT<sub>1A</sub> and an agonist at serotonin 5-HT<sub>2B</sub> and 5-HT<sub>2A</sub> and histamine H<sub>1</sub> receptors.<sup>2</sup>

### *Bipolar disorder and pregnancy*

Bipolar disorder is a chronic mental illness that occurs in females of reproductive potential. The management of bipolar disorder during pregnancy requires benefit/risk consideration of drug treatment versus potential symptom exacerbation with not treating the disorder. In the past, pregnant women with bipolar disorder were told by their health care provider to stop their medication during pregnancy.<sup>3</sup> However, recently studies have shown that women with bipolar disorder have a 50% chance of reoccurrence during pregnancy.<sup>3</sup> In addition, post-partum hospitalization rates are high in female patients with bipolar disorder.<sup>4</sup> Approximately, 25% to 40% of post-partum patients with bipolar disorder will experience a mood episode, such as a manic episode, major depressive episode, hypomanic episode, mixed episode or rapid cycling and approximately 30% may experience post-partum psychosis.<sup>5</sup> It is important that healthcare providers closely monitor and consider the potential effects of untreated mental illness during

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<sup>1</sup> Citrome, L. (2013). Cariprazine in Bipolar Disorder: Clinical Efficacy, Tolerability, and Place in Therapy. *Advanced Therapy*, 30(20), 102-112.

<sup>2</sup> Citrome, L. (2013). Cariprazine: chemistry, pharmacodynamics, pharmacokinetics, and metabolism, clinical efficacy, safety and tolerability. *Expert Opinion on Drug Metabolism and Toxicology*, 9(2), 193-206.

<sup>3</sup> Viguera, A., Whitfield, T., Baldessarini, R., Newport, D., Stowe, Z., Reminick, A, et al. (2007). Risk of Recurrence in Women with Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation. *American Journal of Psychiatry*, 164:1817-1824.

<sup>4</sup> Cohen, L. (2007). Treatment of Bipolar Disorder During Pregnancy. *Journal of Clinical Psychiatry*, 68(9), 4-9.

<sup>5</sup> Connolly, K., Thase, M. (2011). The Clinical Management of Bipolar Disorder: A Review of Evidence-Based Guidelines. *Primary Care Companion CNS Disorders*, 13(4).

pregnancy because untreated mental disorders such as bipolar disorder can increase the risk of adverse pregnancy outcomes, such as preterm birth and microcephaly.<sup>6</sup>

### *Schizophrenia and pregnancy*

Schizophrenia is a disease that presents in early adulthood and is more commonly diagnosed in men than women.<sup>7</sup> Schizophrenia is characterized by hallucinations, lack of insight, delusions and ideas of reference, suspiciousness, flat affect, delusional mood, hearing voices.<sup>7</sup> As in patients with bipolar disorder, patients with schizophrenia are likely to experience pregnancy adverse events such as, premature birth, low birth weight and perinatal hypoxia.<sup>7</sup>

## **DISCUSSION**

### **Pregnancy and Nursing Mothers Labeling**

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

The Drugs and Lactation Database (LactMed)<sup>8</sup> was searched for available lactation data on with the use of cariprazine, and no information was found. 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 information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

## **CONCLUSION**

The pregnancy subsection of cariprazine labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of the cariprazine labeling was revised to comply with current labeling recommendations.

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<sup>6</sup> Boden, R., Lundgren, M., Brandt, L., Reutfors, J., Anderson, M., Kieler, H. (2012). Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilizers for bipolar disorder: population based cohort study. *British Journal of Medicine*, 345.

<sup>7</sup> Picchioni, M., Murray, R. (2007). Schizophrenia. *British Journal of Medicine*, 335:91-5.

<sup>8</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

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CARRIE M CERESA  
07/18/2013

JEANINE A BEST  
07/18/2013

LYNNE P YAO  
07/19/2013

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>NDA</b>	204370
<b>Generic Name</b>	RHG-188 (cariprazine)
<b>Sponsor</b>	Forest Research Institute, Inc.
<b>Indication</b>	1) for the treatment of schizophrenia, and 2) for the treatment of manic or mixed episodes associated with bipolar 1 disorder
<b>Dosage Form</b>	Capsule
<b>Drug Class</b>	potent inhibitors at the 5-hydroxytryptamine (serotonin) type 2A receptor; antagonism of the dopamine D <sub>2</sub> receptor
<b>Therapeutic Dosing Regimen</b>	12 mg
<b>Duration of Therapeutic Use</b>	Acute and the residual phases
<b>Maximum Tolerated Dose</b>	18 mg
<b>Submission Number and Date</b>	SDN 001/19 Nov 2012
<b>Review Division</b>	DPP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effects of cariprazine (a therapeutic dosage 9 mg on day 20) and a suprathreshold dosage of 18 mg on day 34) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between cariprazine and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. However, the largest lower bound of the 2-sided 90% CI for  $\Delta\Delta\text{QTcNi}$  (a type of individual correction) for moxifloxacin was lower than 5 ms suggesting that assay sensitivity was not established. Evidence of assay sensitivity for this TQT study was therefore derived from the slope of the relationship between  $\Delta\Delta\text{QTcF}$  and moxifloxacin concentration (3.3 ms per  $\mu\text{g/mL}$ ), which is consistent with the slope (3.06 ms per  $\mu\text{g/mL}$ ) reported in a previous publication analyzing data from 20 studies (Florian et al., J Clin Pharmacol 2011 51: 1152). Peak moxifloxacin concentrations in this TQT study were approximately 40% lower than those reported in the literature (Florian et al.) If moxifloxacin concentrations had reached levels typically observed following a single 400 mg moxifloxacin dose, it is reasonable to conclude that assay sensitivity would have been established using traditional ICH E14 interpretation.

In this multicenter, randomized, double-blind, placebo, and moxifloxacin-controlled, 3-group, parallel-group study, 129 subjects received cariprazine 9 mg, cariprazine 18 mg, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Cariprazine (9 mg and 18 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta QTcNi$ (ms)	90% CI (ms)
Cariprazine 9 mg on Day 20	4	0.9	(-1.4, 3.3)
Cariprazine 18 mg on Day 34	8	1.4	(-1.1, 3.8)
Moxifloxacin 400 mg*	3	6.6	(4.3, 8.9)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 3.4 ms

According to the Sponsor's proposed label, the maximum intended therapeutic dose is (b) (4) mg/day for bipolar mania. (b) (4)

The Division previously agreed to a suprathapeutic dose of 18 mg (IRT Review 01/09/2012) due to concerns regarding tolerability at higher doses. CYP3A4 is the major enzyme responsible for the metabolism of cariprazine. Coadministration of ketoconazole with cariprazine resulted in an increase in  $C_{max}$  and  $AUC_{0-\infty}$  of cariprazine by 3.42 and 3.88-fold, respectively. In the presence of ketoconazole, systemic exposure of DCAR was reduced by about 35% while for DDCAR it increased by about 43%. Therefore, using 18 mg as suprathapeutic dose does not appear to be sufficient to cover this scenario. We note, however, that the proposed label proposes a dose reduction of one-half in the presence of a strong CYP3A4 inhibitor. If the (b) (4) mg dose is reduced by one-half in the presence of a strong CYP3A4 inhibitor, (b) (4)

## 1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

1. Is there evidence that treatment with cariprazine causes QT prolongation or other significant cardiovascular effects?

***QT-IRT Response: No.***

2. Is there a dose-response relationship?

***QT-IRT Response: No.***

3. Do you have specific recommendations for labeling regarding QT prolongation or other cardiovascular findings?

***QT-IRT Response: See Section 2.2 of this review.***

## **2 PROPOSED LABEL**

### **2.1 SPONSOR'S PROPOSED LABEL**

#### **12.2 Pharmacodynamics**

(b) (4)

### **2.2 QT-IRT PROPOSED LABEL**

#### **12.6 Cardiac Electrophysiology**

At a dose 1.5 times the maximum recommended dose, cariprazine does not prolong QTc to any clinically relevant extent.

## **3 BACKGROUND**

### **3.1 PRODUCT INFORMATION**

Cariprazine is a partial agonist at dopamine and serotonin receptors, being developed for the treatment of schizophrenia and bipolar disorders.

### **3.2 MARKET APPROVAL STATUS**

Cariprazine is not approved for marketing in any country.

### **3.3 PRECLINICAL INFORMATION**

*From QT-IRT consult 29 June 2010*

*Cariprazine increased HR in conscious dogs at exposures 10-fold the C<sub>max</sub> exposure in humans (dose 12.5 mg). Cariprazine inhibits hERG currents, the IC<sub>50</sub> is 10-fold the C<sub>max</sub> human exposure for a 12.5-mg daily dose.*

### **3.4 PREVIOUS CLINICAL EXPERIENCE**

The NDA described 11 deaths, not likely to represent proarrhythmia. ECG abnormalities and cardiovascular adverse events were uncommon.

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of cariprazine's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 71,958. The sponsor submitted the study report RHG-MD-02 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

## **4.2 TQT STUDY**

### **4.2.1 Title**

Evaluation of the Effects of Sequential Multiple-Dose Regimens of Cariprazine on Cardiac Repolarization in Patients with Schizophrenia

### **4.2.2 Protocol Number**

RHG-MD-02

### **4.2.3 Study Dates**

First Patient First Visit: 15 Jun 2011

Last Patient Last Visit: 19 Jan 2012

### **4.2.4 Objectives**

To assess the effects of a therapeutic dosage (9 mg) and a suprathreshold dosage (18 mg) of cariprazine on cardiac repolarization as determined by manually verified measurements of heart-rate-corrected QT intervals on digitally recorded Holter recordings of electrocardiograms (ECGs) in patients with schizophrenia.

### **4.2.5 Study Description**

#### **4.2.5.1 Design**

Multicenter, randomized, double-blind, placebo, and moxifloxacin-controlled, 3-group, parallel-group study. Patients meeting all study eligibility criteria were randomized (2:1:1) in parallel to receive cariprazine (Group 1) or placebo/moxifloxacin/risperidone which was further divided into Group 2A (moxifloxacin/placebo-risperidone) and Group 2B (placebo-risperidone/moxifloxacin).

#### **4.2.5.2 Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

#### **4.2.5.3 Blinding**

The investigational product was administered in a double-blinded manner.

### **4.2.6 Treatment Regimen**

#### **4.2.6.1 Treatment Arms**

Patients were randomized (1:1) to receive cariprazine (Group 1) or placebo/risperidone (Group 2). The placebo/risperidone group was subsequently further divided (1:1) into Group 2A and Group 2B.

Group 1: Patients randomized to cariprazine received double-blind placebo for the first 5 days; they were then up-titrated to the therapeutic dosage of cariprazine (9 mg) by Day 10 and received 9 mg from Day 10 through Day 20; they were then up-titrated to the suprathreshold dosage (18 mg) by Day 25 and received 18 mg from Day 25 through

Day 35. This group of patients also received moxifloxacin-matched placebo from Day 1 through Day 35.

Group 2A: Patients randomized to Group 2A (moxifloxacin/placebo-risperidone) received double-blind placebo for the first 5 days, 1 dose of moxifloxacin (400 mg) on Day 6, risperidone 4 mg from Day 7 through Day 15, and placebo from Day 16 through Day 20. They received risperidone again from Day 21 through Day 29 and placebo from Day 30 through Day 35. This group of patients also received moxifloxacin-matched placebo on Day 1 through Day 5 and Day 7 through Day 35.

Group 2B: Patients randomized to Group 2B (placebo-risperidone/moxifloxacin) received double-blind placebo for the first 6 days, risperidone 4 mg from Day 7 through Day 15, placebo from Day 16 through Day 20, risperidone 4 mg from Day 21 through Day 29, placebo from Day 30 through Day 34, and 1 dose of moxifloxacin (400 mg) on Day 35. This group of patients also received moxifloxacin-matched placebo from Day 1 through Day 34.

#### 4.2.6.2 Sponsor's Justification for Doses

The therapeutic dosage was evaluated to adequately characterize the dose response of cariprazine. The highest therapeutic dosage in patients with schizophrenia is expected to be 9 mg/day. The projected concentrations of cariprazine, DC, and DDC at the highest therapeutic dosage of 9 mg/day are approximately 26, 7.7, and 59 ng/mL, respectively. The escalation strategy described has been used in the clinical program and has been determined to be safe and tolerable.

The suprathreshold dosage of 18 mg/day chosen for this study is based on a separate MTD study in patients with schizophrenia (Study RGH-MD-18, 2012) that was completed before the initiation of this intensive QT study. In Study RGH-MD-18, 36 patients (27 cariprazine, 9 placebo) were enrolled in 4 cohorts. The dosage of cariprazine ranged from 1.5 to 21 mg/day, and the treatment period was 28 days. In 2 cohorts that were aimed to reach 24 mg/day, dosing was discontinued at 21 mg/day, indicating that the MTD was 18 mg/day.

In a separate cohort that was aimed to reach 21 mg/day, this dosage was tolerated and no MTD was reached. Generally, higher doses appear to be poorly tolerated, causing frequent akathisia and subject dropout that could potentially compromise the adequate collection of ECG data. The projected concentrations of cariprazine, DC, and DDC at the suprathreshold dosage of 18 mg/day are approximately 52, 15, and 118 ng/mL, respectively.

*Reviewer's Comment: According to the Sponsor's proposed label, the maximum intended therapeutic dose is (b) (4) mg/day for bipolar mania.*

*The Division previously agreed to a suprathreshold dose of 18 mg (IRT Review 01/09/2012) due to concerns regarding tolerability at higher doses. Co-administration of cariprazine with*

*ketoconazole yields more than 3-fold in the exposure of cariprazine alone. The supratherapeutic dose of 18 mg does not appear to cover this scenario. We note, however, that the proposed label proposes a dose reduction of one-half in the presence of a strong CYP3A4 inhibitor. If the <sup>(b) (4)</sup> mg dose is reduced by one-half in the presence of a strong CYP3A4 inhibitor, the <sup>(b) (4)</sup>*

#### **4.2.6.3 Instructions with Regard to Meals**

All investigational products were administered orally on Days 1 through 35 as a single daily dose approximately 30 minutes after the end of the patient's morning meal.

*Reviewer's Comment: In a previous review (3/15/2011), IRT agreed to dosing 30 minutes after a meal. Compared to fasted condition, cariprazine and desmethyl cariprazine with high-fat breakfast had 21% and 5% lower C<sub>max</sub> and didesmethyl cariprazine showed 7% higher C<sub>max</sub>.*

#### **4.2.6.4 ECG and PK Assessments**

PK blood sampling to determine cariprazine, DC, DDC, and moxifloxacin plasma concentrations was done 3 minutes after completing the 20-minute Holter recording intervals with the patients in the semireclined position.

- Days 6, 20, 34 and 35: -1 (predose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose. A 24-hour postdose sample was also obtained after the Day 6, 20, and 35 doses
- Days 18, 19, and 33: 0 hour (predose)

Twelve-lead Holter recordings were obtained for 14 hours on Days 5, 6, 20, 34, and 35. On these days, ECG data was extracted, from 20-minute periods in which patients were in a semireclined position at intervals ending at -1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours relative to dosing.

*Reviewer's Comment: The both PK and ECG sampling scheme is acceptable as it was enough to cover T<sub>max</sub>.*

#### **4.2.6.5 Baseline**

The sponsor used time-matched QTc on Day 5 as baseline values.

#### **4.2.7 ECG Collection**

Twelve-lead Holter monitoring was used to obtain digital ECGs. Subjects were semi-recumbent around nominal sample times.

## 4.2.8 Sponsor's Results

### 4.2.8.1 Study Subjects

A total of 129 patients were randomized to receive double-blind treatment; 85 patients completed the study.

### 4.2.8.2 Statistical Analyses

#### 4.2.8.2.1 Primary Analysis

The primary endpoint was the largest time-matched mean differences between cariprazine (9 mg and 18 mg) and placebo in QTcNi. The therapeutic dose of cariprazine 9 mg and the suprathreshold dose of cariprazine 18 mg versus placebo, the placebo QTc data from Group 2A and Group 2B were combined at the corresponding time point. The sponsor used a mixed effects model and the results are presented in Table 2. The model included treatment, sex, study center, time, and treatment-by-time interaction as the fixed effects; subject, subject-by-treatment, and subject-by-time as random effects; and time-matched baseline and baseline-by-time interaction as covariates effects. The upper limits of the 2-sided 90% CI for cariprazine 9 mg on day 20 and cariprazine 18 mg on day 34 were below 10 ms.

**Table 2: Sponsor Results  $\Delta$ QTcNi and  $\Delta\Delta$ QTcNi for Cariprazine 9 mg on Day 24 and Cariprazine 18 mg on Day 34**

Treatment	Time-Matched Mean		Largest Difference in LSM	Two-Sided 90% CI for Difference in LSM
	Placebo (N1 = 58)	Cariprazine (N1 = 47)		
Cariprazine 9 mg on day 20	6	5.96	–	–5.533, 3.537
Cariprazine 18 mg on day 34	3	5.03	1.71	–2.986, 6.412

*Reviewer's Comments: We will provide our independent analysis results in Section 5.2.*

#### 4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the  $\Delta$ QTcNi effect for moxifloxacin. For Group 2A, Day 6 moxifloxacin was compared with Day 34 placebo. For Group 2B, Day 35 moxifloxacin was compared with Day 5 placebo. The analysis results were presented in Table 3. The largest lower limit of the 2-sided 90% CI from 1-hour, 2-hour, 3-hour, 4-hour, and 5-hour time points was compared with the threshold of 5 ms. The lower limit of the two-sided 90% CI was greater than 5 ms. Thus, assay sensitivity in this thorough QTcNi study was established.

**Table 3: Sponsor’s Results  $\Delta \Delta$ QTcNi for Moxifloxacin 400 mg**

<i>Time point, hour</i>	<i>Moxifloxacin Versus Placebo</i>		
	<i>Estimated time-matched <math>\Delta\Delta</math>QTcNi</i>	<i>2-sided 90% CI for difference in least squares mean</i>	<i>Adjusted p-value<sup>a</sup></i>
-1	-1.206	-3.518, 1.106	—
0	0.596	-1.720, 2.911	—
<b>1</b>	<b>2.079</b>	<b>-0.236, 4.394</b>	0.9809
<b>2</b>	<b>4.976</b>	<b>2.679, 7.273</b>	0.9809
<b>3</b>	<b>7.016</b>	<b>4.720, 9.312</b>	0.2971
<b>4</b>	<b>7.431</b>	<b>5.147, 9.714</b>	0.2001 <sup>b</sup>
<b>5</b>	<b>6.522</b>	<b>4.245, 8.798</b>	0.4068
6	6.033	3.756, 8.309	—
7	4.889	2.604, 7.173	—
8	4.845	2.553, 7.137	—
9	5.335	3.058, 7.612	—
10	4.213	1.935, 6.492	—
11	5.117	2.830, 7.404	—
12	5.402	3.093, 7.711	—

Note: Only patients from Group 2A and Group 2B were included for analyses.

Source: *Clinical Study Report No., Section 11.5.2.1, Table 11.5.2-1, Pg 104/3320*

*Reviewer’s Comments: We will provide our independent analysis result in Section 5.2. Our results do not support the sponsor’s findings. The largest unadjusted 90% lower confidence interval is 4.3 ms, which indicates that an at least 5 ms QTcNi effect of moxifloxacin cannot be detected from the study. This reviewer also performs analyses in QTcF. The largest unadjusted 90% lower confidence interval is 4.0 ms, which is below 5-ms threshold we set for showing assay sensitivity. However, our analyses described in section 5.3 conclude that there is adequate evidence of assay sensitivity..*

#### **4.2.8.2.3 Categorical Analysis**

Categorical analysis was used to summarize in the categories of QTc  $\leq$ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $>$ 500 ms, and changes from baseline QTc  $\leq$ 30 ms, between 30 and 60 ms, and  $>$ 60 ms. No subject’s absolute QTc  $>$  480 ms and  $\Delta$ QTc  $>$ 60 ms.

**Table 4 : Sponsor’s Categorical Analyses**

<i>ECG Parameter Criterion (unit)</i>	<i>Placebo (N = 59)</i>			<i>Cariprazine (N = 47)</i>		
	<i>Day 5 n/N1 %</i>	<i>Day 20 n/N1 %</i>	<i>Day 34 n/N1 %</i>	<i>Day 5 n/N1 %</i>	<i>Day 20 n/N1 %</i>	<i>Day 34 n/N1 %</i>
<b>QTc Interval (msec)</b>						
> 450	1/59 (1.7)	1/58 (1.7)	1/49 (2.0)	0	0	0
> 480	0	0	0	0	0	0
> 500	0	0	0	0	0	0
<b>Change from Baseline in QTc Interval (msec)</b>						
> 30	—	2/58 (3.4)	0	—	1/47 (2.1)	0
> 60	—	0	0	—	0	0
Baseline is defined as the time-matched measurement on Day 5.						

#### 4.2.8.3 Safety Analysis

No cardiovascular adverse events are described.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

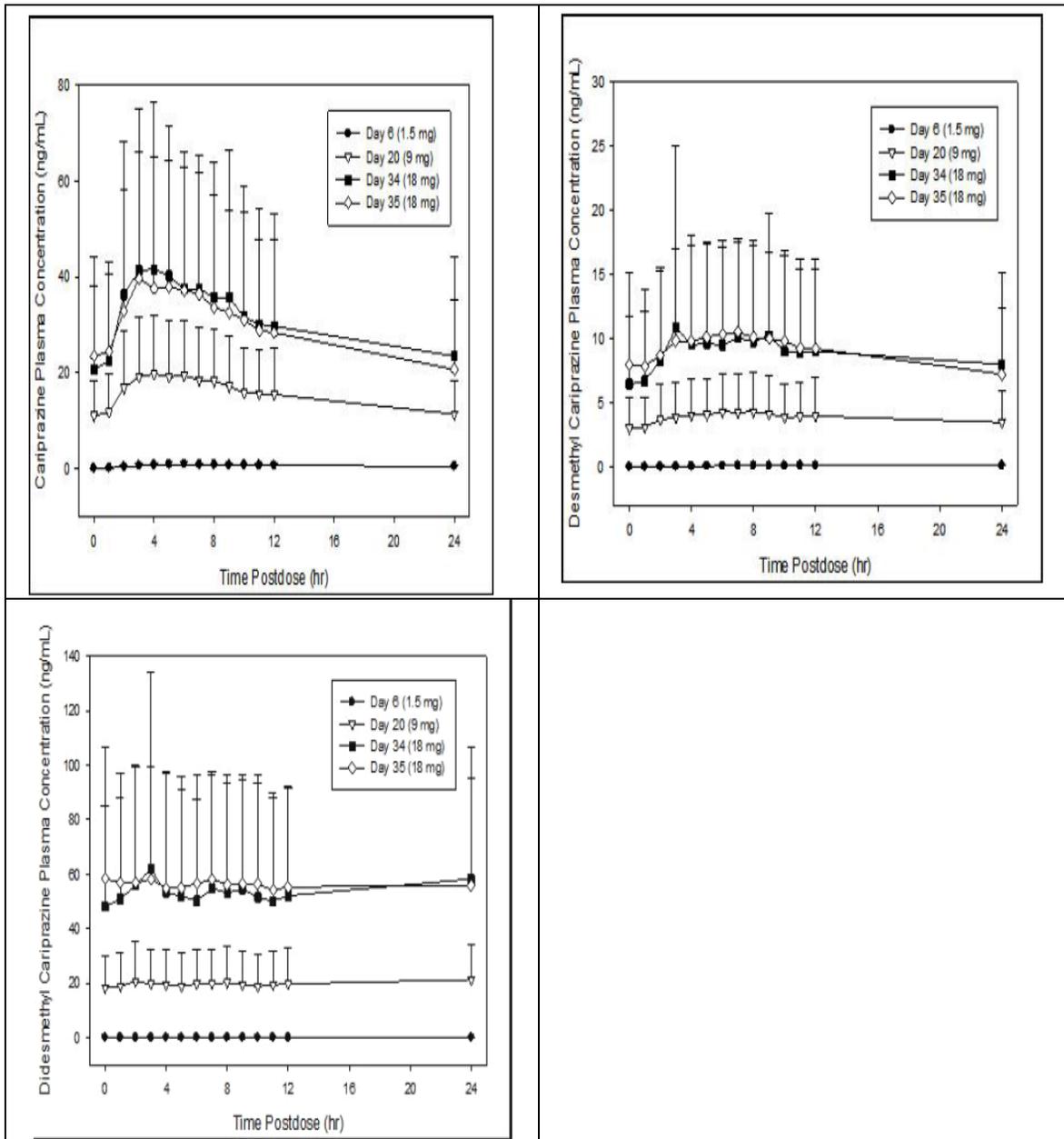
The PK results are presented in Table 5 and Figure 1. C<sub>max</sub> and AUC values at 18 mg, the suprathreshold dose were approximately 2-fold, 2.5-fold and 3-fold for cariprazine, desmethyl and didesmethyl, respectively C<sub>max</sub> and AUC values at 9 mg.

**Table 5: PK parameters for Cariprazine, Desmethyl Cariprazine and Didesmethyl Cariprazine at days 6, 20, 34 and 35.**

Analyte	PK Parameter	Day 6 (1.5 mg) (N = 57)	Day 20 (9 mg) (N = 45)	Day 34 (18 mg) (N = 34)	Day 35 (18 mg) (N = 33)
Cariprazine	AUC <sub>0-24</sub> (ng•hr/mL)	13.37 ± 7.61	351.24 ± 219.34	730.63 ± 582.80	683.10 ± 469.61
	C <sub>max</sub> (ng/mL)	1.08 ± 0.64	22.76 ± 13.25	48.79 ± 38.18	45.83 ± 28.29
	T <sub>max</sub> (hr)	5.35 ± 1.91 <sup>b</sup> 5.0 (1.0-10.0) <sup>a,b</sup>	4.45 ± 2.49 4.0 (0.0-12.0) <sup>a</sup>	4.35 ± 2.31 3.5 (1.0-11.0) <sup>a</sup>	4.21 ± 2.53 4.0 (0.0-12.0) <sup>a</sup>
	C <sub>av</sub> (ng/mL)	0.56 ± 0.32	14.63 ± 9.14	30.44 ± 24.28	28.46 ± 19.57
	C <sub>min</sub> (ng/mL)	0.47 ± 0.27	11.36 ± 7.06 <sup>d</sup>	23.43 ± 20.61 <sup>f</sup>	20.68 ± 14.68
	Fluctuation	1.51 ± 3.09 <sup>b</sup>	0.80 ± 0.46 <sup>d</sup>	0.87 ± 0.46 <sup>f</sup>	1.27 ± 1.49
	Swing	1.34 ± 0.77 <sup>c</sup>	1.00 ± 0.50 <sup>e</sup>	1.25 ± 0.74 <sup>f</sup>	2.08 ± 3.68
Desmethyl Cariprazine (DC)	AUC <sub>0-24</sub> (ng•hr/mL)	1.91 ± 1.57	87.88 ± 64.98	210.89 ± 174.10	210.60 ± 148.22
	C <sub>max</sub> (ng/mL)	0.12 ± 0.09	4.84 ± 3.34	13.42 ± 15.60	11.96 ± 8.03
	T <sub>max</sub> (hr)	17.49 ± 8.02 <sup>b</sup> 24.0 (3.0-24.0) <sup>a,b</sup>	7.29 ± 5.41 <sup>d</sup> 6.0 (0.0-24.0) <sup>a,d</sup>	7.34 ± 5.15 <sup>i</sup> 7.0 (1.0-24.0) <sup>a,i</sup>	5.45 ± 2.66 <sup>j</sup> 6.0 (0.0-10.0) <sup>a,j</sup>
	C <sub>av</sub> (ng/mL)	0.08 ± 0.07	3.66 ± 2.71	8.79 ± 7.25	8.78 ± 6.18
	C <sub>min</sub> (ng/mL)	0.10 ± 0.08	3.39 ± 2.52 <sup>d</sup>	8.00 ± 7.13 <sup>f</sup>	7.22 ± 5.11
	Fluctuation	0.58 ± 3.35 <sup>b</sup>	0.42 ± 0.33 <sup>e</sup>	0.70 ± 1.19 <sup>j</sup>	1.75 ± 3.97 <sup>j</sup>
	Swing	0.10 ± 0.20 <sup>c</sup>	0.49 ± 0.38 <sup>h</sup>	0.63 ± 0.69 <sup>k</sup>	2.55 ± 7.12 <sup>k</sup>
Didesmethyl Cariprazine (DDC)	AUC <sub>0-24</sub> (ng•hr/mL)	0.87 ± 4.60 <sup>l</sup>	458.00 ± 309.53	1292.15 ± 999.14	1326.86 ± 925.76
	C <sub>max</sub> (ng/mL)	0.05 ± 0.22 <sup>l</sup>	23.05 ± 15.65	74.79 ± 80.25	68.24 ± 49.66
	T <sub>max</sub> (hr)	16.14 ± 10.07 <sup>m</sup> 24.0 (0.0-24.0) <sup>a,m</sup>	10.16 ± 8.65 8.0 (0.0-24.0) <sup>a</sup>	9.41 ± 8.65 6.5 (0.0-24.0) <sup>a</sup>	6.06 ± 6.64 3.0 (0.0-24.0) <sup>a</sup>
	C <sub>av</sub> (ng/mL)	0.04 ± 0.19 <sup>l</sup>	19.08 ± 12.90	53.84 ± 41.63	55.29 ± 38.57
	C <sub>min</sub> (ng/mL)	0.04 ± 0.21	21.33 ± 12.97 <sup>e</sup>	58.27 ± 48.23 <sup>f</sup>	55.82 ± 39.16
	Fluctuation	6.89 ± 11.69 <sup>m</sup>	0.14 ± 0.22 <sup>e</sup>	0.25 ± 0.43 <sup>f</sup>	0.88 ± 2.37
	Swing	0.05 ± 0.11 <sup>n</sup>	0.15 ± 0.22 <sup>e</sup>	0.26 ± 0.47 <sup>f</sup>	1.45 ± 4.35

Source: the sponsor's report, page 99-100.

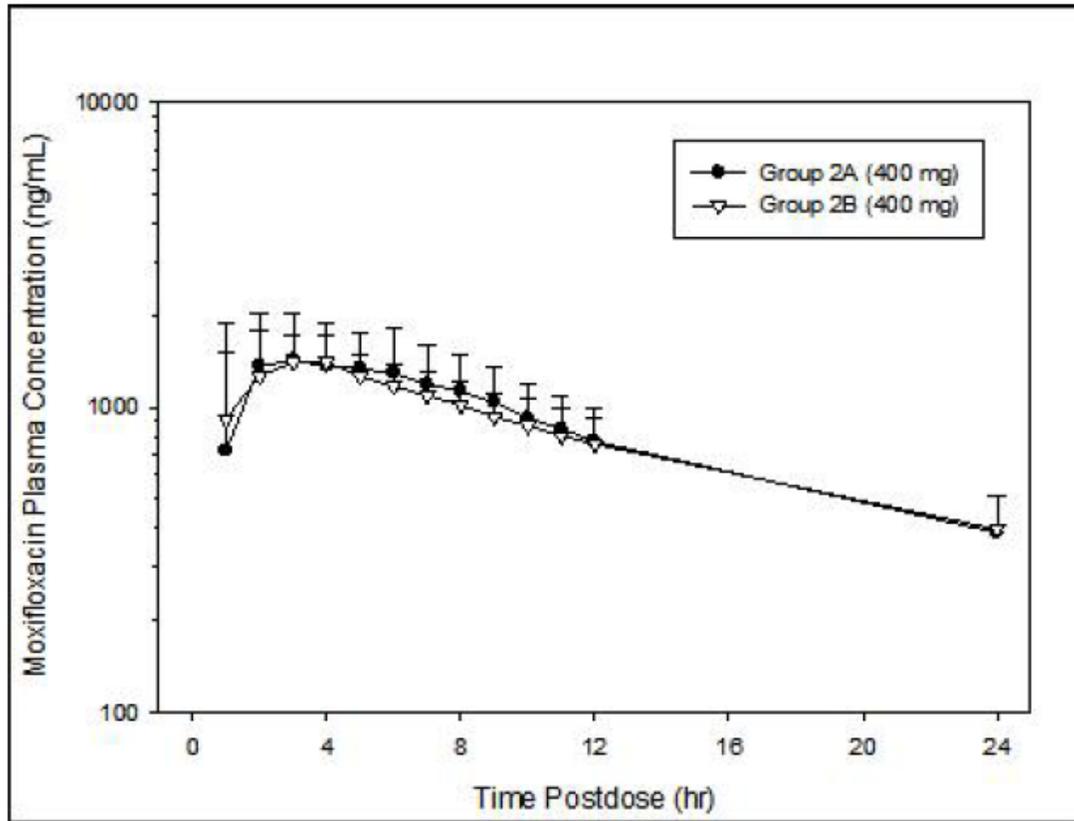
**Figure 1: Mean Plasma Concentration – Time profiles for Cariprazine (top, left), Desmethyl Cariprazine (top, right) and Didesmethyl Cariprazine (bottom, left).**



Source: the sponsor's report, page 96-97.

The PK profile for moxifloxacin is illustrated in Figure 2 and the parameter estimates are presented in Table 6.

**Figure 2: Mean ( $\pm$ SD) Moxifloxacin Plasma Concentration Versus Time Profiles**



Source: the sponsor's report, page 101.

**Table 6: Pharmacokinetic Parameters (Mean  $\pm$  SD) for Moxifloxacin**

PK Parameter	Group 2A (N = 28)	Group 2B (N = 19)	Groups 2A and 2B (N = 47)
AUC <sub>0-∞</sub> , ng•hr/mL	26680 $\pm$ 5759	27228 $\pm$ 6285	26901 $\pm$ 5916
AUC <sub>0-t</sub> , ng•hr/mL	19992 $\pm$ 3767	19508 $\pm$ 3647	19796 $\pm$ 3687
C <sub>max</sub> , ng/mL	1881 $\pm$ 455	1766 $\pm$ 386	1835 $\pm$ 428
T <sub>max</sub> , hours	2.93 $\pm$ 1.59 3.0 (1.0-6.1) <sup>a</sup>	2.74 $\pm$ 1.56 3.0 (1.0-6.0) <sup>a</sup>	2.85 $\pm$ 1.56 3.0 (1.0-6.1) <sup>a</sup>
T <sub>1/2</sub> , hours	11.59 $\pm$ 2.38	13.09 $\pm$ 2.69	12.19 $\pm$ 2.59

Note: 7 patients with no measurable plasma concentrations of moxifloxacin did not have evaluable PK parameters; therefore, per the pre-specified PK Analysis Population, they were excluded from the analyses shown in this table.

a median (range).

AUC<sub>0-∞</sub> = area under the plasma concentration versus time curve from time 0 to infinity; AUC<sub>0-t</sub> = area under the plasma concentration versus time curve from time 0 to the last measurable plasma drug concentration;

C<sub>max</sub> = maximum plasma drug concentration; Group 2A = moxifloxacin/placebo-risperidone; Group 2B = placebo-risperidone/moxifloxacin; PK = pharmacokinetic; T<sub>max</sub> = time of maximum plasma drug concentration;

T<sub>1/2</sub> = terminal elimination half-life.

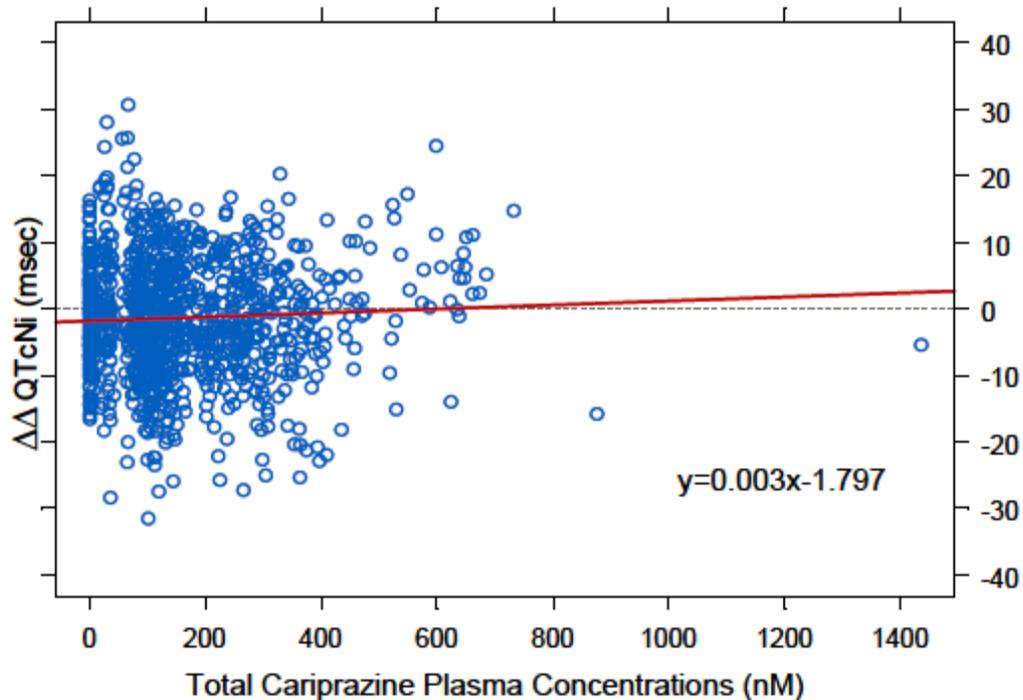
Source: the sponsor's report, page 102.

*Reviewer's Comment: The reported  $C_{max}$  for moxifloxacin in this study was 1835 ng/mL, which is 62% of the value previously reported as typical for moxifloxacin (2952 ng/mL) (Florian et. al., J Clin Pharmacol 2011 51: 1152).*

#### **4.2.8.4.2 Exposure-Response Analysis**

There was no apparent relationship between total cariprazine concentrations and the time matched  $\Delta\Delta$ QTcNi intervals (Figure 3).

**Figure 3: Total Cariprazine Concentration (sum of cariprazine and desmethyl cariprazine and didesmethyl cariprazine plasma concentrations) versus the Time-matched Baseline adjusted QTcNi Change from Placebo.**

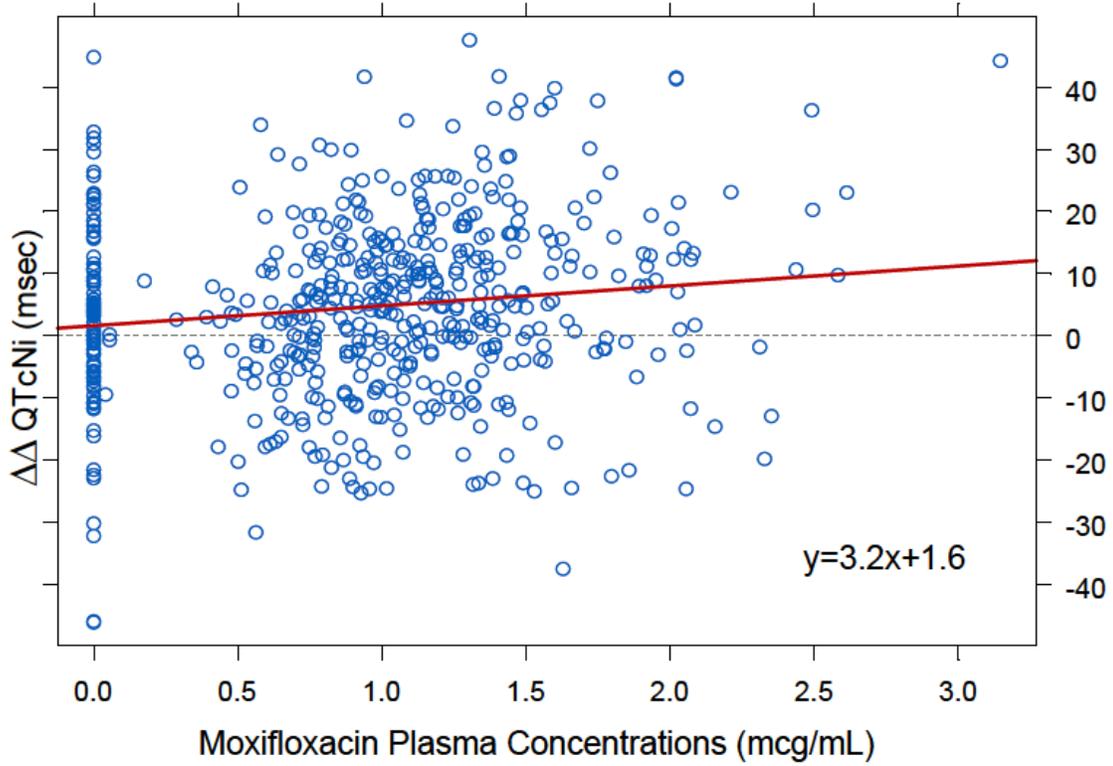


*Source: the sponsor's report, page 119.*

*Reviewer's Analysis: We performed an independent analysis using a linear mixed effect model. The result is presented in section 5.*

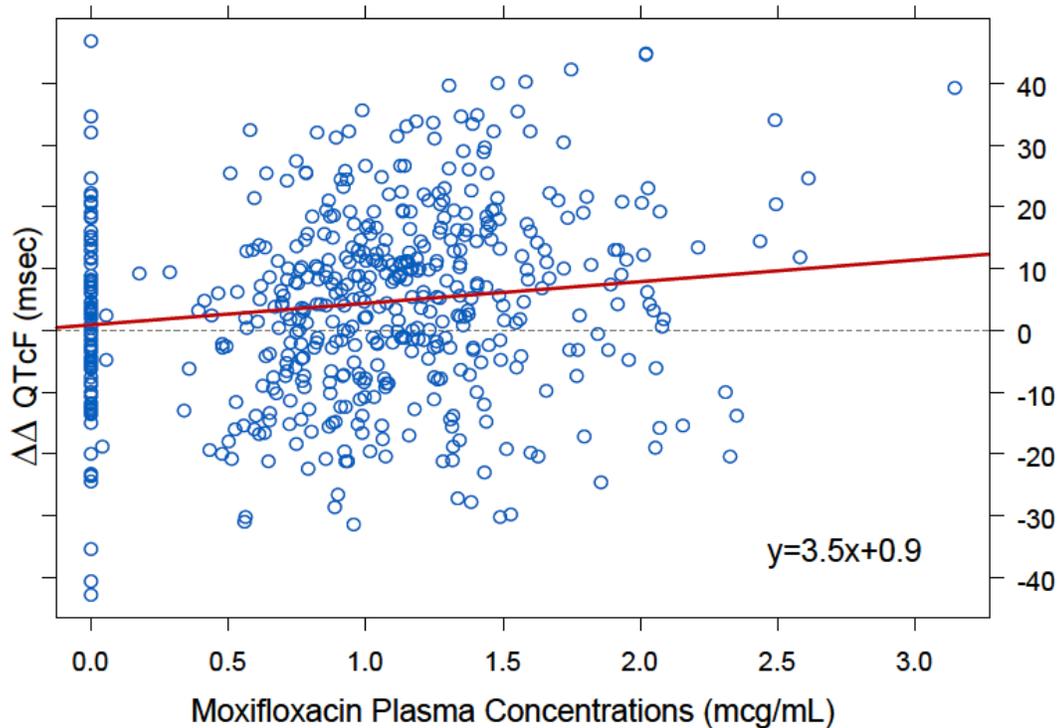
Mixed-effects models were used to quantify the relationship between moxifloxacin concentrations and time-matched  $\Delta\Delta$ QTcNi and  $\Delta\Delta$ QTcF. The dataset included 39 patients who received moxifloxacin and had measurable moxifloxacin concentrations. The results demonstrated a positive significant linear relationship between moxifloxacin plasma concentrations and  $\Delta\Delta$ QTcNi (slope = 3.2 ms per  $\mu\text{g/mL}$ ) and  $\Delta\Delta$ QTcF (slope = 3.5 ms per  $\mu\text{g/mL}$ ). Plots of  $\Delta\Delta$ QTcNi and  $\Delta\Delta$ QTcF versus moxifloxacin plasma concentrations are presented in Figure 4 and Figure 5, respectively.

**Figure 4: Scatterplot of Placebo-Corrected  $\Delta\Delta$ QTcNi Versus Moxifloxacin Concentration**



*Source: the sponsor's report, page 117.*

**Figure 5: Scatterplot of Placebo-Corrected  $\Delta\Delta$ QTcF Versus Moxifloxacin Concentration**



*Source: the sponsor's report, page 117.*

*Reviewer's Analysis: We performed an independent analysis using a linear mixed effect model. The result is presented in section 5.*

## **5 REVIEWERS' ASSESSMENT**

### **5.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

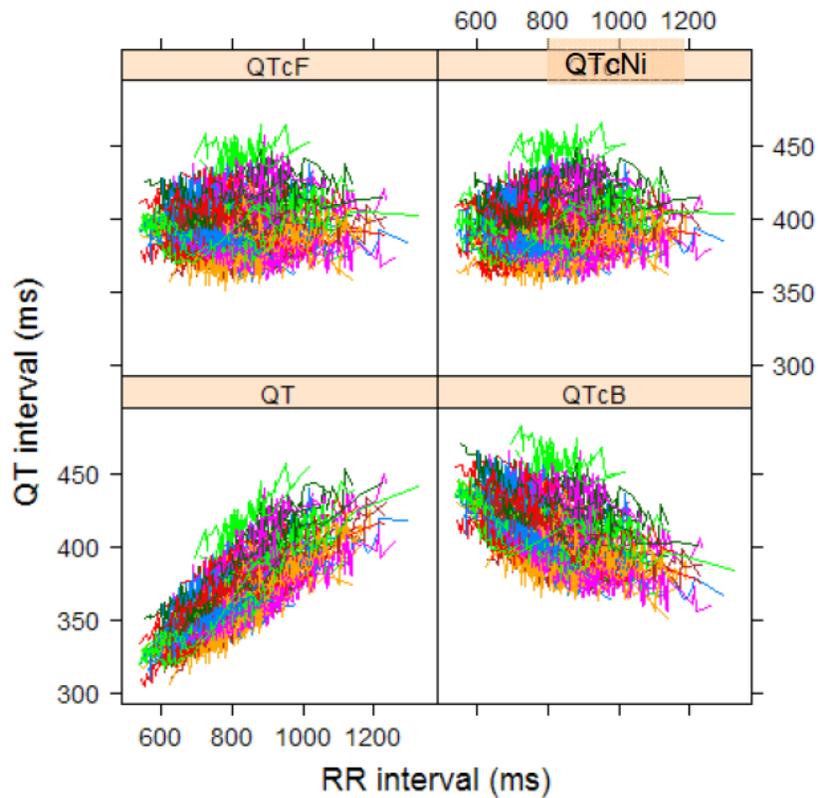
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it appears that QTcNi and QTcF are equally better than QTcB correction. To be consistent with the sponsor's analyses, we choose to present QTcNi results.

**Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Treatment Group	Correction Method					
	QTcB		QTcF		QTcNi	
	N	MSSS	N	MSSS	N	MSSS
<b>Cariprazine 18 mg</b>	36	0.0090	36	0.0022	36	0.0028
<b>Cariprazine 9 mg</b>	47	0.0118	47	0.0024	47	0.0029
<b>Moxifloxacin 400 mg</b>	53	0.0099	53	0.0016	53	0.0023
<b>Placebo</b>	125	0.0104	125	0.0024	125	0.0006
<b>All</b>	125	0.0098	125	0.0017	125	0.0013

The QT-RR interval relationship is presented in Figure 6 together with the Bazett's (QTcB, Fridericia (QTcF) and an Individual correction (QTcNi).

**Figure 6: QT, QTcB, QTcF, QTcNi vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcNi effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between Cariprazine 9 mg and placebo, and between Cariprazine 18 mg and placebo are 3.3 ms and 3.8 ms, respectively.

**Table 8: Analysis Results of  $\Delta$ QTcNi and  $\Delta\Delta$ QTcNi for Cariprazine 9 mg, Cariprazine 18 mg and Moxifloxacin 400 mg**

Time (h)	Cariprazine 18 mg on Day 34			Cariprazine 9 mg on Day 20			Moxifloxacin 400 mg Groups 2A and 2B			
	$\Delta$ QTcNi	$\Delta\Delta$ QTcNi		$\Delta$ QTcNi	$\Delta\Delta$ QTcNi		$\Delta$ QTcNi	$\Delta\Delta$ QTcNi		
	N	LS Mean	90% CI	N	LS Mean	90% CI	N	LS Mean	Unadjusted 90% CI	Adjusted* 90% CI
1	36	-1.1	(-3.6, 1.4)	44	-0.7	(-3.0, 1.6)	51	1.6	(-0.6, 3.8)	(-1.4, 4.5)
2	35	-1.1	(-3.7, 1.4)	46	-0.4	(-2.7, 1.9)	53	4.7	(2.5, 6.9)	(1.7, 7.7)
3	35	-2.4	(-5.1, 0.3)	44	0.6	(-1.8, 3.1)	52	6.6	(4.3, 8.9)	(3.4, 9.8)
4	35	-0.9	(-3.5, 1.7)	44	0.9	(-1.4, 3.3)	52	5.7	(3.5, 7.9)	(2.6, 8.8)
5	36	-1.1	(-4.0, 1.7)	44	-0.4	(-3.0, 2.2)	52	5.3	(2.8, 7.7)	(1.9, 8.6)
6	36	-2.6	(-5.4, 0.2)	44	-2.6	(-5.2, 0.0)	52	5.0	(2.6, 7.4)	(1.7, 8.3)
7	36	-1.2	(-4.0, 1.6)	43	-1.1	(-3.7, 1.5)	52	5.0	(2.6, 7.4)	(1.7, 8.2)
8	36	1.4	(-1.1, 3.8)	43	-0.3	(-2.5, 2.0)	52	5.2	(3.2, 7.3)	(2.4, 8.1)
9	35	0.0	(-2.8, 2.8)	43	-0.8	(-3.4, 1.7)	53	4.3	(1.9, 6.7)	(1.1, 7.6)
10	36	-0.3	(-3.2, 2.5)	42	-0.1	(-2.8, 2.6)	52	3.9	(1.4, 6.3)	(0.5, 7.3)
11	35	0.5	(-2.2, 3.3)	42	0.3	(-2.2, 2.9)	52	4.4	(2.1, 6.8)	(1.2, 7.6)
12	35	0.5	(-2.1, 3.1)	40	-1.7	(-4.2, 0.7)	50	4.3	(2.1, 6.6)	(1.2, 7.4)

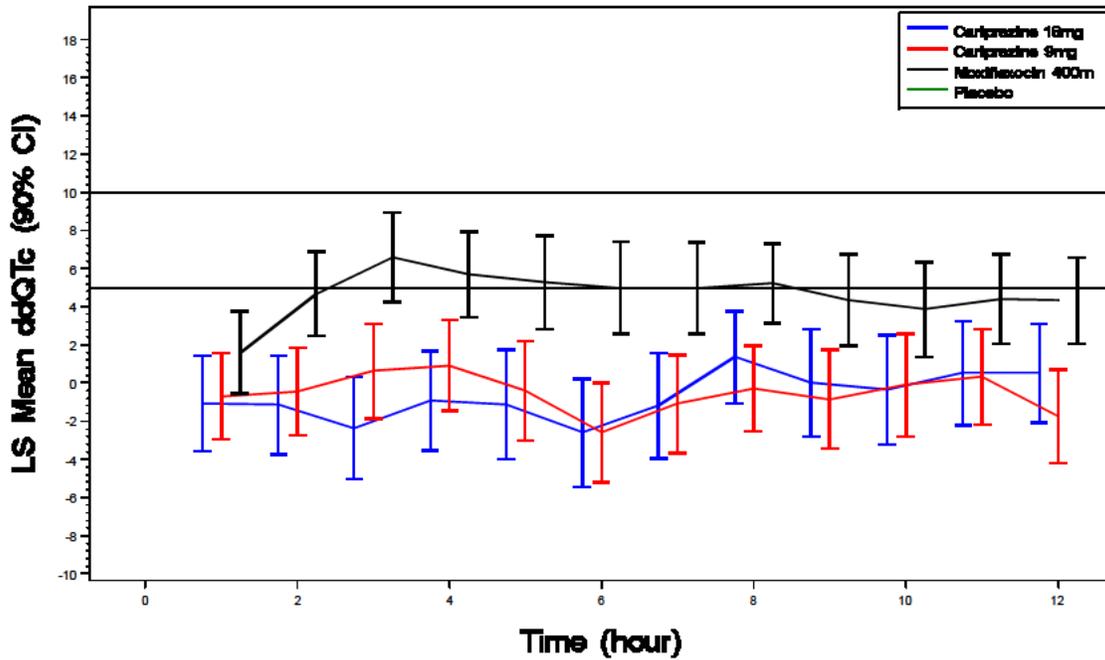
### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 4.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 3.4 ms, which indicates that an effect of moxifloxacin of at least 5 ms QTcNi effect due to moxifloxacin cannot be detected from the study.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcNi Over Time

Figure 7 displays the time profile of  $\Delta\Delta$ QTcNi for cariprazine treatment groups and moxifloxacin 400 mg.

**Figure 7: Mean and 90% CI  $\Delta\Delta$ QTcNi Time Course for Cariprazine 9 mg, Cariprazine 18 mg and Moxifloxacin 400 mg**



#### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcNi values are  $\leq 450$  ms, between 450 ms and 480 m, and between 480 ms and 500 ms. No subject's QTcNi was above 480 ms. No subject's change from baseline was above 60 ms (see Table 10).

**Table 9: Categorical Analysis for QTcNi**

Treatment Group	Total N	Value $\leq 450$ ms	450 ms < Value $\leq 480$ ms	480 ms < Value $\leq 500$ ms
Cariprazine 18 mg	36	36 (100%)	0 (0.0%)	0 (0.0%)
Cariprazine 9 mg	47	47 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	53	49 (92.5%)	4 (7.5%)	0 (0.0%)
Placebo	125	123 (98.4%)	2 (1.6%)	0 (0.0%)

**Table 10: Categorical Analysis for  $\Delta QTC_{Ni}$**

Treatment Group	Total N	Value $\leq 30$ ms	30 ms < Value $\leq 60$ ms
Cariprazine 18 mg	36	36 (100%)	0 (0.0%)
Cariprazine 9 mg	47	46 (97.9%)	1 (2.1%)
Moxifloxacin 400 mg	52	50 (96.2%)	2 (3.8%)
Placebo	64	61 (95.3%)	3 (4.7%)

### 5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the  $\Delta HR$  effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between Cariprazine 9 mg and placebo, and between Cariprazine 18 mg and placebo are 8.7 bpm and 11.6 bpm, respectively. Table 12 presents the categorical analysis of HR. Eleven subjects who experienced HR interval greater than 100 bpm are in cariprazine groups.

**Table 11: Analysis Results of  $\Delta HR$  and  $\Delta\Delta HR$  for Cariprazine 9 mg, Cariprazine 18 mg and Moxifloxacin 400 mg**

Time (h)	Cariprazine 18 mg On Day 34			Cariprazine 9 mg On Day 20			Moxifloxacin 400 mg Groups 2A and 2B		
	$\Delta HR$	$\Delta\Delta HR$		$\Delta HR$	$\Delta\Delta HR$		$\Delta HR$	$\Delta\Delta HR$	
	N	LS Mean	90% CI	N	LS Mean	90% CI	N	LS Mean	90% CI
1	36	7.4	(4.6, 10.1)	44	5.9	(3.4, 8.4)	51	0.3	(-2.0, 2.7)
2	35	9.1	(6.5, 11.6)	46	6.4	(4.1, 8.7)	53	-0.1	(-2.3, 2.1)
3	35	6.5	(3.9, 9.2)	44	2.7	(0.2, 5.1)	52	-0.7	(-3.0, 1.6)
4	35	5.5	(2.9, 8.1)	44	3.5	(1.1, 5.9)	52	-0.1	(-2.4, 2.1)
5	36	4.1	(1.5, 6.7)	44	3.6	(1.3, 6.0)	52	-1.1	(-3.3, 1.1)
6	36	3.8	(1.2, 6.4)	44	5.5	(3.1, 7.9)	52	-0.7	(-2.9, 1.6)
7	36	5.1	(2.4, 7.7)	43	5.0	(2.5, 7.5)	52	0.1	(-2.2, 2.3)
8	36	5.9	(3.4, 8.4)	43	4.6	(2.2, 6.9)	52	1.6	(-0.5, 3.8)
9	35	3.0	(0.6, 5.5)	43	2.5	(0.3, 4.7)	53	-0.9	(-3.0, 1.1)
10	36	3.5	(1.1, 5.9)	42	4.8	(2.5, 7.0)	52	-0.2	(-2.2, 1.9)
11	35	2.4	(-0.3, 5.2)	42	5.8	(3.3, 8.3)	52	0.5	(-1.9, 2.8)
12	35	4.5	(2.1, 6.9)	40	6.4	(4.1, 8.7)	50	1.4	(-0.7, 3.6)

**Table 12: Categorical Analysis for HR**

Treatment Group	Total N	HR < 100 bpm	HR >=100 bpm
Cariprazine 18 mg	36	28 (77.8%)	8 (22.2%)
Cariprazine 9 mg	47	41 (87.2%)	6 (12.8%)
Moxifloxacin 400 mg	53	51 (96.2%)	2 (3.8%)
Placebo	125	111 (88.8%)	14 (11.2%)

### 5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the  $\Delta$ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between cariprazine 9 mg and placebo, and between cariprazine 18 mg and placebo are 1.5 ms and 3.6 ms, respectively. Table 14 presents the categorical analysis of PR. Four subjects who experienced PR interval greater than 200 ms are in cariprazine groups.

**Table 13: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Cariprazine 9mg, Cariprazine 18 mg and Moxifloxacin 400 mg**

Time (h)	Cariprazine 18 mg On Day 34			Cariprazine 9 mg On Day 34			Moxifloxacin 400 mg From Groups 2A and 2B		
	$\Delta$ PR	$\Delta\Delta$ PR		$\Delta$ PR	$\Delta\Delta$ PR		$\Delta$ PR	$\Delta\Delta$ PR	
	N	LS Mean	90% CI	N	LS Mean	90% CI	N	LS Mean	90% CI
1	36	-0.7	(-3.9, 2.6)	44	-3.0	(-6.0, -0.0)	51	-1.1	(-3.9, 1.7)
2	35	-2.8	(-5.8, 0.1)	46	-2.5	(-5.2, 0.1)	53	-0.7	(-3.2, 1.9)
3	35	-1.1	(-4.1, 2.0)	44	-1.3	(-4.1, 1.5)	52	-1.1	(-3.8, 1.5)
4	35	-1.8	(-4.8, 1.3)	44	-2.9	(-5.7, -0.1)	52	-1.1	(-3.7, 1.5)
5	36	-0.5	(-3.4, 2.5)	44	-2.9	(-5.6, -0.2)	52	-0.7	(-3.2, 1.8)
6	36	-0.8	(-3.7, 2.2)	44	-2.7	(-5.4, 0.0)	52	-1.1	(-3.6, 1.5)
7	36	-0.4	(-3.6, 2.7)	43	-3.7	(-6.7, -0.8)	52	-2.0	(-4.7, 0.7)
8	36	-0.8	(-3.9, 2.2)	43	-3.3	(-6.2, -0.5)	52	-2.4	(-5.0, 0.2)
9	35	0.5	(-2.4, 3.4)	43	-2.1	(-4.8, 0.5)	53	0.1	(-2.4, 2.5)
10	36	0.7	(-2.1, 3.6)	42	-2.1	(-4.8, 0.6)	52	-0.1	(-2.5, 2.4)
11	35	0.3	(-2.8, 3.5)	42	-1.4	(-4.3, 1.5)	52	0.2	(-2.5, 2.9)
12	35	0.1	(-3.1, 3.2)	40	-3.2	(-6.2, -0.3)	50	-0.6	(-3.3, 2.2)

**Table 14: Categorical Analysis for PR**

Treatment Group	Total N	PR < 200 ms	PR ≥200 ms
Cariprazine 18 mg	36	33 (91.7%)	3 (8.3%)
Cariprazine 9 mg	47	46 (97.9%)	1 (2.1%)
Moxifloxacin 400 mg	53	49 (92.5%)	4 (7.5%)
Placebo	125	113 (90.4%)	12 (9.6%)

**5.2.4 QRS Analysis**

The statistical reviewer used mixed model to analyze the  $\Delta$ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between cariprazine 9 mg and placebo, and between cariprazine 18 mg and placebo are 1.2 ms and 0.9 ms, respectively. Table 16 presents the categorical analysis of QRS. No subject who experienced QRS interval greater than 110 ms is in cariprazine group.

**Table 15: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Cariprazine 9mg, Cariprazine 18 mg and Moxifloxacin 400 mg**

Time (h)	Cariprazine 18 mg On Day 34			Cariprazine 9 mg On Day 20			Moxifloxacin 400 mg Groups 2A and 2B		
	$\Delta$ QRS	$\Delta\Delta$ QRS		$\Delta$ QRS	$\Delta\Delta$ QRS		$\Delta$ QRS	$\Delta\Delta$ QRS	
	N	LS Mean	90% CI	N	LS Mean	90% CI	N	LS Mean	90% CI
1	36	-1.9	(-2.9, -0.9)	44	-1.1	(-2.0, -0.1)	51	-0.6	(-1.5, 0.3)
2	35	-1.9	(-3.0, -0.8)	46	-1.1	(-2.1, -0.2)	53	-0.5	(-1.5, 0.4)
3	35	-1.2	(-2.2, -0.1)	44	0.1	(-0.9, 1.1)	52	0.1	(-0.9, 1.0)
4	35	-0.4	(-1.6, 0.7)	44	0.1	(-1.0, 1.1)	52	0.0	(-0.9, 1.0)
5	36	-0.4	(-1.7, 0.9)	44	0.0	(-1.1, 1.2)	52	-0.6	(-1.7, 0.4)
6	36	-0.8	(-2.1, 0.5)	44	-0.3	(-1.5, 0.8)	52	-0.1	(-1.2, 1.0)
7	36	-1.8	(-2.9, -0.7)	43	-1.2	(-2.2, -0.2)	52	-0.5	(-1.4, 0.5)
8	36	-1.2	(-2.2, -0.1)	43	-0.5	(-1.5, 0.5)	52	-0.8	(-1.7, 0.2)
9	35	-1.9	(-3.0, -0.7)	43	-1.5	(-2.6, -0.4)	53	-0.4	(-1.4, 0.6)
10	36	-0.9	(-1.9, 0.2)	42	-0.1	(-1.1, 0.9)	52	-1.0	(-1.9, -0.1)
11	35	-1.9	(-2.9, -0.8)	42	-0.8	(-1.7, 0.2)	52	-1.0	(-1.9, -0.1)
12	35	-0.8	(-1.9, 0.3)	40	-0.8	(-1.9, 0.2)	50	-0.5	(-1.4, 0.5)

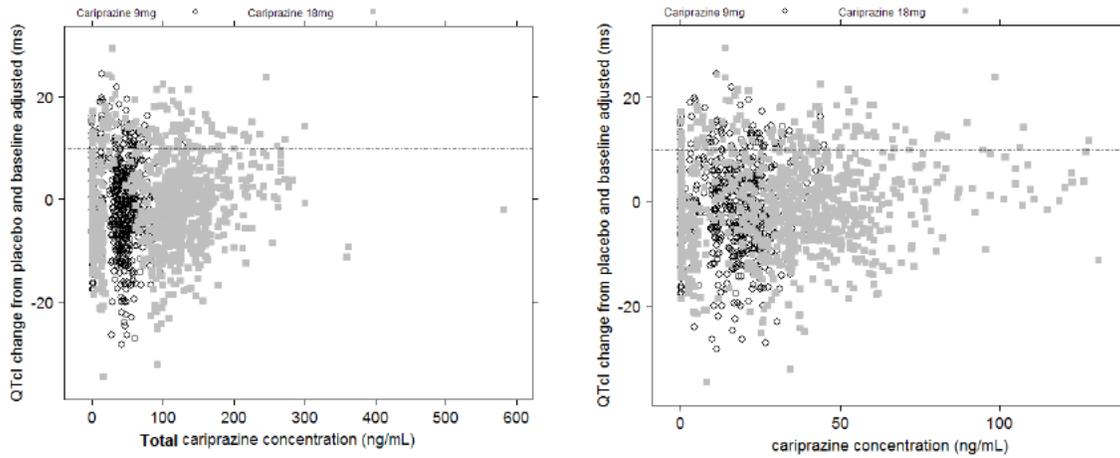
**Table 16: Categorical Analysis for QRS**

Treatment Group	Total N	QRS < 110 ms	QRS $\geq$ 110 ms
Cariprazine 18mg	36	36 (100%)	0 (0.0%)
Cariprazine 9mg	47	47 (100%)	0 (0.0%)
Moxifloxacin 400mg	53	53 (100%)	0 (0.0%)
Placebo	125	124 (99.2%)	1 (0.8%)

**5.3 CLINICAL PHARMACOLOGY ASSESSMENTS**

The relationship between  $\Delta\Delta\text{QTcNi}$  and cariprazine concentrations was assessed with cariprazine concentration (right graph) as well as total cariprazine concentration which is sum of cariprazine, desmethyl and didesmethyl concentrations (left graph). The exposure-response analyses for desmethyl and didesmethyl could not be performed due to the flat PK profiles of the two metabolites. The results are visualized in Figure 5 with no evident exposure-response relationship.

**Figure 8:  $\Delta\Delta\text{QTcNi}$  vs. Cariprazine Concentration**



The relationship between  $\Delta\Delta QTcF$  and moxifloxacin concentrations was investigated by linear mixed-effects modeling.  $QTcF$  was chosen to be consistent with reports in the literature. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

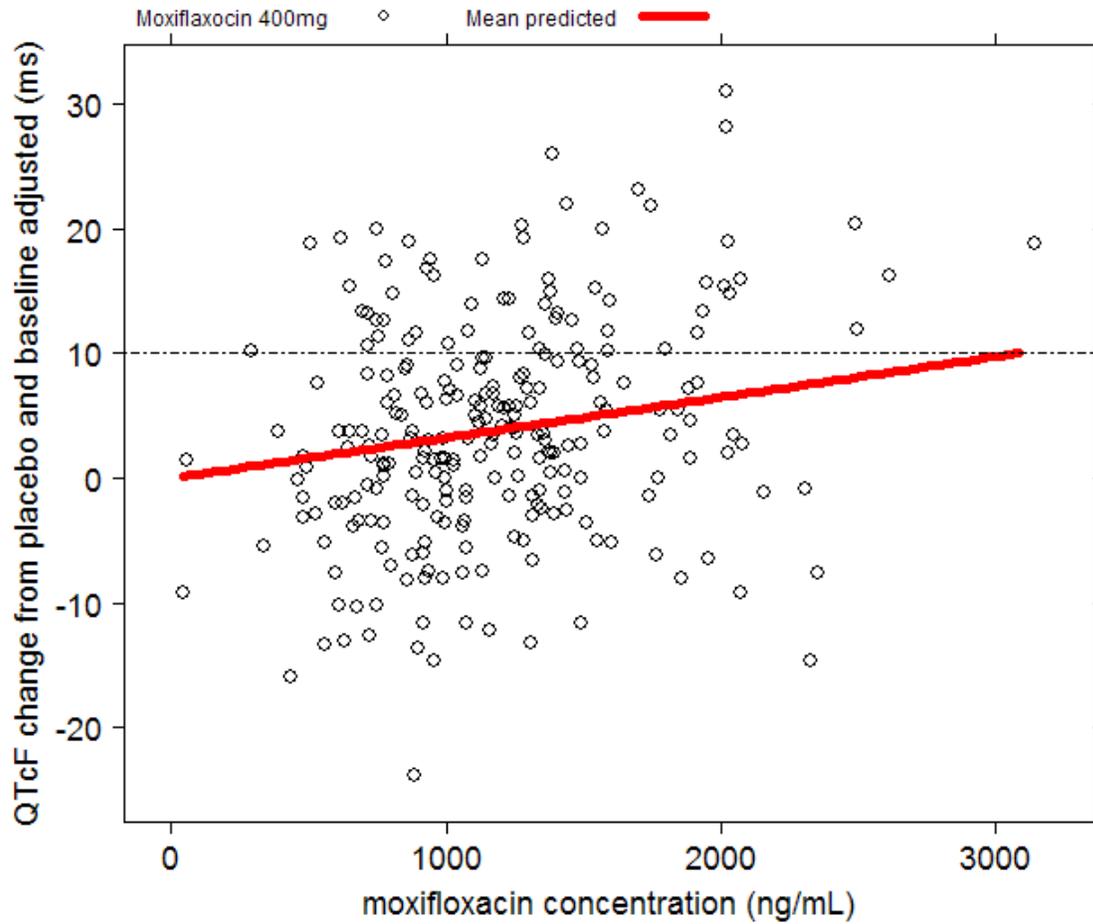
A significant slope was identified for Model 2 and Model 3. Model 2 was used for further analysis because it was found to best fit the data based on AIC. Table 17 summarizes the results of the analysis.

**Table 17: Parameter Estimates of Exposure-Response Model of Moxifloxacin**

Parameter	Estimate	p-value	Inter-individual Variability
$\Delta\Delta QTc = \text{slope} * \text{Moxifloxacin Concentration}$			
Intercept (ms)	0		5.56
Slope (ms per $\mu\text{g/mL}$ )	3.3	0.012	1.75
Residual Variability (ms)	6.26		

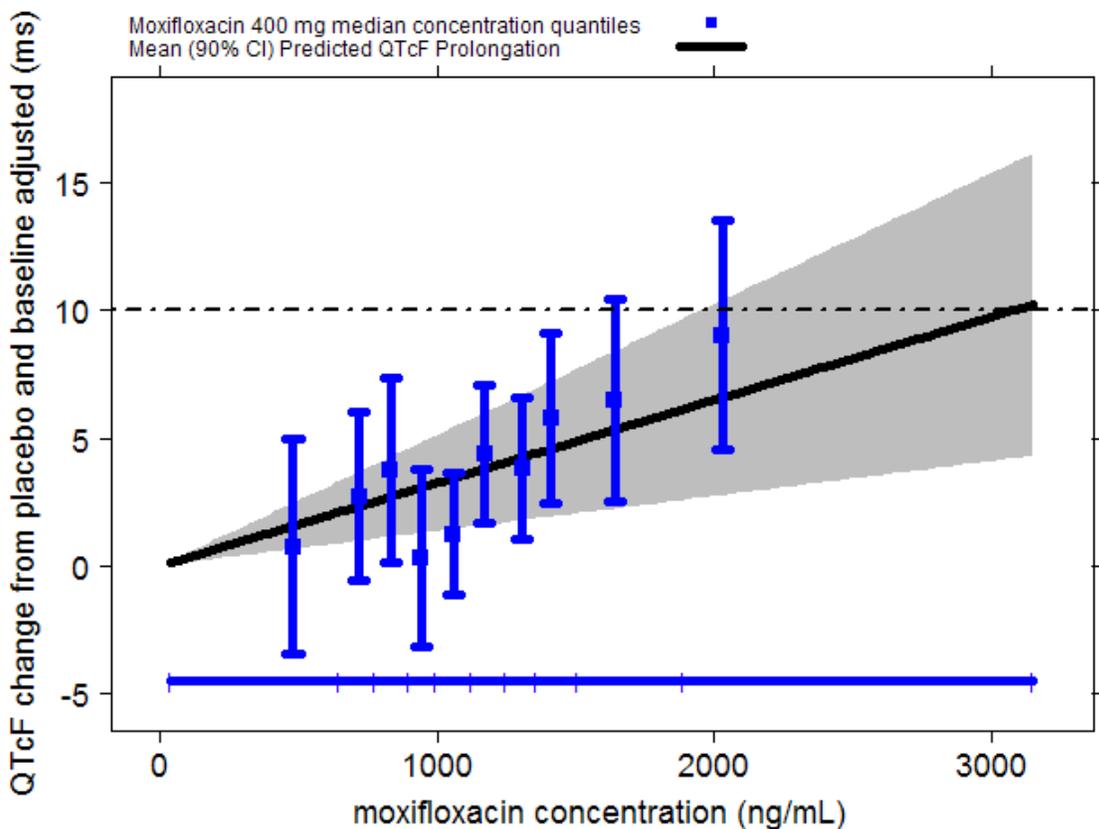
The exposure-response relationship between  $\Delta\Delta QTcF$  and moxifloxacin concentrations is visualized in Figure 9.

**Figure 9: Observed  $\Delta\Delta\text{QTcF}$  Versus Moxifloxacin Concentrations Together with the Population Prediction (solid red line)**



The goodness-of-fit plot in Figure 10 shows the observed moxifloxacin concentration grouped into quantiles and associated mean (90% CI)  $\Delta\Delta\text{QTcF}$  together with the mean (90% CI) predicted  $\Delta\Delta\text{QTcF}$ .

**Figure 10: Observed Moxifloxacin Concentration (Quantiles) and Associated Mean (90% CI)  $\Delta\Delta$ QTcF (colored dots) with the Mean (90% CI) Predicted  $\Delta\Delta$ QTcF (black line with shaded grey area)**



The slope of the relationship between  $\Delta\Delta$ QTcF and moxifloxacin concentration (3.3 ms per  $\mu\text{g}/\text{mL}$ ) is consistent with slope (3.06 ms per  $\mu\text{g}/\text{mL}$ ) reported in a previous publication analyzing data from 20 studies (Florian et. al., J Clin Pharmacol 2011 51: 1152) and therefore provides evidence of assay sensitivity for this thorough QT study. Furthermore, the time course is consistent with expectation as the peak effect is seen at 3 hours post-dose and declines thereafter. If moxifloxacin concentrations in this study had reached levels typically observed following a single 400-mg moxifloxacin dose, it is likely that assay sensitivity would have been established using traditional ICH E14 interpretation.

## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

#### **5.4.2 ECG assessments**

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

#### **5.4.3 PR and QRS Interval**

There were no clinically relevant effects on PR or QRS.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	12 mg/day	
Maximum tolerated dose	The highest dose studied in the completed MTD study in patients with schizophrenia (RGH-MD-01) was 12.5 mg and the MTD was not reached. A second MTD study (RGH-MD-18) is currently ongoing. This is a cohort sequential study and plans to explore cariprazine doses up to 36 mg to determine the suprathreshold dose for use in Study RGH-MD-02.	
Principal adverse events	Common adverse events reported in $\geq 5\%$ of schizophrenia and bipolar mania patients treated with cariprazine include headache, insomnia, extrapyramidal disorder, akathisia, constipation, nausea, sedation, dizziness, dyspepsia, restlessness, vomiting, and anxiety [Note: Based on pooled data from 5 studies in patients with schizophrenia and bipolar mania (N = 870)].	
Maximum dose tested	Single Dose	2.5 mg in healthy volunteers
	Multiple Dose	12.5 mg/day for 27 days in patients with schizophrenia
Exposures Achieved at Maximum Tested Dose	Single Dose	<p><u>Cariprazine:</u> 2.5 (32% CV) ng/mL for <math>C_{max}</math>, 136.7 (17% CV) ng•h/mL for <math>AUC_{0-\infty}</math></p> <p><u>Desmethyl cariprazine:</u> 0.37 (21% CV) ng/mL for <math>C_{max}</math>, 30.1 (30% CV) ng•h/mL for <math>AUC_{0-\infty}</math></p> <p><u>Didesmethyl Cariprazine:</u> 0.31 (25% CV) ng/mL for <math>C_{max}</math>, 308.5 (16% CV) ng•h/mL for <math>AUC_{0-\infty}</math></p>
	Multiple Dose	<p><u>Cariprazine:</u> 40.3 (21% CV) ng/mL for <math>C_{max}</math>, 593 (9% CV) ng•h/mL for <math>AUC_{0-24\text{ hr}}</math></p> <p><u>Desmethyl cariprazine:</u> 12.7 (36% CV) ng/mL for <math>C_{max}</math>, 251 (41% CV) ng•h/mL for <math>AUC_{0-24\text{ hr}}</math></p> <p><u>Didesmethyl cariprazine:</u> 83.0 (16% CV) ng/mL for <math>C_{max}</math>, 1826 (16% CV) ng•h/mL for <math>AUC_{0-24\text{ hr}}</math></p> <p>(Note: data on Day 30)</p>

Range of linear PK	Multiple doses up to 12.5 mg/day (for both C <sub>max</sub> and AUC <sub>0-24 hr</sub> )	
Accumulation at steady state	6-7 fold (1.0 mg/day for 21 days)	
Metabolites	Desmethyl cariprazine, didesmethyl cariprazine (active metabolites measured in all clinical studies) Hydroxy cariprazine, hydroxy cariprazine glucuronide, hydroxy cariprazine sulfate, hydroxy desmethyl cariprazine glucuronide, hydroxy didesmethyl cariprazine glucuronide (measured only in one clinical study)	
Absorption	Absolute/Relative Bioavailability	<u>Absolute bioavailability:</u> No human data available (55% in rats and 70% in dogs) <u>Relative bioavailability:</u> The tablet formulation was 65% bioavailable relative to the capsule formulation.
	T <sub>max</sub>	<u>Cariprazine:</u> 3-5 h (range: 2-12 h) <u>Desmethyl cariprazine:</u> 3-8 h (range: 2-12 h) <u>Didesmethyl cariprazine:</u> 2-12 h (range: 1-72 h)
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	V <sub>d</sub> /F was 6959 (36% CV) L for males and 3966 (28% CV) L for females. (Note: Mean body weight in females was 9% lower than that in males.)
	% bound	96% in human, rat, and dog plasma

Elimination	Route	<p>Average daily excretion of cariprazine and its metabolites in urine was 20.8% of the daily dose following 12.5 mg/day orally.</p> <p>Average daily excretion of cariprazine and its metabolites in feces was 40.1% of the daily dose following 12.5 mg/day orally.</p> <p>(Note: Based on data from RGH-MD-01.)</p>
	Terminal $T_{1/2}$	<p><u>Cariprazine</u>: 2-3 days (1 day as functional <math>T_{1/2}</math>)</p> <p><u>Desmethyl cariprazine</u>: 2-3 days (1 day as functional <math>T_{1/2}</math>)</p> <p><u>Didesmethyl cariprazine</u>: 2-3 weeks (5-6 days as functional <math>T_{1/2}</math>)</p> <p>(Note: Functional <math>T_{1/2}</math> was calculated based on population PK modeling and simulations.)</p>
	CL/F or CL	<p>CL/F was 26.84 (34% CV) L/h for males and 22.07 (32% CV) L/h for females.</p>

Intrinsic Factors	Age	No data available
	Sex	Compared to males, females had 50% higher $C_{max}$ and 24% higher AUC for cariprazine; 61% higher $C_{max}$ and 49% higher AUC for desmethyl cariprazine; 58% higher $C_{max}$ and 24% higher AUC for didesmethyl cariprazine (Note: Mean body weight in females was 9% lower than that in males.)
	Race	No data available
	Hepatic & Renal Impairment	Compared to healthy subjects, patients with either mild or moderate hepatic impairment had 2-3% higher $C_{max}$ and 8% lower to 14% higher AUC for cariprazine; 23-40% lower $C_{max}$ and 35-42% lower AUC for desmethyl cariprazine; 18-26% lower $C_{max}$ and 27-31% lower AUC for didesmethyl cariprazine.  No data available for renal impairment

Extrinsic Factors	Drug interactions	Compared to cariprazine alone, cariprazine coadministered with ketoconazole had 232% higher $C_{max}$ and 278% higher AUC for cariprazine; 38% lower $C_{max}$ and 35% lower AUC for desmethyl cariprazine; 33% higher $C_{max}$ and 33% higher AUC for didesmethyl cariprazine.
	Food Effects	<p>Compared to fasted condition, cariprazine coadministered with a high-fat breakfast had 21% lower <math>C_{max}</math> and 3% higher AUC for cariprazine; 5% lower <math>C_{max}</math> and 25% higher AUC for desmethyl cariprazine; 7% higher <math>C_{max}</math> and 2% lower AUC for didesmethyl cariprazine (based on data from the capsule formulation).</p> <p>Compared to fasted condition, cariprazine coadministered with a high-fat breakfast had 6% lower <math>C_{max}</math> and 17% higher AUC for cariprazine; 13% lower <math>C_{max}</math> and 2% lower AUC for desmethyl cariprazine; 12% lower <math>C_{max}</math> and 7% higher AUC for didesmethyl cariprazine (based on data from the tablet formulation).</p>

Expected High Clinical Exposure Scenario	<p>The TQT study RGH-MD-02 will assess the effects of a therapeutic dose (12 mg/day) and a suprathereapeutic dose (up to 36 mg/day) of cariprazine on QT<sub>c</sub> interval. The selected maximum suprathereapeutic dose of 36 mg/day would produce ~3-fold higher exposure to cariprazine and desmethyl cariprazine and ~2- to 2.5-fold higher exposure to didesmethyl cariprazine compared to what is expected to be observed in a therapeutic dose of 12 mg/day at steady state. Among the known effect modifiers that might be present in the target population, the drug-drug interaction between cariprazine and the strong CYP3A4 inhibitor ketoconazole has the greatest significant effect on the exposure of cariprazine (2- to 3-fold increase), desmethyl cariprazine (35-38% decrease), and didesmethyl cariprazine (33% increase). Other factors such as hepatic impairment, high-fat meals, and genders have minimal effects on the exposure of cariprazine and the metabolites. Therefore, this selected maximum suprathereapeutic dose should provide adequate exposure (C<sub>max</sub> and AUC) to embrace maximally possible exposure increases caused by the interaction of cariprazine with any known effect modifiers.</p>
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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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MOH JEE NG  
03/14/2013

QIANYU DANG  
03/14/2013

JOO YEON LEE  
03/14/2013

KEVIN M KRUDYS  
03/14/2013

NORMAN L STOCKBRIDGE  
03/14/2013

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

**Application:** 204370

**Application Type:** New NDA

**Name of Drug:** cariprazine capsules (1.5, 3, 4.5, 6 (b) (4) mg)

**Applicant:** Forest Laboratories, Inc.

**Submission Date:** November 19, 2012

**Receipt Date:** November 19, 2012

## 1.0 Regulatory History and Applicant's Main Proposals

This NME was received on November 12, 2012 and will be reviewed under the requirements of the "The Program". Forest is proposing cariprazine for the treatment of mixed or manic episodes associated with bipolar I disorder and for the treatment of schizophrenia. The PDUFA date is November 19, 2013.

## 2.0 Review of the Prescribing Information (PI)

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

## 3.0 Conclusions/Recommendations

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

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

## 5.0 Appendix

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### Selected Requirements of Prescribing Information (SRPI)

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

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### Highlights (HL)

#### GENERAL FORMAT

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

***Comment:*** *Left margin is 0.3".*

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

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

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

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

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

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

***Comment:***

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

***Comment:***

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

***Comment:***

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

***Comment:***

## Selected Requirements of Prescribing Information (SRPI)

**YES**

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

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

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

*Comment:*

**YES**

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

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

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

*Comment:*

#### Highlights Limitation Statement

**YES**

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

*Comment:*

#### Product Title

**YES**

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

*Comment:*

#### Initial U.S. Approval

**NO**

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

*Comment:* *There is a space between the product title and the statement "Initial U.S. Approval:"*

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

- YES** 12. All text must be **bolded**.  
Comment:
- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
Comment:
- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
Comment:

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.  
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage

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

## Selected Requirements of Prescribing Information (SRPI)

### Dosage Forms and Strengths

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

**Comment:** *Capsule formulation only.*

### Contraindications

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

**Comment:**

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

**Comment:** *Only one contraindication listed.*

### Adverse Reactions

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

**Comment:**

### Patient Counseling Information Statement

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

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

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

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

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

**Comment:**

### Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

**Comment:** *M/Year is bracketed.*

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

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

**Comment:**

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

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
*Comment:*
- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
*Comment:* *The language for the Boxed Warning is not listed at the beginning of TOC.*
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
*Comment:*
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
*Comment:*
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
*Comment:*
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”  
*Comment:*

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.  
*Comment:*
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
*Comment:*
- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

## Selected Requirements of Prescribing Information (SRPI)

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

**Comment:** Subsection title 9.2 should read "Abuse" and a new subsection, 9.3, titled "Dependence" should be created.

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.
- Comment:** No PI, IFU, or MG submitted with original application
- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].
- Comment:**
- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- NO** 42. All text is **bolded**.
- Comment:** Reference at the end of statement is not bolded.
- YES** 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").
- Comment:**
- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

## Selected Requirements of Prescribing Information (SRPI)

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

**Comment:**

### Adverse Reactions

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

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

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

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### Patient Counseling Information

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

**Comment:**

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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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KIMBERLY S UPDEGRAFF  
01/17/2013

**RPM FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # 204370	NDA Supplement # -----	Efficacy Supplement Type -----
Proprietary Name: Pending Established/Proper Name: cariprazine Dosage Form: capsules Strengths: 1.5 mg, 3 mg, 4.5 mg, 6 mg (b) (4)		
Applicant: Forest Laboratories, Inc. Agent for Applicant (if applicable): NA		
Date of Application: 11/19/2012 Date of Receipt: 11/19/2012 Date clock started after UN: NA		
PDUFA Goal Date: 11/19/2013		Action Goal Date (if different):
Filing Date: 1/18/2013		Date of Filing Meeting: 1/10/13
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Tx of manic/mixed episodes of bipolar I disorder; Tx of schizophrenia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

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

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

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

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

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?	X			
<ul style="list-style-type: none"> <li>If yes, were all of them submitted on time?</li> </ul>	X			
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</b></p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>For NMEs:</u></b>  <b>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</b></p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><b><u>For non-NMEs:</u></b>  <b>Date of consult sent to Controlled Substance Staff:</b></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		
<p><b>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?</b></p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b>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)?</b></p> <p><i>If no, request in 74-day letter</i></p>		X		The sponsor's deferral request per FDCA Section 505B(a)(3), includes a reason for requesting waiver/ deferral of pediatric studies in children and adolescents. However, the statement provided by the sponsor to serve as evidence, that the studies are being conducted or will be conducted with due diligence at the earliest possible time was not acceptable. DPP will request the sponsor revise the statement in the 74-day letter or separate IR letter specifically for pediatric request(s).
<p><b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b></p> <p>Is this submission a complete response to a pediatric Written</p>		X		

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

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

Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			The sponsor provided the safety summary but did not include a separate cover sheet with references. A request for the additional information was sent to the sponsor on 1/15/13.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK?			X	

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

(send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: QT, Endocrinology</i>	X			QT – will send within the next few weeks (currently with OCP review team) Endocrinology – will send within the next few weeks (currently with PharmTox review team)
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 1/14/2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> CMC: 2/16/2012 ; Clinical/NonClinical: 5/24/2012 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 3/18/2010 (Carci-SPA) <i>If yes, distribute letter and/or relevant minutes before filing</i>	X			

APPEARS THIS WAY ON ORIGINAL

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 10, 2013

**NDA #:** 204370

**PROPRIETARY NAME:** Pending

**ESTABLISHED/PROPER NAME:** cariprazine

**DOSAGE FORM/STRENGTH:** capsules (1.5 mg, 3 mg, 4.5 mg, 6 mg, (b) (4))

**APPLICANT:** Forest Laboratories, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

- 1) Tx of mixed/manic episodes associated with bipolar I disorder
- 2) Tx of schizophrenia

**BACKGROUND:** This NME was received on November 12, 2012 and will be reviewed under the requirements of the “The Program”. Forest is proposing cariprazine for the treatment of mixed or manic episodes associated with bipolar I disorder and for the treatment of schizophrenia. Dr. Temple is signatory authority. This will be reviewed under a STANDARD review clock and the he PDUFA date is November 19, 2013.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Updegraff	Y
	CPMS/TL:	Paul David/Keith Kiedrow	N
Cross-Discipline Team Leader (CDTL)	Robert Levin		Y
Clinical	Reviewer:	Francis Becker	Y
	TL:	Robert Levin	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Huixia Zhang	Y
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	Eiji Ishida	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elzbieta Chalecka-Franaszek	Y
	TL:	Aisar Atrakchi	Y
Statistics (carcinogenicity)	Reviewer:	Karl Lin	N
	TL:		
Ophthalmology	Reviewer:	William Boyd	Y
	TL:	Wiley Chambers	Y
Product Quality (CMC)	Reviewer:	Sherita McLamore-Hines	Y
	TL:	Chhagan Tele	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	John Lee (GCP)	N
	TL:	Susan Leibenhaut	N
Office of Clinical Pharmacology (ONDQA)	Reviewer:	Sandra Suarez	Y
	TL:	Angelica Dorantes	N
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> None</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> OSI consult sent 12/21/12</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> Ophthalmology and clinical do not feel a PDAC will be needed/beneficial. Dr. Mathis will discuss with signatory authority.</p> <p><b>If no, for an NME NDA or original BLA, include the reason. For example:</b></p> <ul style="list-style-type: none"> <li>this drug/biologic is not the first in its class</li> <li>the clinical study design was acceptable</li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined <ul style="list-style-type: none"> <li>Reason: <i>the application did not raise significant safety or efficacy issues beyond ophthalmological issues that DTOP feels can be</i></li> </ul>

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> OCP will have a couple of information requests</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO per Hao Zhu
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> Reviewer has an information request.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Methods Validation Consult completed by CMC on 11/27/12</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> Applicant claims categorical exclusion.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Per CMC reviewer, the manufacturing, testing, and packaging sites for drug substance and drug product are in EES and OC will determine if/which sites need to be inspected.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments: None</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Dr. Temple</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 4/12/13</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>Comments: None</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p><b>ACTIONS ITEMS</b></p>	
<p><input checked="" type="checkbox"/></p>	<p>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).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by</p>

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

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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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KIMBERLY S UPDEGRAFF  
01/17/2013