

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204370Orig1Orig2s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

204370

NAME OF APPLICANT/NDA HOLDER

Forest Laboratories, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

cariprazine hydrochloride

STRENGTH(S)

1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg (b) (4)

DOSAGE FORM

Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

7,943,621

b. Issue Date of Patent

May 17, 2011

c. Expiration Date of Patent

December 20, 2028

d. Name of Patent Owner

Richter Gedeon Vegyészeti Gyár Rt.

Address (of Patent Owner)

Gyömrői út, 19-21.

City/State

Budapest, Hungary

ZIP Code

1103

FAX Number (if available)

(36-1) 432-6005

Telephone Number

(36-1) 431-4000

E-Mail Address (if available)

intprop@richter.hu

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Melina Cioffi, Pharm.D.

Associate Director, Regulatory Affairs

Forest Laboratories, Inc.

Address (of agent or representative named in 1.e.)

Harborside Financial Center, Plaza V, Suite 1900

City/State

Jersey City, NJ

ZIP Code

07311

FAX Number (if available)

Telephone Number

(201) 427-8326

E-Mail Address (if available)

melina.cioffi@frx.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

*Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:*

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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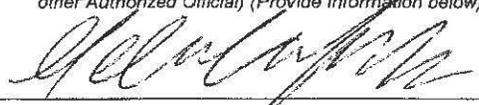
**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	10/12/2012

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Melina Cioffi, Pharm.D., Associate Director, Regulatory Affairs	
Address Forest Laboratories, Inc. Harborside Financial Center, Plaza V, Suite 1900	City/State Jersey City, NJ
ZIP Code 07311	Telephone Number (201) 427-8326
FAX Number (if available)	E-Mail Address (if available) melina.cioffi@frx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use**

NDA NUMBER

204370

NAME OF APPLICANT/NDA HOLDER

Forest Laboratories, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

cariprazine hydrochloride

STRENGTH(S)

1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg (b) (4)

DOSAGE FORM

Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

7,737,142

b. Issue Date of Patent

June 15, 2010

c. Expiration Date of Patent

March 27, 2027

d. Name of Patent Owner

Richter Gedcon Vegyészeti Gyár Rt.

Address (of Patent Owner)

Gyömrői út, 19-21.

City/State

Budapest, Hungary

ZIP Code

1103

FAX Number (if available)

(36-1) 432-6005

Telephone Number

(36-1) 431-4000

E-Mail Address (if available)

intprop@richter.hu

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Melina Cioffi, Pharm.D.

Associate Director, Regulatory Affairs

Forest Laboratories, Inc.

Address (of agent or representative named in 1.e.)

Harborside Financial Center, Plaza V, Suite 1900

City/State

Jersey City, NJ

ZIP Code

07311

FAX Number (if available)

Telephone Number

(201) 427-8326

E-Mail Address (if available)

melina.cioffi@frx.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 14-18, 21-23 and 26-28 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)  
 TRADENAME is indicated for the treatment of schizophrenia. See Section I of the approved package insert for TRADENAME.  
 TRADENAME is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder. See Section I of the approved package insert for TRADENAME.

**5. No Relevant Patents**

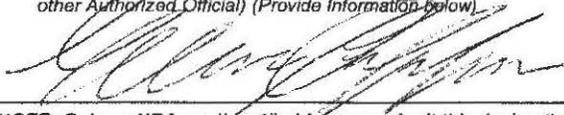
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1** *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2** Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

10/12/2012

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Melina Cioffi, Associate Director, Regulatory Affairs

Address

Forest Laboratories, Inc.  
Harborside Financial Center, Plaza V, Suite 1900

City/State

Jersey City, NJ

ZIP Code

07311

Telephone Number

(201) 427-8326

FAX Number (if available)

E-Mail Address (if available)

melina.cioffi@frx.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- \* To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- \* Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- \* Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
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- \* Only information from form 3542 will be used for Orange Book publication purposes.
- \* Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- \* The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- \* Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**I. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 204370

SUPPL # NA

HFD # 130

Trade Name Vraylar

Generic Name cariprazine

Applicant Name Forest Research Institute, Inc., an affiliate of Forest Laboratories, LLC

Approval Date, If Known September 17, 2015

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the

application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND #                      YES                       ! NO   
! Explain:

Investigation #2  
IND #                      YES                       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES                       ! NO   
Explain:                      ! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Kimberly Updegraff, RPh, MS

Title: Senior Regulatory Project Manager, Division of Psychiatry Products

Date: September 18, 2015

Name of Office/Division Director signing form: Mitchell Mathis, MD

Title: Division Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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  
09/18/2015

MITCHELL V Mathis  
09/18/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204370	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vraylar Established/Proper Name: cariprazine Dosage Form: capsules		Applicant: Forest Research Institute (affiliate of Forest Laboratories, LLC) Agent for Applicant (if applicable): NA
RPM: Kimberly Updegraff		Division: Division of Psychiatry Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>September 17, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/>
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): 1  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#) )**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other None
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified (1 <sup>st</sup> cycle) <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) CR: 11/19/2013 AP: 9/17/2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included 9-17-15
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 12-17-14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
•	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 9-16-15
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	4/1/2015
• Review(s) <i>(indicate date(s))</i>	3/26/15
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> See 1/17/2013 review DMEPA: <input checked="" type="checkbox"/> 4/27/15; 9/16/2015 DMPP/PLT (DRISK): <input type="checkbox"/> OPDP: <input checked="" type="checkbox"/> 8/25/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> Pediatrics: 5/27/15 Maternal Health: 6/1/15
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	See 1/17/2013 review
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC 10/2/2013 If PeRC review not necessary, explain:</li> </ul>	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	3/14/14; 6/18/14; 8/19/14; 12/31/14; 3/13/15; 3/17/15; 3/27/15; 5/29/15 (Information request letter); 6/2/15; 6/4/15; 6/5/15; 6/8/15; 6/11/15 (REVIEW EXTENSION – Major Amendment); 7/15/15; 9/1/15; 9/9/15; 9/11/15; 9/14/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> After action meeting 4/3/2014
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> See first cycle pkg
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> See first cycle pkg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> See first cycle pkg
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> See first cycle pkg
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	See first cycle pkg
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	NA
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 9/16/15
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 9/16/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> See 9/16/15 Clinical review
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> Included 9/17/15

<b>Clinical</b>	
❖ <b>Clinical Reviews</b>	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	9/16/15
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See first cycle pkg (Clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> OSE/OPE: 4/6/15 DTOP: 5/25/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> See 1 <sup>st</sup> cycle pkg review date 8/13/13
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul>	<input checked="" type="checkbox"/> 5/29/15
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input checked="" type="checkbox"/> See 1 <sup>st</sup> cycle pkg
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 5/31/15
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 9/14/15
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 6/30/15; 8/24/15
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 6/30/15; 8/24/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> DPARP: 7/1/15 CFSAN pathology: 8/17/15
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> See 1 <sup>st</sup> cycle pkg
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> See 1 <sup>st</sup> cycle pkg
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 5/19/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 204370 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vraylar Established/Proper Name: cariprazine Dosage Form: capsules		Applicant: Forest Research Institute  Agent for Applicant (if applicable):
RPM: Kimberly Updegraff		Division: Division of Psychiatry Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)               <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)</li> </ul> </li> </ul> Date of check:
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is _____</li> </ul>		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (confirm chemical classification at time of approval)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#) )

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: CR 11-19-2013 (no label)
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Labeling was not sent with CRL
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Labeling was not sent with CRL
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Labeling was not sent with CRL
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	4/16/2013 4/16/2013
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None 1/17/2013 DMEPA: <input checked="" type="checkbox"/> 8/1/2013; 11/19/2013 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 11/13/2013 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None 8/13/2013 Product Quality <input type="checkbox"/> None Other: <input checked="" type="checkbox"/> PMHS 7/19/2013; 8/12/2013
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	1/17/2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Not Included (CR action)
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC</li> <li>If PeRC review not necessary, explain:</li> </ul>	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	12/3/2012; 1/16/2013; 1/18/2013; 1/31/2013; 2/8/2013; 2/21/2013; 3/12/2013; 3/21/2013; 4/1/2013; 4/8/2015; 5/1/2013; 5/17/2013; 5/30/2013; 6/4/2013; 6/7/2013; 6/14/2013; 6/24/2013; 6/28/2013; 7/17/2013(2); 7/30/2013; 8/1/2013; 8/7/2013; 8/9/2013(2); 9/5/2013; 9/12.2013; 9/27/2013; 10/3/2013; 10/21/2013; 10/23/2013; 10/24/2013; 10/30/2013; 11/6/2013
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> 5/24/2012; 10/25/2012 CMC 2/16/2012; 12/9/2011
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> 1/14/2010 CMC 3/18/2010
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> 5/2/2013
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> 8/16/2013
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	Type C Ocular 9/19/2011 Type C OCP 11/15/2011 Type C Clinical 2/11/2009 Type C OCP 10/21/2013

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 11/19/2013
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 11/18/2013
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 10/16/2013
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	7/22/2013; 10/16/2013
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 2 of 7/22/2013 review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> DCRP: 9/30/2013 QT-IRT: 3/14/2013 OSE/OPE: 9/30/2013 DTOP: 8/27/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> 8/13/2013
❖ Risk Management • REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> ) • REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> ) • Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> 8/16/2013
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> 7/26/2013
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 7/22/2013

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None 7/19/2013
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review 11/6/2013
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review 11/1/2013
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None 7/22/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> DPARP: 8/23/2013 DMEP: 9/10/2013
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 7/11/2013
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> 6/13/2013
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 10/10/2013
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 7/18/2013
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Methods Validation 10/17/2013 Biopharmaceutics 7/16/2013
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Not applicable: CR Action

Day of Approval Activities: Not Applicable	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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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  
09/18/2015

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@actavis.com\)](mailto:Cioffi, Melina (Melina.Cioffi@actavis.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Carton/Container labeling  
**Date:** Monday, September 14, 2015 11:34:16 AM

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, for (cariprazine) capsules and to your December 17, 2014, submission containing a class 2 response to our November 19, 2013 action letter.

We also refer to your email dated September 9, 2015, containing your most recent labeling proposal.

We note the following changes to Section 16.1 How Supplied:

- NDC numbers are different for all products.
- The NDC associated with the 6mg 90-count bottle appears to be incorrect. An NDC associated with a 90-count bottle would most likely have 90 as the last two digits, not 00 as listed.
- The imprint codes are not included for the 1.5 mg and 3 mg tablets for the Blister pack of 7.

We remind you that the Carton and Container Labeling must reflect the changes as well.

Please submit updated Carton and Container Labeling by noon on September 15, 2015.

Regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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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  
09/14/2015



NDA 204370/Original 1  
NDA 204370/Original 2

## PMR/PMC DISCUSSION COMMENTS

Forest Research Institute, Inc.  
Attention: Melina Cioffi, PharmD  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vraylar (cariprazine) capsules.

We also refer to your December 17, 2014, submission containing a complete response to our November 19, 2013, action letter. On June 11, 2015, we issued a Review Extension - Major Amendment letter and you were notified that the goal date for the December 17, 2014 submission was being extended by three months. The extended user fee goal date is September 17, 2015.

We propose the following Postmarketing Requirements:

1. Deferred 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.

Final Protocol Submission: 01/2016  
Study/Trial Completion: 01/2017  
Final Report Submission: 07/2017

2. Deferred 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 definitive toxicity/TK study. TK assessment should include cariprazine and the metabolites DCAR and DDCAR.

Final Protocol Submission: 01/2016  
Study/Trial Completion: 01/2017  
Final Report Submission: 07/2017

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.

Final Protocol Submission: 12/2017  
Study/Trial Completion: 12/2018  
Final Report Submission: 06/2019

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.

Final Protocol Submission: 06/2019  
Study/Trial Completion: 06/2022  
Final Report Submission: 12/2022

5. 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.

Final Protocol Submission: 06/2019  
Study/Trial Completion: 06/2022  
Final Report Submission: 12/2022

6. Deferred long-term, open-label safety study in pediatric patients with schizophrenia (ages 13 to 17).

Final Protocol Submission: 06/2022  
Study/Trial Completion: 06/2024  
Final Report Submission: 06/2025

7. Deferred long-term, open-label safety study in pediatric patients with bipolar disorder, recent manic episodes (ages 10 to 17).

Final Protocol Submission: 06/2022  
Study/Trial Completion: 06/2024  
Final Report Submission: 06/2025

8. Conduct a placebo-controlled, randomized withdrawal, dose-response trial in patients with schizophrenia to assess the long-term, dose-related serious adverse effects of cariprazine, including tardive dyskinesia, akathisia, and extrapyramidal symptoms. The trial will 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. The trial should also assess adrenal function.

Final Protocol Submission: 06/2016

Study/Trial Completion: 06/2019

Final Report Submission: 06/2020

9. Conduct a placebo-controlled, randomized withdrawal, dose-response trial in patients with bipolar I disorder to assess the long-term, dose-related serious adverse effects of cariprazine, including tardive dyskinesia, akathisia, and extrapyramidal symptoms. The trial will 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. The trial should also assess adrenal function.

Final Protocol Submission: 06/2016

Study/Trial Completion: 06/2019

Final Report Submission: 06/2020

10. An in vivo drug-drug interaction study to assess cariprazine exposure when cariprazine is coadministered with a proton pump inhibitor.

Final Protocol Submission: 09/2016

Study/Trial Completion: 09/2017

Final Report Submission: 03/2018

11. In-vitro evaluation of:

- 1) inhibition potential of cariprazine, 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.

Final Protocol Submission: 09/2016

Study/Trial Completion: 12/2016

Final Report Submission: 04/2017

We request a response by September 11, 2015.

NDA 204370/Original 1

NDA 204370/Original 2

Page 4

If you have any questions, please contact me at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, RPh, MS  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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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  
09/09/2015



NDA 204370/Original 1  
NDA 204370/Original 2

## GENERAL ADVICE

Forest Research Institute, Inc.  
Attention: Melina Cioffi, PharmD  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vraylar (cariprazine) capsules.

We also refer to your December 17, 2014 submission, which constituted a complete response to our November 19, 2013 action letter. This NDA, currently under review by the Division, provides for the use of cariprazine for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

This letter provides for recommendations for follow-up and reporting of postmarketing ocular adverse events.

FDA is requesting that you expedite cases (i.e., submit these cases as 15-day Alert reports) of all serious and non-serious reports of the following types of ocular adverse events: a) cataract, lens, or lenticular abnormality or change, opacity, opacification or opalescence; b) blindness, night blindness, visual acuity or vision decrease, abnormality or change, visual acuity test abnormality or change; c) retinal, macular, or optic nerve degeneration, abnormality or change; retinal pigment epithelium detachment, abnormality or change; and d) color vision decrease, abnormality or change. This should include all serious and non-serious ocular adverse events (as described above) reported from IND, non-IND, and NDA studies with cariprazine. Please review, prepare, and submit the 15-day Alert reports as described under 21 CFR 314.80, which includes conducting follow-up (21 CFR 314.80(c)(1)(ii)).

Current FDA guidance<sup>1</sup> recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up postmarketing adverse event reports, especially for reports of serious events, and encourages sponsors to use trained health care practitioners to query reporters. Every effort should be made to obtain

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<sup>1</sup> *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, page 4, March 2005.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071696.pdf>

NDA 204370/Original 1

NDA 204370/Original 2

Page 2

thorough and complete follow-up of ocular adverse events, including making every effort to obtain results from ophthalmology consults, assessments, or evaluation of patients with any type of the above ocular events. The clinical information collected in this manner will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports.

In addition, we request that you include a summary and analysis of all ocular adverse events (as described above) reported for cariprazine in the submission of the periodic reports for each reporting period.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

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/s/  
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MITCHELL V Mathis  
09/11/2015

**From:** [Updegraff, Kimberly](#)  
**To:** [Olchaskey, Michael \(Michael.Olchaskey@actavis.com\)](#); [Cioffi, Melina \(Melina.Cioffi@actavis.com\)](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Information Request  
**Date:** Tuesday, September 01, 2015 7:18:28 PM

---

Dear Drs. Olchaskey and Cioffi,

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, for (cariprazine) capsules. We also refer to your December 17, 2014, submission containing a class 2 response to our November 19, 2013 action letter.

Please advise if any of the safety data submitted in the December 17, 2014, submission includes data from patients enrolled at sites under Dr. Joseph Kwentus. If so, please identify the number of patients and where the data is located in the submission.

We request a response by *September 4, 2015*.

Best regards,

Kim Updegraff

.....  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF

09/08/2015

Request dated 9/1/2015

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@actavis.com\)](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Request (pathology slides)  
**Date:** Wednesday, July 15, 2015 5:40:07 PM

---

Dear Dr. Cioffi,

Please refer to your New Drug Application, NDA 204370, for cariprazine. We also refer to your December 17, 2014 resubmission and to your recent submission dated June 8, 2015 which contained a response to our May 29, 2015 information request. We acknowledge your offer to provide the histopathology slides for the lung findings in the 1 year dog toxicity study. We ask that you provide the slides for our evaluation. We note that your re-assessment was provided as a narrative. We ask that you submit a table along with the slides, similar to the histopathology summary table in the original report with number of animals, severity score, and pathology findings.

We kindly request that you provide the actual slides (in addition to the digital version) by July 21, 2015 if possible.

Thank you,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
07/15/2015



NDA 204370/Original 1  
NDA 204370/Original 2

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Forest Research Institute, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vraylar (cariprazine) capsules.

On June 8, 2015, we received your June 8, 2015, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 17, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 3, 2015.

If you have any questions, please contact Kimberly Updegraff, Senior Regulatory Project Manager, at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
06/11/2015



NDA 204370/Original 1  
NDA 204370/Original 2

**ADVICE**

Forest Research Institute, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyralar (cariprazine) capsules.

NDA 204370 provides for the use of Vyralar (cariprazine) capsules for the following indications which, for administrative purposes, we have designated as follows:

- NDA 204370/Original 1 - Acute treatment of manic or mixed episodes associated with bipolar I disorder
- NDA 204370/Original 2 – Treatment of schizophrenia

We have completed our review of the carton and container labeling and we have the following comments:

-  (b) (4)

If you have any questions, please contact Kimberly Updegraff, Senior Regulatory Project Manager, at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.

CAPT, USPHS

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
06/08/2015

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@actavis.com\)](mailto:Cioffi, Melina (Melina.Cioffi@actavis.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Drug Trials Snapshot request  
**Date:** Friday, June 05, 2015 4:08:29 PM  
**Attachments:** [NDA204370--mania.xls](#)  
[NDA204370--schizo.xls](#)

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Dear Dr. Cioffi,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, cariprazine, currently under review in the Division. As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on [www.fda.gov/drugtrialsnapshot](http://www.fda.gov/drugtrialsnapshot).

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- “MORE INFORMATION” sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at [Drugs@FDA](mailto:Drugs@FDA)

We are requesting that you submit this information no later than Friday, June 12, 2015.

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
06/05/2015

**From:** [Updegraff\\_Kimberly](#)  
**To:** [Cioffi\\_Melina \(Melina.Cioffi@actavis.com\)](#)  
**Cc:** [Updegraff\\_Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Nonclinical comments (follow-up to June 4, 2015 conversation)  
**Date:** Thursday, June 04, 2015 2:24:17 PM  
**Attachments:** [image001.png](#)

Dear Dr. Cioffi,

We refer to our June 3, 2015 telephone conversation between the Division of Psychiatry Products and members of your team to discuss your planned response to our May 29, 2015 information 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**

<i>Dose (mg/kg/day)</i>	<i>0</i>		<i>1</i>		<i>2</i>		<i>4</i>		<i>6</i>	
	<i>Male</i>	<i>Female</i>								
<i>N=4</i>										
<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

We acknowledge and agree with your June 4, 2015 email request for an extension of the response date. Please submit your response by COB on Monday, June 8, 2015.

Sincerely,

Kimberly Updegraff, RPh, MS, RAC

Senior Regulatory Project Manager  
 Division of Psychiatry Products  
 FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
 301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
06/04/2015



NDA 204370

**ACKNOWLEDGE CORPORATE  
NAME/ADDRESS CHANGE**

Forest Laboratories, LLC  
Attention: Melina Cioffi, PharmD.  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

We acknowledge receipt on April 21, 2015, of your April 21, 2015 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

Forest Research Institute, Inc.  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

to

Forest Laboratories, LLC  
Morris Corporate Center III  
400 Interpace Parkway  
Parsippany, New Jersey 07054

for the following new drug application (NDA):

NDA 204370 for Vraylar (cariprazine) capsules

We have revised our records to reflect this change.

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their DMFs and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please contact me at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, M.S., RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KIMBERLY S UPDEGRAFF  
06/02/2015



NDA 204370/Original 1  
NDA 204370/Original 2

## INFORMATION REQUEST

Forest Research Institute, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vraylar (cariprazine) capsules.

We also refer to your December 17, 2014 submission containing a class 2 response to our November 19, 2013 action letter.

We note that cariprazine is a cationic amphiphilic compound (CAD) and literature shows that such compounds can cause phospholipidosis (PLD). In the absence of other histopathological findings, PLD alone may be considered an adaptive response rather than an adverse toxic response. However, there is evidence that some phospholipogenic compounds are associated with toxicity, both nonclinical and clinical (e.g., amiodarone). Inflammation with/without hemorrhage accompanying PLD was observed in the lungs of rats treated with cariprazine in repeat dose studies, including the 2-year carcinogenicity study. Similarly, in the 1-year dog toxicity study, PLD with inflammation/fibrosis was observed in the lungs, sometimes with hemorrhage. In addition, there was no NOEL found, or when a NOEL was determined, the safety margin relative to the maximum clinical dose of 6 mg/day or to the exposure/AUC to the active moiety was either small or less than 1.

During the Late Cycle Meeting between representatives of your firm and the FDA on August 16, 2013, we expressed concern about toxicity findings in the adrenal cortex in dogs and the extent of drug-induced phospholipidosis observed in the lungs and/or adrenal cortex of rats, dogs, and mice. In addition, in a General Advice letter issued on June 18, 2014, we requested that an assessment of the risks of adrenal and pulmonary toxicity at the proposed doses based on pre-clinical findings (i.e., phospholipidosis in the adrenal cortex and phospholipidosis, inflammation, and fibrosis in the lungs) be included in the resubmission package for NDA 204370.

As we review your December 17, 2014 submission, we continue to be concerned about the animal toxicity findings in the lungs, particularly the inflammation/fibrosis in the dog and its clinical relevance. We acknowledge the information included in the Safety Update Report under Module 5.3.5.3. You state that the information was obtained by searching the NDA clinical database for treatment-emergent adverse events (TEAEs) of the Respiratory, Thoracic and Mediastinal Disorders and that cough, oropharyngeal pain, and nasal congestion were consistently the most common respiratory TEAEs recorded. However, we note that specific assessment of pulmonary safety was not included in the safety monitoring.

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.

Please contact us if you have any questions. We kindly request a response by June 5, 2015.

If you have any questions, please contact Kimberly Updegraff, Senior Regulatory Project Manager, at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
05/29/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993

NDA 204370

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Forest Laboratories, Inc.  
Harborside Financial Center, Plaza V, Suite 1900  
Jersey City, NJ 07311

ATTENTION: Melina Cioffi, PharmD  
Director, Regulatory Affairs

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated, and received November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cariprazine Capsules, 1.5 mg, 3 mg, 4.5 mg, and 6 mg.

We also refer to:

- Your correspondence, dated and received January 22, 2015, requesting review of your proposed proprietary name, Vraylar
- Our email, dated January 28, 2015, requesting clarification of the strengths
- Your amendment, dated and received January 29, 2015, clarifying the strengths

We have completed our review of the proposed proprietary name, Vraylar and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 22, and 29, 2015, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact Kimberly Updegraff, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
04/01/2015

**From:** Ayalasonmayajula, Vasantha  
**To:** "Cioffi, Melina"  
**Cc:** [Flowers, Louis](#); [Jenkins, Darrell](#); [Makela, Cristina](#); [Updegraff, Kimberly](#)  
**Subject:** Requesting clarification on strengths: Proprietary Name Review submission - NDA 204370 (Cariprazine)  
**Date:** Wednesday, January 28, 2015 10:39:00 AM

---

Dear Ms.Cioffi,

In reference to your Proprietary Name/Request for Review for the New drug Application, NDA 204370 (Cariprazine) dated and received on January 22, 2015, the PI and the Request for Proprietary Name Review both contain 4 strengths (see below), however C&C was sent for 1.5 mg, 3 mg only.

Please verify the proposed strengths for this current PNR request. You will need to send an amendment to the current PNR clarifying which strengths are to be reviewed for this request and submit additional C&C if needed. The amendment should include the SDN, eCTD and date of submission of the current PNR request.

### 3.4 Product Strength

The proposed product strengths are 1.5 mg, 3 mg, 4.5 mg, or 6 mg.

### *Prescribing Information*

-----DOSAGE FORMS AND STRENGTHS-----

Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg (3)

we request you to submit cover letters to include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold, capital letters on the first page of each submission (also include the NDA number) as outlined in the attached guidance

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf>

You will need to reference the original NDA submissions (eCTD #, SDN, and date).

Thanks.

\*\*\*\*\*

Sincerely,

Vasantha Ayala

Senior Regulatory Project Manager

Office of Surveillance and Epidemiology | Project Management Staff

Ph: 240-402-5035 (O)

Email: [Vasantha.ayalasonmayajula@fda.hhs.gov](mailto:Vasantha.ayalasonmayajula@fda.hhs.gov)

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/s/

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VASANTHA S AYALASOMAYAJULA  
03/27/2015

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@actavis.com\)](mailto:Cioffi, Melina (Melina.Cioffi@actavis.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Request (PV Plan)  
**Date:** Tuesday, March 17, 2015 1:08:47 PM  
**Attachments:** [Good PV practices Guidance 2005.pdf](#)  
[E2E PV guidance.pdf](#)

---

Dear Dr. Cioffi,

Please refer to your New Drug Application, NDA 204370, for cariprazine. We also refer to your December 17, 2014 submission containing a complete response to our November 19, 2013 action letter. We are currently reviewing your application and request that you develop and submit a Pharmacovigilance Plan developed to detect new safety risks and to further evaluate identified safety risks following market approval. Guidance for the Pharmacovigilance Plan can be found in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005) and FDA Guideline on E2E Pharmacovigilance Planning (2005). Both guidance documents are attached for reference.

Let us know if you have any questions.

Best regards,

Kim

.....  
*Kimberly Updegraff*  
*Regulatory Project Manager*  
*Division of Psychiatry Products*  
*FDA/CDER/OND*  
*301-796-2201*

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/s/  
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KIMBERLY S UPDEGRAFF  
03/17/2015

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@actavis.com\)](mailto:Cioffi, Melina (Melina.Cioffi@actavis.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Labeling configuration request  
**Date:** Friday, March 13, 2015 4:18:46 PM

---

Dear Dr. Cioffi,

We acknowledge your December 17, 2014 submission for NDA 204370. We are having difficulty piecing together the information specific to labeling. To ensure that we have the correct labeling information necessary to conduct our review, we are requesting a single list of all proposed labels for all configurations that you intend to market to include professional samples.

We request that the submitted list identifies the date and sequence number for each submission containing proposed labeling.

Given our review timelines, we request a response *no later than Wednesday, March 18, 2015*.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Division of Psychiatry Products  
FDA/CDER/OND  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
03/16/2015



NDA 204370/Original 1  
NDA 204370/Original 2

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07981

Dear Dr. Cioffi:

We acknowledge receipt on December 17, 2014, of your December 17, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine capsules 1.5 mg, 3 mg, 4.5 mg, and 6 mg.

We consider this a complete, class 2 response to our November 19, 2013 action letter. Therefore, the user fee goal date is June 17, 2015.

If you have any questions, call me, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, M.S.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KIMBERLY S UPDEGRAFF  
12/31/2014

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** RE: NDA 204370: cariprazine - SAP comments  
**Date:** Tuesday, August 19, 2014 3:59:10 PM

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Hi Melina,

We appreciate your efforts to help us efficiently conduct our review. We agree to your proposal and have no further questions at this moment. We use SAS (9.2 and 9.3) on PC platform.

Kim

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**From:** Cioffi, Melina [mailto:Melina.Cioffi@frx.com]  
**Sent:** Thursday, August 14, 2014 4:02 PM  
**To:** Updegraff, Kimberly  
**Subject:** Re: NDA 204370: cariprazine - SAP comments

Hi Kim,

We thank the reviewers again for their prompt feedback to our recent submission. Please share these points of clarification with the statistical reviewers in reference to the feedback received below:

**SAS analysis datasets that were used to generate the planned analyses:** Forest agrees to include SAS analysis datasets in the cariprazine NDA resubmission. Specifically, we will submit analysis datasets from which TFLs for the resubmission will be generated for ISS Groups 1A, 1B, 2A, and 2B (in legacy format), and Studies RGH-MD-06, RGH-MD-56, and RGH-MD-75 (in ADaM format). For Study A002-A11, Forest will submit both raw datasets and analysis datasets (in legacy format). Forest believes that the analysis datasets will be sufficient in the event that the reviewers will create their own analyses of our data and that raw/SDTM data sets are not needed for Studies RGH-MD-06, RGH-MD-56, and RGH-MD-75. These studies are for different indications and Forest will provide the full study datasets in future applications to support these other indications. Please confirm whether the reviewers agree.

-

**SAS programs that were used to generate the planned analyses:** Forest agrees to include the SAS programs from which TFLs for the resubmission will be generated for ISS Groups 1A, 1B, 2A, and 2B, and Studies RGH-MD-06, RGH-MD-56, and RGH-MD-75, but would like to point out that we are expecting approximately 1000 TFLs for the resubmission and we expect that similar number of programs will be provided. If needed, we will convert the SAS programs in order to be compatible with the operating system used at FDA. Please confirm which operating system (e.g., PC SAS, Unix, or Linux) is used by the reviewers to run SAS programs. Details with respect to the version or any special settings of the operating system would be helpful.

**SAS programs with which we generated the SAS analysis datasets in the submission:** Forest agrees to submit the SAS programs from which we generated the SAS analysis datasets for ISS Groups 1A, 1B, 2A, and 2B, and Studies RGH-MD-06, RGH-MD-56, and RGH-MD-75.

Forest would like to do all that's possible to facilitate FDA's review of the resubmission. We appreciate that the SAS programs will facilitate the review, and we will aim to provide the programs be ready to run.

Kind regards,

Melina

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**From:** Updegraff, Kimberly [<mailto:Kimberly.Updegraff@fda.hhs.gov>]  
**Sent:** Friday, August 08, 2014 4:00 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: cariprazine - SAP comments

Dear Dr. Cioffi,

Please refer to your New Drug Application, NDA 204370, for cariprazine. We also refer to your submission received on July 28, 2014, containing your proposed statistical analysis plan to be included in the NDA resubmission for NDA 204370.

We have reviewed your submission and we have following comment:

- Please include SAS analysis datasets and programs that were used to generate the planned analyses and SAS programs with which you generated the SAS analysis datasets in the submission. For efficiency of the FDA review activities, we request that the SAS programs be ready to run with minimum modifications.

Regards,

Kim

.....  
Kimberly Updegraff, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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KIMBERLY S UPDEGRAFF

09/04/2014

Please note email date of 8/19/14.



NDA 204370/Original 1  
NDA 204370/Original 2

**GENERAL ADVICE**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Associate Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated November 19, 2012, received November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyralar (cariprazine) capsules.

We also refer to your submission, dated and received on April 17, 2014, containing an overview of the proposed plan for the resubmission package in response to our November 19, 2013 Complete Response Letter (CRL).

We have reviewed the referenced material and have the following comments/requests:

**Clinical**

In general, we agree with your proposal for resubmission. We are particularly interested in the following adverse events and laboratory abnormalities and their association to cariprazine dose: akathisia, extrapyramidal symptoms (EPS), elevated blood pressure, hepatic toxicity and transaminase elevations, and rhabdomyolysis and CPK elevations. For the new data and any exploratory analyses you choose to conduct that will be submitted in your resubmission, it will be important to assess these adverse events and laboratory abnormalities as they relate to: time to onset, relationship to dose, and time to resolution.

We request that the same criteria for submitting narratives that you have proposed for studies RGH-MD-06 (open-label phase), RGH-MD-56, and RGH-MD-75 as specified in section 4.4 of your proposed resubmission be utilized for study A002-A11 as well.

In addition, please provide:

- narratives for studies A002-A11, RGH-MD-06 (open-label phase), RGH-MD-56, and RGH-MD-75 for all cases of adverse events consistent with the terms hepatitis, liver function test/transaminase elevated, liver injury, and jaundice, or AE of rhabdomyolysis or related terms;

- updated ocular data including 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 (overall and for new safety data);
- liver data (transaminase, bilirubin, and GGT) in a format that can be entered into eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) program;
- your complete argument for not exploring alternative dosing regimens (b) (4);
- an assessment of the risks of adrenal and pulmonary toxicity at the proposed doses based on pre-clinical findings (i.e. phospholipidosis in the adrenal cortex and phospholipidosis, inflammation, and fibrosis in the lungs); include re-calculated safety margins based on human and animal systemic exposures to cariprazine and active metabolites (please describe the source of data you used and the method of calculation).

If you provide us with the statistical analysis plan and the table and graph shells, we would be able to comment on the planned analyses and data presentations.

### **Statistical**

In addition to the legacy-raw, SDTM and analysis datasets in the original and new submissions, we request you submit data (SAS datasets) of dose as specified below.

1. This request applies to each of the studies MD-03, MD-04, MD-16, MD-05, MD-31, MD-32, and MD-33 of the original NDA submission, and studies A002-A11, RGH-MD-06 [open-label phase], RGH-MD-56, and RGH-MD-75 of the planned resubmission.
2. The requested additional datasets of dose must have the same data structure ready for data manipulations such as “merging”, across the 11 studies, with unique subject IDs. In the original NDA, we are aware that dose information, such as mean daily dose and total dose, was included in an analysis dataset for dose as *d\_dose*, *ddose*.
3. The documented data structure should be submitted; for this, you may choose to submit a SAS dataset that contains the data structure information.
4. Please also submit a detailed document that provides definitions of derived analysis variables of dose that explicitly describes how you created them from the *raw (CRF) data variables*.
  - Please note that the derivations of variables of dose need to be clearly defined from *raw data variables*, even when you choose to generate the requested data sets from analysis datasets you have already derived or plan to derive according to your production process.

5. The requested datasets should include the following variables of dose.

- ***Interval mean daily dose:***

1) *An interval mean daily dose*, for an interval between the previous and the current visit, may be defined as a dose taken during the period from the previous visit to the current visit.

2) *An overall mean daily dose* may be defined as the average daily dose over the entire exposure time.

- ***Accumulated dose:***

3) *An interval accumulated dose*, for an interval between the previous and the current visit, may be defined as a dose taken during the period from the first dosing visit to the current visit.

4) *An overall accumulated dose* may be defined as a dose accumulated up to the planned last visit of the exposure period.

6. The requested datasets should also contain the numbers of days from the first dosing day associated with interval mean daily doses and accumulated doses.

7. In the actual derivation of these variables, relevant information such as compliance, numbers of capsules given and returned, missing data may need to be taken into account.

### **Office of Clinical Pharmacology**

We recommend that you update the population pharmacokinetic model by including data from Study A002-A11. The updated model should be able to describe the concentrations of Cariprazine, DCAR, and DDCAR during the titration phase as well as maintenance phase. If you have excluded any data during the development of the already submitted population pharmacokinetic model, we recommend that you re-include it to improve prediction of observed data using the model.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
06/18/2014

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Friday, March 14, 2014 9:40 AM  
**To:** Cioffi, Melina (Melina.Cioffi@frx.com)  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Information request

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA) for cariprazine. We also refer to your submission dated and received on February 14, 2014, containing a meeting request and briefing document referencing our November 19, 2013, action letter for cariprazine.

We note in the briefing document that you refer to requests from the Japanese Regulatory Agency – Pharmaceuticals and Medical Devices Agency (PDMA). Please provide any information regarding the application to include if/when the application was submitted to PDMA, regulatory decisions, interactions, advice, etc.

Regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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KIMBERLY S UPDEGRAFF  
05/01/2014



NDA 204370/Original 1  
NDA 204370/Original 2

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD.  
Associate Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyralar (cariprazine) capsules 1.5mg, 3mg, 4.5 mg, 6 mg <sup>(b)</sup><sub>(4)</sub>

We also refer to the meeting between representatives of your firm and the FDA on April 3, 2014. The purpose of the meeting was to discuss the Complete Response letter (CRL) issued on November 19, 2013, and to discuss the plans for a complete response submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** End of Review

**Meeting Date and Time:** April 3, 2014  
**Meeting Location:** White Oak Building 22, Room 1315

**Application Number:** NDA 204370/Original 1  
NDA 204370/Original 2

**Product Name:** Vyralar (cariprazine)  
**Indication:** Treatment of manic or mixed episodes associated with bipolar I disorder (Original 1) / Treatment of schizophrenia (Original 2)

**Sponsor/Applicant Name:** Forest Research Institute, Inc.

**Meeting Chair:** Robert Temple, M.D.  
**Meeting Recorder:** Kimberly Updegraff, M.S.

**FDA ATTENDEES**

Ellis Unger, MD	Director, Office of Drug Evaluation I
Robert Temple, MD	Deputy Director, Office of Drug Evaluation I and Deputy Center Director for Clinical Science
Mitchell Mathis, MD	Division Director, Division of Psychiatry Products (DPP)
Robert Levin, MD	Medical Team Leader, DPP
Francis Becker, MD	Clinical Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Elzbieta Chalecka-Franaszek, PhD	Pharmacology/Toxicology Reviewer, DPP
Eiji Ishida, MS	Biometrics Reviewer, Office of Biometrics (OB)
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Vikram Sinha, PhD	Director, Division of Pharmacometrics, OCP
Atul Bhattaram, PhD	Pharmacometrics Reviewer, OCP
Kevin Krudys, PhD	Pharmacometrics Acting Team Leader, OCP
Kimberly Updegraff, MS	Senior Regulatory Project Manager, DPP

**SPONSOR ATTENDEES**

Marco Taglietti	Executive Vice President, Drug Development & Research, Forest Research Institute, Inc. (FRI)
Parviz Ghahramani	Vice President, Scientific Affairs, FRI

Antonia Periclou	Senior Director, Clinical Pharmacology, FRI
Tatiana Khariton	Senior Principal Scientist, Modeling & Simulation, FRI
Armin Szedgedi	Vice President, Clinical Development – CNS, FRI
Willie Earley	Senior Director, Clinical Development, FRI
Suresh Durgam	Senior Director, Clinical Development, FRI
Kaifeng Lu	Director, Biostatistics, FRI
(b) (4)	External Expert
(b) (4)	External Expert
Zsolt Szombathelyi	Research Director, Gedeon Richter
George Nemeth	Head of Medical Affairs, Gedeon Richter
Melina Cioffi	Associate Director, Regulatory Affairs, FRI
Michael Olchaskey	Executive Director, Regulatory Affairs, FRI
June Bray	Senior Vice President, FRI

## 1.0 BACKGROUND

Cariprazine is an oral atypical antipsychotic. NDA 204370 was submitted by Forest Research Institute for the use of cariprazine in the treatment of schizophrenia and bipolar mania. Cariprazine is a New Molecular Entity (NME) and is pharmacologically similar to other (approved) atypical antipsychotics in that it has activity at dopamine (D2 and D3) and serotonin (5-HT1A) receptors. The activity of cariprazine at D2 is partial agonism (as it is with aripiprazole) rather than primarily antagonism (as with the other atypical antipsychotics); the contribution of activity at D3 to clinical efficacy is unknown. Cariprazine is pharmacokinetically distinct from the other (approved) atypical antipsychotics in that it has a long half-life for both the parent drug cariprazine (3-6 days) and the major accumulating active (equipotent to parent) metabolite didesmethylcariprazine (DDCAR - estimated half-life of 3 weeks).

On November 19, 2013, the Division issued a Complete Response Letter (CRL) citing dose-related toxicity (b) (4). FDA concluded that the studies demonstrated the efficacy of cariprazine in the treatment of schizophrenia and mania associated with bipolar disorder. However, there were significant dose-related toxicities, including akathisia and other extrapyramidal symptoms, increased blood pressure, elevations in creatinine phosphokinase, and elevations in transaminases. The Division has been concerned about the long half-lives of cariprazine and the active metabolite (DDCAR), along with the significant accumulation of the total active moiety. The Division concluded that (b) (4), and the dose-related toxicities could possibly be mitigated by an alternative dosing regimen, for example, one that would provide a prompt initial response, followed by lower doses which would maintain effective blood levels while reducing the level of toxicity.

Forest requested a meeting to discuss the action letter, obtain an understanding of the deficiencies, and discuss what would be required before the application can be approved. The sponsor submitted a briefing package in preparation for the meeting that included new, observed PK data from the recently completed study A002-A11; new, blinded PK data from ongoing study RGH-MD-06; NDA safety database of 2758 total patients and long term safety database of 364 cariprazine-treated patients with at least 24 weeks of exposure and 239 with at least 48 weeks of exposure. In addition, (b) (4)

(b) (4), based on the reassessment of the overall benefit/risk profile and the new safety analyses. The sponsor believes that the new data and analyses provided in the briefing book adequately address the FDA concerns raised in the CRL regarding cariprazine's PK and benefit-risk profile.

Study A002-A11 is a recently completed randomized, open-label, parallel-group, fixed-dose, PK, efficacy and safety study of cariprazine in 38 patients with schizophrenia, conducted in Japan, to characterize the PK profile of cariprazine, desmethyl-cariprazine (DCAR), and didesmethyl-cariprazine (DDCAR) over 12-weeks of dosing and over 12 weeks following drug discontinuation. Study RGH-MD-06 is an ongoing randomized, double-blind, placebo-controlled, parallel-group schizophrenia relapse prevention study (maximum duration of 72 weeks) for which a blinded PK data analysis was performed, providing information on elimination of cariprazine, DCAR, and DDCAR based on concentration data collected up to 14 weeks following drug discontinuation. Both studies (A002-A11 and RGH-MD-06) employed rapid up-titration to a final fixed dose of 3 mg, 6 mg, or 9 mg per day.

Based on the new PK data from these two studies, the sponsor concluded that: 1) the total active moiety reached steady state in 3 weeks, consistent with functional half-lives of approximately one week for cariprazine, 1-2 days for DCAR, and 8-9 days for DDCAR; 2) at steady state, total cariprazine plasma concentration was approximately 2-fold the exposure at the end of Week 1, not 3-4 times higher as indicated in the CRL, and thus a considerable portion of steady state concentration was achieved by end of Week 1; and 3) plasma concentration of DDCAR declined by >90% approximately 4 weeks after the last dose, and total cariprazine concentration declined by >90% in about 3 weeks, consistent with the time required to reach steady state. According to the sponsor, the new, observed PK findings support the sponsor's previous findings based on both observed data and predicted population PK modeling.

The sponsor argues that: 1) the relationship between total active moiety concentration and efficacy (change in PANSS) in the three pivotal schizophrenia trials support improvement in efficacy with increase in exposure over the proposed dose range of 1.5 - 6 mg/day; 2) the relationship between total cariprazine concentration and efficacy (change in YMRS) in the three pivotal bipolar mania trials support improvement in efficacy with increase in exposure over the proposed dose range of 3 - 6 mg/day; and 3) additional safety analyses demonstrate a dose-response relationship for transaminase elevations, CPK elevations, increases in blood pressure, and adverse events of akathisia and extrapyramidal symptoms (EPS), which revealed increased risk with cariprazine doses greater than 6 mg/day, relative to lower doses. Furthermore, the sponsor argues that the rate of akathisia and EPS reported per week decreased after 2 to 3 weeks of treatment (consistent with total cariprazine approaching steady state) and that the incidence of ongoing akathisia or EPS after stopping cariprazine was proportionally similar to or lower than the observed comparator treatments (aripiprazole and risperidone). According to the sponsor, analyses of time to resolution and event duration relative to the comparator treatment groups suggest no prolonged time to resolution of adverse events with cariprazine.

Lastly, the sponsor argues that, based on the new PK data, a dose-reduction paradigm, as suggested in the CRL, which limits the plasma exposure to that of Week 1 or Week 2, would not provide optimal efficacy potential because: 1) total cariprazine concentrations at Week 1

following a dose of 6 mg/day are ~50% of steady state and are therefore similar to steady-state concentrations following a dose of 3 mg/day; 2) there are significant increases in efficacy with the higher dose of 6 mg/day at Week 1 and beyond (schizophrenia studies), and 3) total cariprazine concentrations at Week 2 are already approaching steady state. Furthermore, PANSS total scores and YMRS scores demonstrated continued improvement with increasing total cariprazine concentrations, and steady-state simulations based on population PK/PD models showed that increasing doses of cariprazine over the range of 1.5 to 6 mg/day were associated with substantial gains in efficacy with relatively small increased risk of adverse events, according to the sponsor. (b) (4)

## 2. DISCUSSION

### 2.1. New Data (pharmacokinetic and safety) and Dosing

#### Question 1:

Does the Division concur that the PK profile of cariprazine and its major active metabolites can be sufficiently characterized based on new observed data obtained from the recently completed study A002-A11 and ongoing study RGH-MD-06, in combination with the observed and population PK model predicted data submitted in the NDA?

#### FDA Preliminary Response to Question 1:

*The recently completed Study A002-A11 and the ongoing Study RGH-MD-06 will provide additional information on the pharmacokinetic characteristics of cariprazine and its metabolites. However, full clinical reports must be submitted for review before any conclusion can be drawn from these studies. We request that you include in the study reports individual plots of time concentration profiles with matching dosing record. Also please be consistent in the units when reporting concentrations. We encourage you to submit the study report as soon as it becomes available.*

#### Discussion at the Meeting:

*Forest discussed the results of Study A002-A11, stating that steady state for the total moiety was reached in approximately 3 weeks, and the total concentration at steady state was about 2-fold the concentration at the end of Week 1. The Agency emphasized that until the data and study report are submitted and reviewed, no conclusions can be reached. The adequacy of the information will depend on the quality of the data. We encouraged the applicant to submit the information as soon as it is available. The applicant stated the study is complete and the study report is currently being prepared. The report will need to be translated before it is submitted. The Agency also stressed that conclusions about time to steady state and half-life values will be drawn based on the totality of all submitted information, including study reports included in the NDA review cycle.*

**Question 2:**

Does the Division concur that Forest's proposed resubmission package for Cariprazine consisting of:

- New, observed PK data from the recently completed study A002-A11;
- New, blinded PK data from ongoing study RGH-MD-06;
- NDA safety database of 2758 total patients and long term safety database of 364 cariprazine-treated patients with at least 24 weeks of exposure and 239 with at least 48 weeks of exposure; and
- [REDACTED] (b) (4) the reassessment of the overall benefit/risk profile and the new safety analyses

a) Will provide sufficient information to address all of the concerns raised by FDA in the CRL without the need for additional studies preapproval and enable FDA to move forward with the review of the NDA for the treatment of Schizophrenia?

**FDA Preliminary Response to Question 2a:**

*At this time, it is not clear that the proposed submission would adequately address the concerns outlined in the Complete Response Letter.* [REDACTED] (b) (4)

[REDACTED] *he new PK data, as you have summarized, appear to be quite similar to the previous PK findings. In addition, we may have different interpretations and concerns about the PK data than you. We agree that* [REDACTED] (b) (4) *would reduce the risks* [REDACTED] (b) (4)

[REDACTED] *We recommend that, before submitting a response, you explore alternative dosing regimens, i.e., using a loading dose* [REDACTED] (b) (4) *with a subsequent decrease in stable doses* [REDACTED] (b) (4). *This strategy could result in lower exposures that would provide adequate efficacy while reducing the risks of toxicity.*

*We acknowledge that there was a positive dose-response relationship across the range of 1.5 mg to 9 mg, and higher doses generally resulted in earlier onset of efficacy. The early treatment effects were probably largely driven by the parent drug, and efficacy was thus achieved at relatively low total exposures, compared to later exposures. Moreover, after the first few weeks of treatment, the placebo-subtracted treatment effects did not increase substantially over time, despite the considerable accumulation of total active moiety. We think it is possible that effective exposures could be achieved and maintained using loading doses* [REDACTED] (b) (4), *followed by a lower stable daily dose,* [REDACTED] (b) (4). *In the long-term open-label schizophrenia studies, a significant proportion of patients were stabilized on doses as low as 1.5 mg, 3 mg, and 4.5 mg.*

*For a complete response submission, we must discuss the data that will be required. We would like to have all available PK and safety data that was not submitted in the original*

*NDA. This would include PK and safety data from the new PK study (Study A002-A11), all PK and safety data from the maintenance study (MD-06), as well as all new ocular data. We would also request safety and PK data from all completed and ongoing IND studies of cariprazine, for all indications. We would like to discuss obtaining data from any non-IND studies of cariprazine. In addition, we must reach agreement on any new or updated safety analyses for specific safety parameters and adverse events of particular interest.*

*Please provide a status update on all completed, ongoing, and planned cariprazine studies. When do you anticipate completing Study RGH-MD-06?*

**Discussion at the Meeting:**

*Forest summarized their proposal for (b) (4). They feel that the risks are significantly reduced (b) (4). (b) (4) will adequately address the concerns about toxicity. They do not believe that using a loading dose (b) (4) with a subsequent decrease to stable doses (b) (4) is a strategy that would significantly improve the benefit-risk profile. The applicant stated that clinicians can manage concerns about safety and tolerability as they arise, and they can adjust the dose as indicated. Forest emphasized that it is important for the clinicians to make individual decisions about dosing based on clinical judgment, and there will be significant variability in responses among patients.*

*The applicant asked whether defining the optimal dosing strategy could be done post-approval. We stated that we will review the new PK data, new safety data, and proposals for dosing. The Division encouraged the applicant to provide a detailed explanation on why a loading dose strategy is not reasonable for improving the benefit-risk profile of cariprazine treatment.*

*Forest plans a resubmission that will include the new PK and safety data from Study A002-A11, Study RGH-MD-06, and safety data from one adjunctive MDD study, one bipolar depression study, and data from other IND and non-IND studies. Overall, the submission will include new data on 1,800 subjects in cariprazine IND studies. Study A002-A11 has been completed, and the study report is being prepared. Study RGH-MD-06 will be completed at the end of 2014. The applicant will include the safety data from the 20-week, open-label stabilization phase in the resubmission.*

*We discussed the main issues that the Agency will consider: optimal dosing and dose-related toxicities, such as akathisia, EPS, increased CPK and transaminases, and increased blood pressure. We will also review new ocular data. The Division requested that the submission include all new ocular data (as well as ocular narratives), cases of rhabdomyolysis, CPK analyses, hepatic adverse events, hepatic analyses with new data to include an additional eDISH analysis, and blood pressure analyses.*

*In response to our additional requests, Forest stated that they would submit an outline of their planned submission prior to submission of the complete response. The outline submission will include an overview of the submission as well as requests for Agency*

*feedback regarding additional information to include in the submission. The Division requested that Forest submit safety data from ongoing IND and non-IND studies. We agreed that we will discuss the proposed contents of the submission in order to reach agreement.*

**b) Will provide sufficient information to address all of the concerns raised by FDA in the CRL without the need for additional studies preapproval and enable FDA to move forward with the review of the NDA for the treatment of Bipolar Mania?**

**FDA Preliminary Response to Question 2b:**

*We have the same concerns about the bipolar mania program as in the schizophrenia program. We recommend that you conduct a study assessing alternative dosing regimens, in order to determine whether lower exposures could provide adequate efficacy while reducing the risk of toxicity. Akathisia and other EPS were particularly problematic in the mania studies; a very high proportion of patients experienced these reactions, and a relatively high proportion of subjects discontinued from the studies because of these adverse reactions.*

**Discussion at the Meeting:**

*See “Discussion at the Meeting” section under 2a.*

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/s/  
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MITCHELL V Mathis  
04/17/2014



NDA 204370

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine.

We also refer to the teleconference between representatives of your firm and the FDA on October 21, 2013. The purpose of the meeting was to discuss the pharmacokinetics of cariprazine.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director (acting)  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** C  
**Meeting Category:** Guidance

**Meeting Date and Time:** October 21, 2013 2:30 – 3:00 p.m.  
**Meeting Location:** Teleconference

**Application Number:** 204370  
**Product Name:** Vyralar (Cariprazine)  
**Indication:** Treatment of bipolar I disorder  
Treatment of schizophrenia

**Sponsor/Applicant Name:** Forest Research Institute

**Meeting Chair:** Robert Temple, M.D.  
**Meeting Recorder:** Kimberly Updegraff

**FDA ATTENDEES**

Robert Temple, MD	Deputy Director, Office of Drug Evaluation I and Deputy Center Director for Clinical Science
Ellis Unger, MD	Director, Office of Drug Evaluation I
Mitchell Mathis, MD	Division Director (acting), Division of Psychiatry Products (DPP)
Robert Levin, MD	Medical Team Leader, DPP
Francis Becker, MD	Clinical Reviewer, DPP
Marc Stone, MD	Clinical Reviewer, DPP Safety Team
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Ramana Uppoor, PhD	Clinical Pharmacology Deputy Division Director, Office of Clinical Pharmacology (OCP)
Hao Zhu, PhD	Clinical Pharmacology Team Leader, OCP
Huixia Zhang, PhD	Clinical Pharmacology Reviewer, OCP
Atul Bhattaram, PhD	Clinical Pharmacology Pharmacometrics Team Leader, OCP
Kimberly Updegraff, MS	Senior Regulatory Project Manager, DPP

**SPONSOR ATTENDEES**

June Bray	Senior Vice President, Regulatory Affairs
Michael Olchaskey	Senior Director, Regulatory Affairs
Melina Cioffi	Associate Director, Regulatory Affairs
Gavin Corcoran	Executive Vice President, Global Medicines Development

Willie Early	Senior Director, Clinical Development
Tatiana Khariton	Senior Principal Scientist, Modeling & Simulation
Antonia Periclou	Senior Director, Clinical Pharmacology & Drug Dynamics
Yih Lee	Senior Principal Scientist, Clinical Pharmacology & Drug Dynamics
Parviz Ghahramani	Vice President, Experimental Medicine and Science
Patricia Jacala	Senior Manager, Regulatory Affairs, Forest
Margit Kapas	Head of Department, Developmental Drug Metabolism & Pharmacokinetics, Gedeon Richter
Amol Parekh	Pharm-D Fellow, Regulatory Affairs, Forest

## 1.0 BACKGROUND

A Late Cycle Meeting for NDA 204370 was held on August 16, 2013 between FDA and Forest. During the meeting FDA noted concerns with the long elimination half-life of the active metabolite, didesmethyl-cariprazine (DDCAR), and its possible influence on the appropriate dose. There were also questions surrounding the population PK model and predicted steady state of the parent compound and its metabolites.

On September 6, 2013, Forest requested a teleconference to further discuss the issues surrounding the pharmacokinetics of cariprazine. A briefing document was provided along with the meeting request and was reviewed by FDA in preparation for the teleconference.

## 2. DISCUSSION

The Division initiated the discussion noting that we planned to focus on two main points, functional half life and dose linearity of DDCAR. The discussion would be based on the observed data submitted in the briefing document.

The Division stated that: 1) it believed the functional half life for cariprazine is significantly underestimated; 2) for DDCAR, we are uncertain about time to reach steady state (SS) and the degree of accumulation at SS, but we are not convinced, at this point, that DDCAR has reached SS “in 4 weeks or less” following once daily treatment; 3) multiple Phase 1 trials indicated greater than dose proportional increase in DDCAR exposure in wide dose range (1.5-12.5/18 mg).

The Division stated that we agree with the sponsor about the half life of the initial decline phase and terminal phase for cariprazine and DDCAR. However, we do not agree that the functional half life is always best characterized by the half life of the initial decline phase. Depending on the relative contribution of the different phases on the pharmacokinetic profile, the functional half life may be longer than that of the initial phase. This is illustrated by the functional half life estimate of parent cariprazine. The sponsor reported functional half life for cariprazine of 1 day, which appears to be consistent with the half life of the initial decline phase for cariprazine after treatment discontinuation. The Division pointed out that for a drug with a functional half life of 1 day, with a once daily dosing regimen, the estimated accumulation would be about 2 fold, but that was not what was observed in the clinical trials. As a matter of fact, on Page 2658 in study

report for Study RGH-188-002, a more than 6-fold accumulation of cariprazine was reported for cohorts with different dosing regimens (post meeting comment). In addition, the current data suggest that time to reach approximately 90% of the steady state of cariprazine is much longer than 3-4 days, which is what would be expected if the pertinent half life were 1 day.

The sponsor also stated that [REDACTED] (b) (4)  
[REDACTED] As a post meeting comment, we disagree with the sponsor's statement.

Forest stated that they believe SS for DDCAR is reached by week 4, referencing Table 6.1-1 of the briefing document. We questioned the data that was used to generate the summary table and asked them to redo the analysis with only fixed dose data (study RGH-MD-04 and study RGH-MD-16), excluding subjects who, based on PK judgment, are suspected to discontinue the treatment or have dose adjustment. We also note that Figure 7.1-1 suggests substantially accumulating activity of DDCAR at day 23, even when treatment was stopped at day 21 (post meeting comment).

We asked about the long half life and its effect on adverse events (akathisia, EPS, hypertension etc.). The sponsor stated that the adverse events were similar to others in the class. We expressed concern regarding accumulation and asked if it is known where the accumulation occurs and if it continues after the drug is discontinued.

### 3.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
<b>FDA requested the following information:</b>		
Summary statistics of observed individual plasma concentration of DDCAR post-dose stratified by study week and by dose, using data only from the two fixed-dose 6-week study (RGH-MD-04, -16). In one table please include data from all subjects, in a second table please exclude subjects who, based on PK judgment, are suspected to discontinue the treatment or have dose adjustment. Data can be presented in the same way as Table 6.1-1 of your briefing document dated September 6, 2013.	Sponsor	October 28, 2013  **NOTE** Response received on October 29, 2013 (Dated October 28, 2013)

### 4.0 ATTACHMENTS AND HANDOUTS

- 1) FDA Slides sent to sponsor on October 21, 2013.

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/s/  
-----

MITCHELL V Mathis  
11/14/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Melina.Cioffi@frx.com)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Packaging labeling request  
**Date:** Wednesday, November 06, 2013 2:34:56 PM

---

Dear Melina,

Thank you for your timely submission of the revised labels for Vraylar (Cariprazine), NDA 204370, on November 1, 2013. Regarding the professional sample blister cards, you stated the product identifying information is printed on foil. It is unclear whether the print on foil has sufficient contrast to ensure readability of the information. Please provide a photograph or other pictorial that shows what the printed foil on the blister card looks like. If the product identifying information on the HUD blisters is also printed on foil, we request you provide a picture of the HUD blister as well.

We request a response by COB on November 7, 2013.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
Kimberly.Updegraff@fda.hhs.gov  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
11/07/2013

**PeRC PREA Subcommittee Meeting Minutes**  
**October 2, 2013**

**PeRC Members Attending:**

Lynne Yao  
Hari Cheryl Sachs  
Karen Davis-Bruno  
Tom Smith  
Andrew Mulberg (Did not review NON RESPONSIVE )  
Wiley Chambers  
Donna Katz  
Robert “Skip” Nelson  
Shrikant Pagay  
Lily Mulugeta  
Andrew Mosholder  
Kevin Krudys  
Barbara Buch  
Susan McCune  
Daiva Shetty  
Martha Nguyen  
Peter Starke  
Ruthianna Davi  
Gregory Reaman  
Jane Inglese  
William Rodriguez  
George Greeley  
Coleen LoCicero  
Robert “Skip” Nelson  
Rachel Witten  
Maura O’Leary

**Guests Attending:**

Nichella Simms (PMHS)	Amy Taylor (PMHS)
Erica Radden (PMHS)	GT Wharton (OPT)
Courtney Suggs (OCP)	Gilbert Burckart (OCP)
Donna Snyder (PMHS)	Robert Levin (DPP)
Dionna Green (OCP)	Owen McMaster (DAIP)
Alison Rodgers (DAIP)	Ronald L. Ariagno (OPT/PMHS)
Jian Wang (OCP)	Ellen Fields (DAAAP)
Elizabeth Kilgore (DAAAP)	Dominic Chiapperino (DAAAP)
Aisar Atrakdei (DPP)	Kim Updegraff (DPP)
Hao Zhu (OCP)	Yun Xu (OCP)

**Agenda**

9:00 NDA

NON RESPONSIVE

9:20 NDA

204370 Cariprazine Partial Waiver/Deferral/Plan

9:40 NDA

NON RESPONSIVE

NDA

NDA

NDA

NDA

NON RESPONSIVE

NON RESPONSIVE

**Cariprazine Partial Waiver/Deferral/Plan**

- NDA 204370, Cariprazine, capsule seeks marketing approval for the treatment of schizophrenia and for the treatment of manic or mixed episodes associated with bipolar I disorder.
- The supplement was submitted on November 19, 2012 and has a PDUFA goal date of November 19, 2013.
- The product triggers PREA as a new: active ingredient, indication, dosage form, dosing regimen, and route of administration.
- A waiver is being requested for pediatric patients aged birth to 12 years for Schizophrenia and birth to 9 years for Bipolar I Disorder because studies are impossible or highly impractical.
- *Division justification for waiver:* Studies are impossible or highly impractical because there is a very low incidence of bipolar diagnosed prior to age 10 or schizophrenia diagnosed prior to age 13. Therefore, it is unlikely that it would be possible to conduct sufficiently large studies of these age groups within a reasonable time frame. This is consistent with other products reviewed for these indications.
- A deferral is being requested for pediatric patients ages 13 to 17 years for Schizophrenia and ages 10 to 17 years for Bipolar I Disorder because the product is ready for approval in adults.
- The PeRC agreed to the proposed timelines for the deferred studies. The Division stated that the studies can be done concurrently.

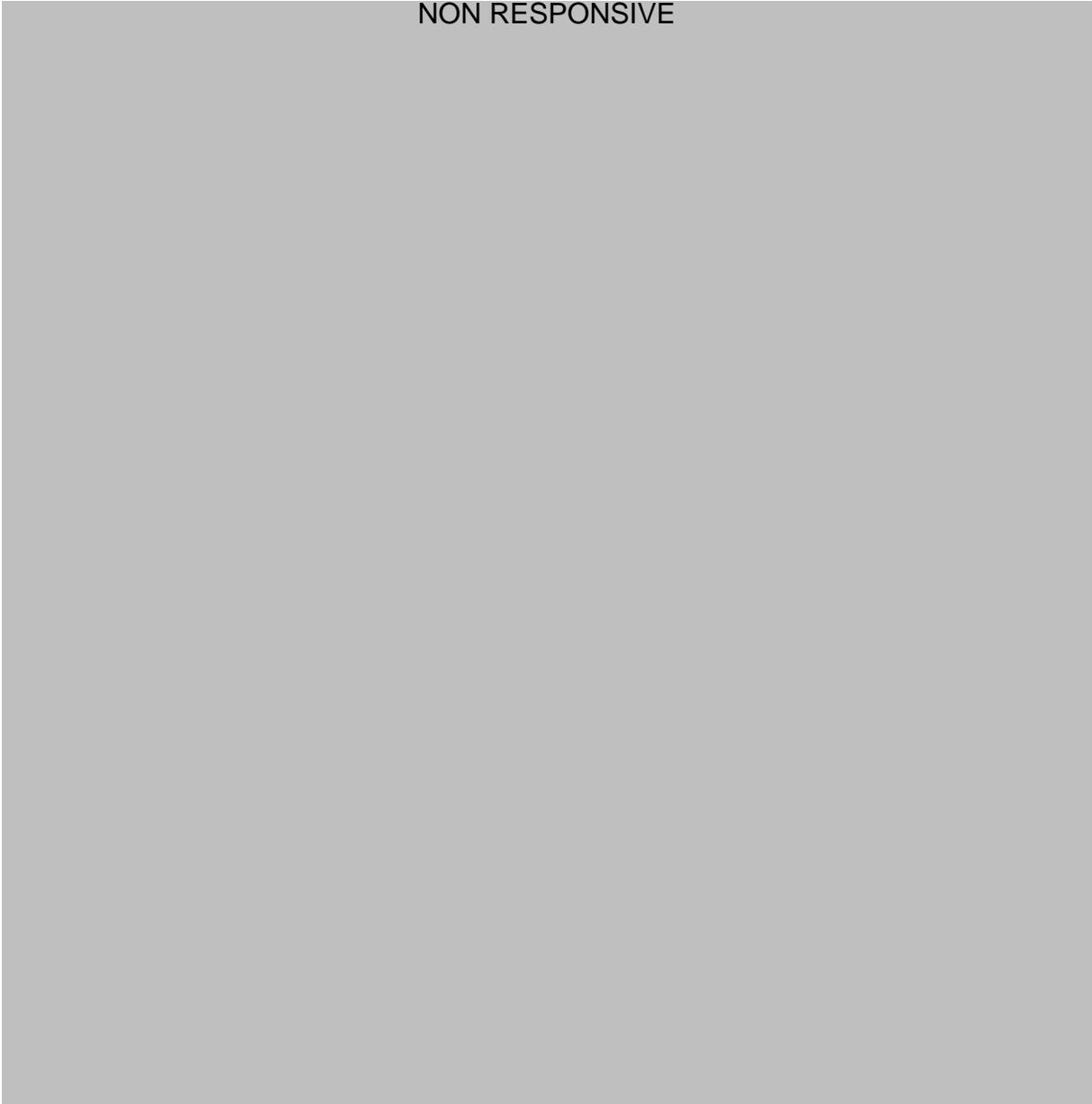
*PeRC Recommendations:*

- The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to 12 years for Schizophrenia and birth to 9 years for Bipolar I Disorder because studies are impossible or highly impractical. This is consistent with other products approved to treat Schizophrenia and Bipolar I Disorder.
- The PeRC agreed with the Division to grant a deferral for pediatric patients ages 13 to 17 years for Schizophrenia and ages 10 to 17 years for Bipolar I Disorder because the product is ready for approval in adults.

Additional PeRC Recommendations:

- The PeRC reminded the Division that timelines need to be established for each of the deferred studies.
- The PeRC reminded the Division that the PREA PMR maybe fulfilled with a specific protocol as agreed upon with the Division (e.g., a single long-term study could fulfill more than one PREA PMR).

NON RESPONSIVE



3 Page(s) have been Withheld in Full as Non Responsive immediately following this page

NON RESPONSIVE

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/s/  
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GEORGE E GREELEY  
11/06/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Cioffi, Melina (Melina.Cioffi@frx.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Packaging/labeling comments  
**Date:** Wednesday, October 30, 2013 4:49:13 PM  
**Attachments:** [image003.png](#)

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Dear Dr. Cioffi,

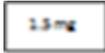
Please refer to your New Drug Application, NDA 204370, for cariprazine. We also refer to our October 3, 2013 request which contained package and labeling comments and your response dated October 11, 2013, received on October 15, 2013.

We have completed our review of your submission and we have the following comments/requests:

A. All Bottle Labels

The proprietary name, established name and strength lack prominence. Increase the size of the proprietary name, established name and strength.

B. Hospital Unit Dose Blisters (1.5 mg)

The 1.5 mg statement of strength is small and difficult to see. In order to highlight the strength, consider enclosing it in an open box (i.e., ) or some other means to bring attention to it.

BEST  
AVAILABLE  
COPY

C. All Professional Sample 7-count Blister Cards

1. Show the location of the lot and expiration date.
2. Provide directions for use of the blister card on the blister card itself.
3. Please clarify whether the product identifying information is printed on foil or paper backing.

We request a response by COB on Friday, November 1, 2013.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
10/30/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Cioffi, Melina (Melina.Cioffi@frx.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Packaging/labeling comments  
**Date:** Thursday, October 03, 2013 1:42:33 PM

---

Dear Melina,

We have the following labeling and packaging recommendations for cariprazine:

A. All Bottle Labels, **NON** 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.

We request that you submit revised labeling October 11, 2013.

Best Regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
10/30/2013  
Please note sent date: 10-3-13

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine -- OCP Request for Information  
**Date:** Thursday, October 24, 2013 12:01:15 PM

---

Dear Dr. Cioffi,

As a follow-up to our email dated October 23, 2013, we would like to add the following request:

*Please provide in writing your subject exclusion criteria from the dataset, individual concentration time plot for each subject with three moieties in one plot, SAS code used to generate tables and figures, and the dataset used in the analysis.*

Thank you,

Kim

---

**From:** Updegraff, Kimberly  
**Sent:** Wednesday, October 23, 2013 8:05 PM  
**To:** Cioffi, Melina (Melina.Cioffi@frx.com)  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine -- OCP Request for Information

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. As discussed during our teleconference on October 21, 2013, we have the following request:

*Please provide summary statistics of observed individual plasma concentration of DDCAR post-dose stratified by study week and by dose, using data only from the two fixed-dose 6-week study (RGH-MD-04, -16). In one table, please include data from all subjects, in a second table please exclude subjects who, based on PK judgment, are suspected to discontinue the treatment or have dose adjustment. Data can be presented in the same way as Table 6.1-1 of your briefing document dated September 6, 2013. Please perform similar analysis for cariprazine and DCAR.*

We request a response by COB on Monday, October 28, 2013.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
10/24/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Cioffi, Melina (Melina.Cioffi@frx.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine -- OCP Request for Information  
**Date:** Wednesday, October 23, 2013 8:05:30 PM

---

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. As discussed during our teleconference on October 21, 2013, we have the following request:

*Please provide summary statistics of observed individual plasma concentration of DDCAR post-dose stratified by study week and by dose, using data only from the two fixed-dose 6-week study (RGH-MD-04, -16). In one table, please include data from all subjects, in a second table please exclude subjects who, based on PK judgment, are suspected to discontinue the treatment or have dose adjustment. Data can be presented in the same way as Table 6.1-1 of your briefing document dated September 6, 2013. Please perform similar analysis for cariprazine and DCAR.*

We request a response by COB on Monday, October 28, 2013.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
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KIMBERLY S UPDEGRAFF  
10/23/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Cioffi, Melina (Melina.Cioffi@frx.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Clinical/Statistical information request  
**Date:** Monday, October 21, 2013 10:50:08 AM  
**Importance:** High

---

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, for cariprazine. We are currently reviewing your application and we have the following request:

For each study of flexible-dose and fixed/flexible-dose studies (2 schizophrenia and 3 bipolar studies), we would like to have SAS datasets and programs that you used to generate the following CSR tables:

Study	Table of CSR
MD-03	Table 10.5.1-1. Extent of Exposure: Safety Population
MD-05	Table 12.1-2. Summary of Overall Mean, Modal, and Final Daily Dosage—Safety Population
MD-31	Table 10.5.1-1. Extent of Exposure—Safety Population
MD-32	Table 12.1-2. Summary of Overall Mean, Modal, and Final Daily Dosage—Safety Population
MD-33	Table 12.1-2. Summary of Overall Mean, Modal, and Final Daily Dosage—Safety Population

Please include in the submission a document for each study that describes the definition(s) of overall mean (modal and final, when appropriate) daily dosage using the dataset variables. The document should also have the definitions described in plain language.

Please respond by noon on Wednesday, October 23, 2013.

Thank you,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
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KIMBERLY S UPDEGRAFF  
10/22/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Cioffi, Melina (Melina.Cioffi@frx.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Clinical Information Request  
**Date:** Thursday, September 12, 2013 2:34:31 PM  
**Importance:** High

---

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are requesting additional information regarding subject number 0110618 who participated in Study RGH-MD-06 and was diagnosed with rhabdomyolysis. Please provide a complete patient profile as well as any follow-up information regarding the patient's hospitalization and outcome.

We request a response by COB on Monday, September 16, 2013.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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/s/  
-----

KIMBERLY S UPDEGRAFF

10/07/2013

Please note email date: 9/12/13

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine for bipolar and schizophrenia --- NME (Postmarketing/Labeling)  
**Date:** Wednesday, August 07, 2013 4:39:21 PM  
**Attachments:** [204370 FDA Label 8-1-13 SENT to sponsor.doc](#)  
[DNP - Oxtellar XR \(oxcarbazepine\) - format review of the prescribing information.pdf](#)

---

Dear Melina,

As a follow-up to the postmarketing and labeling comments the Division sent on August 1, 2013, please see the attached Word version of labeling. We request that you use the attached document when responding to our labeling proposal. Please use tracked changes to denote your responses.

Also, I've attached a copy of a checklist developed by the Study Endpoints and Labeling Development (SEALD) Team that is used to identify critical format elements. The attached checklist is a previously completed, publically available form. Please be sure that your labeling incorporates all of the critical elements.

Thank you,

Kim

---

**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Thursday, August 01, 2013 3:38 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine for bipolar and schizophrenia --- NME (Postmarketing/Labeling and Late Cycle Meeting Package)

Dear Melina,

In accordance with PDUFA Reauthorization Performance Goals and Procedures, please see the attached document containing preliminary postmarketing commitments/requirements as well as revised draft labeling.

Please let me know if you have any questions.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF

10/07/2013

Please note email date of 8/7/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](mailto:Cioffi, Melina (Melina.Cioffi@frx.com))  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: cariprazine - Clinical information request  
**Date:** Friday, September 27, 2013 1:53:58 PM  
**Importance:** High

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we have the following requests:

- Please provide the dataset for individual daily doses administered: to include Subject ID, study number, treatment group, and the definition used to define individual daily exposure;
- Narratives and patient profiles for cases of: 1) hypertensive crisis, and 2) blood pressure immeasurable;
- For the AE table recently provided (AE for 1A and 2A combined; dose groups 1.5-3 mg, 4.5-6 mg, 9-12 mg), please combine: 1) all terms related to extrapyramidal symptoms, 2) all terms related to increased blood pressure and hypertension, 3) all terms related to increased CPK, and 4) all terms related to increased transaminase;
- Using the dose groups above, please provide EPS tables analogous to the EPS tables in the ISS (tables 7.6.3.1-1, 7.6.3.1-2, and 7.6.3.2-1.).

We request a response *by COB* on Monday, September 30, 2013. Please send your response via email to my attention, followed by a formal submission to the NDA.

Best regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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KIMBERLY S UPDEGRAFF  
09/27/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina \(Melina.Cioffi@frx.com\)](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Clinical Information Request  
**Date:** Thursday, September 05, 2013 5:12:07 PM  
**Importance:** High

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we have the following requests:

**A. Blood Pressure Analyses**

1. Please provide Kaplan-Meier analyses and figures for time to first blood pressure event, defined as: a) SBP = 140-159 or DBP = 90-99; and b) SBP  $\geq$ 160 or DBP  $\geq$  100. Please pool data from Groups 1A and 2A, and present the analyses by the following dose groups: 1.5-3 mg, 4.5-6 mg, and 9-12 mg, compared with placebo and active comparators. Provide similar analyses for pooled groups 1B and 2B.
2. Provide shift tables using the following baseline and on-treatment blood pressure criteria. Pool Groups 1A and 2A, and present the data by the dose groups above. Provide the same analysis for pooled groups 1B and 2B.

Baseline Blood Pressure	SBP < 120 and DBP < 80 N (%)	SBP = 120-139 or DBP = 80-89 N (%)	SBP = 140-159 or DBP = 90-99 N (%)	SBP $\geq$ 160 or DBP $\geq$ 100 N (%)
SBP < 120 & DBP < 80				
SBP 120-139 or DBP 80-89				
SBP 140-159 or DBP 90-99				
SBP $\geq$ 160 or DBP $\geq$ 100				

3. If you have you performed any similar Kaplan-Meier analyses of BP outliers or shift analyses, please provide any relevant analyses.

**B. Adverse Events Tables**

1. For Groups 1A and 2A, please provide Adverse Events (AE) tables by the following dose groups: 1.5-3 mg; 4.5-6 mg; and 9-12 mg. Provide a similar AE table for pooled groups 1B and 2B.

**C. Clinical Laboratory Analyses**

1. Provide analyses and figures displaying the mean CPK over time in pooled groups 1A and 2A and in pooled groups 1B and 2B pooled, including all follow-up assessments post-treatment. Provide analyses for cariprazine dose groups combined, as well as by individual cariprazine dose groups (1.5-3 mg; 4.5-6 mg; 9-12 mg).
2. Provide tables presenting the proportion of individual CPK outliers with CPK = 5-10 X ULN; >10-40 X ULN, and >40 X ULN in each treatment group, for the cariprazine dose groups combined, as well as by cariprazine dose groups: 1.5-3 mg, 4.5-6 mg, and 9-12 mg (for pooled groups 1A and 2A and for pooled groups 1B and 2B).
3. Provide analyses of individuals with CPK > ULN and concurrent creatinine increases  $\geq$ 20% from baseline for pooled groups 1A and 2A and for pooled groups 1B and 2B. Provide analyses for all cariprazine doses combined, as well as by dose individual dose groups (1.5-3 mg; 4.5-6 mg; 9-12 mg).

4. CPK outliers (above ULN) with concurrent hematuria, as described in Item C.3.
5. Analyses of CPK outliers (above ULN) with concurrent myalgia, muscle pain, muscle weakness, or related AE terms as described above.
6. Provide an analysis of mean creatinine over time (with figures) as outlined in Item C.1 above.
7. Provide similar analyses of mean ALT and mean bilirubin (direct, indirect, and total) over time as described in Item C.1 above.

**D. Ongoing AE and Lab Abnormalities**

1. Please provide Kaplan-Meier Analyses (with figures) of ongoing adverse events and clinical laboratory abnormalities for all subjects in the program. Provide analyses of time to resolution of specific AEs and laboratory after discontinuation of study drug treatment for the following: EPS, akathisia or restlessness, anxiety, insomnia, hypertension, suicidal ideation or behavior, orthostatic hypotension, somnolence, vomiting, nausea, and elevations of CPK, transaminase, bilirubin (direct, indirect, total), and creatinine. Please provide separate analyses for each AE or laboratory parameter. Provide analyses for all cariprazine dose groups combined, as well as for individual dose groups.
2. Provide tables presenting the proportions of subjects with resolved AEs/lab abnormalities vs. those with unresolved findings at last the contact.
3. Provide spaghetti plots for individual subjects regarding the time profile of ongoing AE/lab abnormality by individual AE/lab parameter.

**We request a response by COB on Monday, September 9, 2013.**

Best Regards,

Kim

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)  
301-796-2201

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KIMBERLY S UPDEGRAFF  
09/09/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370 - Cariprazine - Additional Clinical request RE: Grand Jury Investigation  
**Date:** Wednesday, August 07, 2013 3:40:28 PM

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We also refer to your submission dated July 12, 2013, containing information regarding a grand jury inquiry for two investigators involved with clinical studies submitted to the NDA and your July 25, 2013 response to our July 17, 2013 information request.

We have the following additional request:

For each study, please provide a comparison of mean point-estimates (for this site, for all other sites, and for the study overall) for the major efficacy endpoints, the total number of SAEs, and the scope/extent of sponsor monitoring (numbers of monitors, total monitoring time/duration, and number of monitoring visits).

We request a response by August 14, 2013.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
(301)796-2201  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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KIMBERLY S UPDEGRAFF  
08/13/2013

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Friday, August 09, 2013 4:32 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: cariprazine - Information Request - Adverse Events/Clinical laboratory Abnormalities  
**Attachments:** 204370 Ongoing AE.xlsx

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and one of our main concerns is the persistence of adverse events (AE) and clinical laboratory abnormalities after discontinuation of treatment. The attached Excel sheet has a list of patients who were reported as having ongoing EPS, akathisia, restlessness, or elevation of transaminases, bilirubin, or CPK. The general request is to clarify for each patient the number of days post-treatment at which the AE or lab abnormality was last reported as ongoing. In many cases it is not clear when the AE or abnormality was last determined to be ongoing. Some of these appear to have been reported during the planned safety follow-up period. In addition, there are cases in which the finding was reported to be ongoing as of the time of writing the study report. This suggests the possibility that there may have been contacts on specific dates that were not documented specifically in the narratives, patient profiles or case report forms.

We would appreciate clarifying information on these cases.

We would like to discuss our concerns during the Late Cycle Meeting (LCM) on August 16, 2013. We will most likely discuss this issue along with Agenda item 2 (Long Half-life, Accumulation, and Reversibility of Adverse Reactions) as outlined in the LCM briefing document provided to you on August 1, 2013.

Please let me know if you have any questions. We request a response on/by Monday, August 19, 2013.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
(301)796-2201  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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KIMBERLY S UPDEGRAFF  
08/10/2013

**Updegraff, Kimberly**

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**Subject:** NDA 204370 - Cariprazine -Clinical request (Hepatic Information)

**Attachments:** eDISHdataRequirement.xlsx

**From:** Updegraff, Kimberly

**Sent:** Friday, August 09, 2013 11:01 AM

**To:** Cioffi, Melina

**Cc:** Updegraff, Kimberly

**Subject:** NDA 204370 - Cariprazine -Clinical request (Hepatic Information)

Hi Melina,

As a follow-up to the email below, we are providing additional details regarding the information we requested. Attached is a document with the types of data requested for eDISH analysis. The data can be submitted in xpt format.

Please provide the following:

- Study number, identifiers for subjects, calendar dates stating when the tests were done, test results, normal reference range (or at least upper limit of range) for at least ALT, AST, ALP, Total Bilirubin, Direct Bilirubin, GGT, and INR (if available). Also include drug dose and the dates that drug treatment started and stopped.
- Clinical narratives (vs. patient profiles) for cases with: 1) marked elevations of ALT or AST >10xULRR or 2) both ALT>3xULRR & TBL>2xULRR.

We request a response by COB on Tuesday, August 13, 2013.

Thank you,

Kim

---

**From:** Updegraff, Kimberly

**Sent:** Wednesday, August 07, 2013 3:49 PM

**To:** Cioffi, Melina

**Cc:** Updegraff, Kimberly

**Subject:** NDA 204370 - Cariprazine -Clinical request

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we request that you submit the following:

- Liver data in a format that we can enter in the eDISH program (evaluation of Drug-Induced Serious Hepatotoxicity).
- Datasets including: all ALT, AST, bilirubin, alkaline phosphatase, and GGT data; include the date of each assessment and the laboratory reference ranges for each parameter.
- Transaminase data in Units per Liter and bilirubin data in mg per dL.

We request a response by August 9, 2013.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER/ODEI  
(301)796-2201  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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KIMBERLY S UPDEGRAFF  
08/10/2013



NDA 204370

**LABELING PMR/PMC DISCUSSION COMMENTS**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your November 19, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine 1.5mg, 3mg, 4.5mg, 6mg, (b) (4) capsules.

We also refer to our January 31, 2013, letter in which we notified you of our target date of August 1, 2013 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On February 14, 2013, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

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

Clinical

- 1) Maintenance Study in Schizophrenia: a placebo-controlled, randomized withdrawal study in schizophrenia to assess the efficacy 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. The main objective is to determine the minimum effective dose required for maintenance treatment.

PREA Studies

- 2) A deferred study in pediatric patients (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.
- 3) A deferred pediatric study 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.

- 4) A deferred pediatric study 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.
- 5) A long-term, open-label safety study in pediatric patients with schizophrenia (ages 13 to 17).
- 6) A long-term, open-label safety study in pediatric patients with bipolar disorder, recent manic episode (ages 10 to 17 years).

#### Clinical Pharmacology

- 1) An *in vivo* drug-drug interaction study to assess cariprazine exposure when cariprazine is coadministered with a proton pump inhibitor.
- 2) *In vitro* evaluation of cariprazine and its two major metabolites on inhibition potential toward CYP2C8.
- 3) *In vitro* evaluation of cariprazine and its two major metabolites on induction potential toward CYP2B6.
- 4) *In vitro* evaluation of cariprazine on induction potential toward CYP3A4 and CYP1A2.
- 5) *In vitro* evaluation of desmethyl-cariprazine and didesmethyl-cariprazine on inhibition potential toward CYP2B6 and CYP2C19.

Depending on the results of the *in vitro* studies, it may be necessary to conduct further *in vivo* studies.

#### Pharmacology/Toxicology

- 1) A juvenile animal study to be conducted in the dog at the appropriate age that corresponds to children age 10 years. The study protocol should be submitted for review and the study must be completed prior to initiation of pediatric clinical studies in children 10 years of age.

If you have any questions, please call me, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Health Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

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

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KIMBERLY S UPDEGRAFF  
08/01/2013



NDA 204370

**DISCIPLINE REVIEW LETTER**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine.

The Division of Medication Error Prevention and Analysis (DMEPA) has completed a review of the proposed [REDACTED] (b) (4) included in your submission and has identified the following deficiencies:

In your May 29, 2013 response, to our May 17, 2013 information request, you stated your intention to [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Robert Levin, M.D.  
Cross Discipline Team Leader  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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ROBERT L LEVIN  
07/30/2013

**NDA 204370 - Cariprazine - Clinical request (Grand Jury Investigation)**

Updegraff, Kimberly

**Sent:** Wednesday, July 17, 2013 3:54 PM  
**To:** Melina.Cioffi@frx.com  
**Cc:** Updegraff, Kimberly  
**Importance:** High

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We also refer to your submission dated July 12, 2013, containing information regarding a recent grand jury inquiry for two investigators involved with clinical studies submitted to the NDA.

We have the following requests/questions:

- Do you have any additional information regarding the concerns related to the investigators?
- How were the concerns identified?
- For the investigator/sites, please share the initial (routine) and follow-up (investigation of allegation) audit findings.
- Please provide site-specific study results.

We request that you respond within one week (NLT July 24, 2013).

Best regards,

Kimberly Updegraff  
Regulatory Project Manager  
FDA/CDER/ODE I/DPP  
301-796-2201

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KIMBERLY S UPDEGRAFF  
07/17/2013

## **NDA 204370 - Cariprazine - CMC request**

Updegraff, Kimberly

**Sent:** Wednesday, July 17, 2013 12:28 PM

**To:** Melina.Cioffi@frx.com

**Cc:** Updegraff, Kimberly

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We request that you provide the final consolidated drug product specifications.

We request a response by COB on July 18, 2013.

Best regards,

Kimberly Updegraff  
Senior Regulatory Project Manager  
FDA/CDER/ODE1/DPP  
301-796-2201

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KIMBERLY S UPDEGRAFF  
07/17/2013

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Friday, June 28, 2013 8:29 AM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Request - Pharmacovigilance Plan

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. FDA encourages sponsors to submit a Pharmacovigilance Plan developed to detect new safety risks and to further evaluate identified safety risks following market approval. Guidance for the Pharmacovigilance Plan has been included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and FDA Guideline on E2E Pharmacovigilance Planning (2005). If the plan is available, please submit it to the NDA application in the appropriate module so it can be reviewed accordingly.

Best regards,

*Kim*

.....  
Kimberly Updegraff  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
CDER, FDA  
Office of Drug Evaluation I  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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KIMBERLY S UPDEGRAFF  
07/01/2013

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Monday, June 24, 2013 12:14 PM  
**To:** Patricia.Jacala@frx.com  
**Cc:** Cioffi, Melina; Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Clinical/Safety Information Request

Dear Patricia,

We are currently reviewing your May 31, 2013 submission and we do not feel a teleconference is necessary. In response to your question posed in the briefing package:

- Does the Division concur with Forest's proposal, and that submission of the data as described will not be a major amendment?

We do not consider this submission a major amendment. We are reviewing the submission and it appears, on the surface, that you provided an adequate response. However, whether we agree with your analysis, is still a matter of review.

Best regards,

Kim

---

**From:** Jacala, Patricia [mailto:Patricia.Jacala@frx.com]  
**Sent:** Tuesday, June 18, 2013 1:31 PM  
**To:** Updegraff, Kimberly  
**Cc:** Cioffi, Melina  
**Subject:** RE: NDA 204370: Cariprazine - Clinical/Safety Information Request

Hi Kim,

Thank you so much for your reply. Starting today, I will be the point of contact until June 26 because Melina is out of the office in preparation for her wedding.

I understand that the teleconference with FDA on June 24, 2013 is currently no longer necessary. When can we anticipate feedback from FDA regarding the question posed in the briefing package? (Does the Division concur with Forest's proposal, and that submission of the data as described above will not be a major amendment?) I am available to speak over the phone anytime as well.

Thank you,  
Patricia

Patricia Jacala, PharmD  
Sr Manager, Regulatory Affairs  
Forest Research Institute  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311  
P: (201) 427-8402  
F: (201) 524-9711

patricia.jacala@frx.com

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**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Tuesday, June 18, 2013 12:28 PM  
**To:** Jacala, Patricia  
**Cc:** Updegraff, Kimberly  
**Subject:** RE: NDA 204370: Cariprazine - Clinical/Safety Information Request

Hi Patricia,

Please see our responses in RED below.

Thanks,

Kim

---

**From:** Jacala, Patricia [mailto:Patricia.Jacala@frx.com]  
**Sent:** Monday, June 17, 2013 8:07 PM  
**To:** Updegraff, Kimberly; Cioffi, Melina  
**Subject:** RE: NDA 204370: Cariprazine - Clinical/Safety Information Request

Hi Kim,

I would like to take this time to introduce myself. I am Patricia Jacala, Sr Manager in Regulatory Affairs. I have been working with Melina on the Cariprazine program.

Thank you for providing the Clinical/Safety Information Request. We are actively working on the response to the Division and just had a few points for clarification.

- Do cases need to meet all of the criteria (transaminases > 2 times upper limit of normal AND bilirubin > 1.5 times upper limit of normal ) or any of the criteria listed in Question #5? **Any**
- Do cases need to meet all of the criteria (positive urine myoglobin AND CPK > 1.5 times upper limit of normal) or any of the criteria listed in Question #6? **Any**
- We plan to provide the patient profiles for questions #5 and #6 from the same source of studies as question #4 (the controlled schizophrenia studies, the controlled bipolar disorder studies, the open-label schizophrenia studies, and the open-label bipolar study). Is this accurate? **The same source of studies as question #4 is acceptable.**

Please feel free to contact me if you have any questions regarding the clarifications above.

Thank you,

Patricia

---

**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Monday, June 17, 2013 3:48 PM

**To:** Cioffi, Melina  
**Cc:** Jacala, Patricia  
**Subject:** NDA 204370: Cariprazine - Clinical/Safety Information Request

Thanks, Melina. That is fine.

Enjoy your time out of the office. I will contact Patricia if we have any questions or needs while you are out.

Best regards,

Kim

---

**From:** Cioffi, Melina [<mailto:Melina.Cioffi@frx.com>]  
**Sent:** Monday, June 17, 2013 3:39 PM  
**To:** Updegraff, Kimberly  
**Cc:** Jacala, Patricia  
**Subject:** RE: NDA 204370: Cariprazine - Clinical/Safety Information Request

Hi Kim,

Thanks-

What we can do is respond to the request #1 below, and add any additional aspects from the midcycle communication re: dose and dose/response to our response to request #1 below.

We can do so by the timeline proposed below (June 28, 2013).

Kind regards,

Melina

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**From:** Updegraff, Kimberly [<mailto:Kimberly.Updegraff@fda.hhs.gov>]  
**Sent:** Monday, June 17, 2013 3:36 PM  
**To:** Cioffi, Melina  
**Subject:** RE: NDA 204370: Cariprazine - Clinical/Safety Information Request

Hi Melina,

We request that you respond to both (i.e., request # 1 below and the comments regarding dose response from the midcycle meeting).

Thanks,

Kim

---

**From:** Cioffi, Melina [<mailto:Melina.Cioffi@frx.com>]  
**Sent:** Monday, June 17, 2013 10:19 AM  
**To:** Updegraff, Kimberly  
**Subject:** RE: NDA 204370: Cariprazine - Clinical/Safety Information Request

Hi Kim,

Did you hear anything about our question below? We ask because this will slightly change the scope of our response, and the response timelines.

Please let us know, thanks.

Kind regards,

Melina

---

**From:** Cioffi, Melina  
**Sent:** Friday, June 14, 2013 4:51 PM  
**To:** Updegraff, Kimberly  
**Subject:** Re: NDA 204370: Cariprazine - Clinical/Safety Information Request

Thanks Kim. I'm confirming receipt. Does request #1 now replace the earlier request to respond to the midcycle communication dose dose response comments?

---

**From:** Updegraff, Kimberly  
**Sent:** Friday, June 14, 2013 4:40 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Clinical/Safety Information Request

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we have the following requests:

1. We request that you submit dose-response and exposure-response analyses in order to support the proposed doses for each indication. Please provide a detailed rationale for the doses, including a discussion of dose-related and exposure-related safety findings. You may use any analyses and presentations that you think would be useful. We do not have more specific requests that would limit your choice of analyses. For exposure analyses, use the total active moiety: cariprazine plus the desmethyl- and di-desmethyl metabolites.
2. Please provide detailed analyses of regional efficacy findings for each indication. We ask you to explore factors that could have contributed to differential efficacy findings between US and non-US subgroups. Please also include regional analyses for Europe, Asia, and South America. Exploratory factors could include (but may not be limited to): age, gender, body weight, other demographic features, baseline severity of illness, history of psychiatric illness and duration of illness, concomitant psychiatric history, use of concomitant medications, or any other factors that you would consider.
3. For Study MD-11, please provide information about the overall mean and modal doses and the final daily doses. Please indicate the proportions of subjects who had final daily doses of: 1) 1.5

mg to 3 mg, 2) 4.5 mg to 6 mg, and 3) 7.5 mg to 12 mg.

4. Provide the following additional outlier analyses for the controlled schizophrenia studies, the controlled bipolar disorder studies, the open-label schizophrenia studies, and the open-label bipolar study:
  - Transaminase  $\geq 2$  times upper limit of normal
  - Bilirubin  $\geq 1.5$  times upper limit of normal
  - CPK  $\geq 1.5$  times upper limit of normal
  - Prolactin  $> 1.5$  times upper limit of normal
5. Provide patient profiles for all cases of transaminases  $\geq 2$  times upper limit of normal, bilirubin  $\geq 1.5$  times upper limit of normal, and cases of adverse events consistent with the terms hepatitis, liver function test/transaminase elevated, liver injury (and any similar terms related to hepatic adverse events).
6. Provide patient profiles for all cases of positive urine myoglobin, CPK  $> 1.5$  times upper limit of normal, or adverse event of rhabdomyolysis or related terms.

The patient profiles should include the following information (but not limited to):

Subject ID, center, study drug treatment history, all adverse events and outcomes, vital sign data, and clinical laboratory data.

We request a response by COB on June 28, 2013.

Best regards,

*Kim*

.....  
Kimberly Updegraff  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
FDA/CDER  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
07/01/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370 - Cariprazine Information Request - NonClinical  
**Date:** Friday, June 07, 2013 2:12:15 PM  
**Importance:** High

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We acknowledge your submissions received on May 22, 2013 and June 4, 2013, containing responses to our information requests dated May 7, 2013 and May 30, 2013.

We have the following additional requests for information:

1. Please provide discussion/tables of correlation between "phospholipidosis" and target organ toxicity in the lungs for the rat carcinogenicity study for all 60 animals per group. Your Table 1 ("**End of Study Incidence of Lung Findings in the Rat Carcinogenicity Study 104 Weeks**") submitted on June 4, 2013, is inadequate because it shows only the incidence/correlation of adverse findings in animals sacrificed at the end of the study excluding animals that died or were sacrificed before scheduled termination.
2. Please explain why the incidence of "phospholipidosis" or inflammation listed in the Table 1 submitted on June 4, 2013, does not correspond to the incidence of relevant findings listed for lungs in the table "**Incidence Summary of Microscopic Findings with Severity Levels Terminal Sacrifice**" included in your rat carcinogenicity study report (pages 247–249). Please describe which of listed histopathology findings for the lungs in the table in your study report you consider to be indicative of "phospholipidosis".
3. Please explain how do you define "phospholipidosis" for your Tables 1 and 2 submitted on May 22, 2013 ("**Incidence of Lung Findings in the 6-Months Repeat Dose Study in Rats**" and "**Incidence of Adrenal and Lung Findings in the 52-Week Dog Study**"). Also, explain where the corresponding data for the incidence of "phospholipidosis"-like findings and inflammation listed in Tables 1 and 2 of the May 22, 2013 submission can be found in the summary histopathology tables in your final reports of the 6-month study in rats and the 52-week study in dogs (please provide the page number).

We request a response NLT COB on Tuesday, June 11, 2013.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
CDER, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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/s/

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KIMBERLY S UPDEGRAFF  
06/07/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370 - Cariprazine Information Request -- NonClinical  
**Date:** Thursday, May 30, 2013 1:35:35 PM  
**Importance:** High

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We acknowledge your May 22, 2013, response to our May 7, 2013, information request. Please see the following additional requests:

- We acknowledge your response to FDA Request #2. We ask that you provide discussion/tables of correlation between phospholipidosis and target organ toxicity for the rat carcinogenicity study similar to these submitted for the 6-month study in rats and 52-week study in dogs. Please include incidence of inflammation and/or hemorrhage observed in this study and the number of animals per group that were positive for both phospholipidosis and inflammation and/or hemorrhage.
- For FDA Request #3, you considered reductions in plasma cholesterol and triglyceride levels to be due to reduced prolactin secretion in rodents. However, studies conducted in rats with cariprazine at doses of 0.5 mg/kg and higher caused significant increase in serum prolactin levels in both male and female rats with much higher levels in females than in male rats. Please discuss this issue and explain the apparent discrepancy.
- Please discuss cariprazine-related adverse effects on fertility and reproductive parameters in the rat and explain whether they are due to an increase or decrease in prolactin levels.

We request a response by **noon on June 4, 2013**.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
*Senior Regulatory Project Manager*  
*Division of Psychiatry Products*  
*Center for Drug Evaluation and Research, FDA*  
*Office of Drug Evaluation*  
*Phone: (301)796-2201*  
*Email: Kimberly.Updegraff@fda.hhs.gov*

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/s/  
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KIMBERLY S UPDEGRAFF

06/07/2013

Late entry ... request sent 5/30/13



NDA 204370

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Alexander Bischoff, PhD  
Associate Director, Regulatory Affairs  
Harborside Financial Center, Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Bischoff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine (RGH-188) capsules.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a written response by June 17, 2013, in order to continue our evaluation of your NDA.

1. Provide the full specification that you will use to release drug substance batches.
2. Provide batch analysis for the drug substance batches used to manufacture the primary stability batches.
3. Update Table 3.2.P.3.4-1 (In-Process Controls During the Manufacture of Cariprazine Capsules) to include all in-process controls.
4. Include in-process controls for (b) (4) the drug product manufacturing process.
5. Provide the composition of the (b) (4) ink used to imprint the capsule.
6. (b) (4)  
(b) (4)
7. Photostability data for the 3.0 and 4.5 mg capsules demonstrate that these potencies are sensitive to light; however, you have not included a "protect from light" statement on the package insert, carton or bottle label. Please update these sections to include storage conditions that are consistent with your stability data.
8. Provide the exact address and FEI number for the drug substance manufacturing facility proposed in your comparability protocol.

If you have any questions, call Teshara Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh K. Sood, Ph. D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
06/04/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine - Clinical/Safety Information Request  
**Date:** Friday, June 14, 2013 4:40:38 PM  
**Importance:** High

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we have the following requests:

1. We request that you submit dose-response and exposure-response analyses in order to support the proposed doses for each indication. Please provide a detailed rationale for the doses, including a discussion of dose-related and exposure-related safety findings. You may use any analyses and presentations that you think would be useful. We do not have more specific requests that would limit your choice of analyses. For exposure analyses, use the total active moiety: cariprazine plus the desmethyl- and di-desmethyl metabolites.
2. Please provide detailed analyses of regional efficacy findings for each indication. We ask you to explore factors that could have contributed to differential efficacy findings between US and non-US subgroups. Please also include regional analyses for Europe, Asia, and South America. Exploratory factors could include (but may not be limited to): age, gender, body weight, other demographic features, baseline severity of illness, history of psychiatric illness and duration of illness, concomitant psychiatric history, use of concomitant medications, or any other factors that you would consider.
3. For Study MD-11, please provide information about the overall mean and modal doses and the final daily doses. Please indicate the proportions of subjects who had final daily doses of: 1) 1.5 mg to 3 mg, 2) 4.5 mg to 6 mg, and 3) 7.5 mg to 12 mg.
4. Provide the following additional outlier analyses for the controlled schizophrenia studies, the controlled bipolar disorder studies, the open-label schizophrenia studies, and the open-label bipolar study:
  - [Transaminase  \$\geq 2\$  times upper limit of normal](#)
  - [Bilirubin  \$\geq 1.5\$  times upper limit of normal](#)
  - [CPK  \$\geq 1.5\$  times upper limit of normal](#)
  - [Prolactin  \$> 1.5\$  times upper limit of normal](#)
5. Provide patient profiles for all cases of transaminases  $\geq 2$  times upper limit of

normal, bilirubin  $\geq 1.5$  times upper limit of normal, and cases of adverse events consistent with the terms hepatitis, liver function test/transaminase elevated, liver injury (and any similar terms related to hepatic adverse events).

6. Provide patient profiles for all cases of positive urine myoglobin, CPK  $> 1.5$  times upper limit of normal, or adverse event of rhabdomyolysis or related terms.

The patient profiles should include the following information (but not limited to):

Subject ID, center, study drug treatment history, all adverse events and outcomes, vital sign data, and clinical laboratory data.

We request a response by COB on June 28, 2013.

Best regards,

*Kim*

.....  
*Kimberly Updegraff*  
*Senior Regulatory Project Manager*  
*Division of Psychiatry Products*  
*FDA/CDER*  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
06/16/2013

Executive CAC

Date of Meeting: June 11, 2013

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Todd Bourcier, Ph.D., DMEP, Alternate Member  
Aisar Atrakchi, Ph.D., DPP, P/T Supervisor  
Elzbieta Chalecka-Franaszek, Ph.D., DPP, Presenting Reviewer

Author of Draft: Elzbieta Chalecka-Franaszek, Ph.D.

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

NDA # 204370

Drug Name: Cariprazine (Vraylar)

Sponsor: Forest Laboratories Inc.

**Background:** The NDA 204370 has been submitted for the approval of cariprazine (RGH-188) for the treatment of schizophrenia and for the treatment of manic or mixed episodes associated with bipolar I disorder. The mechanism of action of cariprazine in schizophrenia and bipolar mania is unknown. The therapeutic effect of cariprazine in schizophrenia may be mediated through a combination of partial agonist activity at central dopamine D<sub>2</sub>, D<sub>3</sub>, and serotonin 5-HT<sub>1A</sub> receptors. The two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) have a similar *in vitro* receptor binding profile as the parent drug.

Cariprazine was not mutagenic in the *in vitro* bacterial reverse mutation assay and human lymphocyte chromosomal aberrations assay and in the *in vivo* mouse micronucleus assay. *In vitro* mouse lymphoma assay was positive (small but statistically significant increases in mutant frequency were observed under conditions of metabolic activation). Based on the negative findings in the three additional mutagenicity studies, the weight of evidence suggests that cariprazine has negligible mutagenic potential. The major active metabolite DDCAR was not mutagenic in the *in vitro* bacterial reverse mutation assay. However, this metabolite was positive in the *in vitro* human lymphocyte chromosomal aberrations assay based on observation of a small increase in the percentage of cells with structural aberrations.

Protocols for the Tg.rasH2 mouse carcinogenicity study were presented to the Executive CAC on March 16, 2010 and October 5, 2010. The protocol for the rat carcinogenicity study was presented on August 1, 2006. The doses used in the mice and rat carcinogenicity studies were those recommended by the ExecCAC.

**Tg.rasH2 Mouse Carcinogenicity Study:** Transgenic [CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras)] mice (25/sex/group) were administered cariprazine by gavage for 26-28 weeks. The vehicle was sterile water for injection. Positive control animals

(15/sex) were administered 1000 mg/kg urethane i.p. on study days 1, 3, and 5. Satellite animals (CByB6F1 nontransgenic littermates) were used for toxicokinetic evaluation. A two-week dose adaptation period preceded the 26-week dosing period for the mid-dose males and high dose males and females. The final oral (gavage) doses of cariprazine were 0, 1, 5, and 15 mg/kg/day (males) and 0, 5, 15, and 50 mg/kg/day (females).

No increases in tumors, relative to vehicle controls and historical control ranges, were noted in cariprazine-treated mice. As expected, statistically significant increases in lung (adenomas and carcinomas) and spleen (hemangiosarcomas) tumors were noted in positive control animals.

**Rat Carcinogenicity Study:** Wistar rats (60/sex/group) were treated with cariprazine by oral gavage for up to 2 years. Following a 2-week dose adaptation period, male rats were administered 0.25, 0.75, and 2.5 mg/kg/day by gavage, while females were administered 1, 2.5, and 7.5 mg/kg/day. Control animals (2 groups/sex) received vehicle only (distilled water). Two groups of satellite animals were used for plasma concentrations (27/sex/treated group) and also for clinical pathology (10/sex/treated group).

No test article-related increases in neoplasms were observed, except for a slight numerical increase in the incidence of benign and malignant pheochromocytomas of the adrenal medulla in female rats administered the high dose of cariprazine (7.5 mg/kg/day). The Applicant provided two separate data sets for the incidence of pheochromocytomas, the original study report and reevaluation by the Pathology Working Group (PWG). Based on the FDA statistical review conducted by Dr. Steven Thomson, the test of trend in pooled benign and malignant pheochromocytoma of the adrenal medulla in female rats was statistically significant only based on the incidence of these neoplasms in the PWG analysis ( $p = 0.002$  which is  $<0.005$ ) and close to significance using the neoplasms diagnosis used by the original toxicologist ( $p = 0.0072 \approx 0.005$ ). However, pairwise comparisons of the test article-treated groups, including the high dose group, to pooled control groups of female rats were not statistically significant. No other comparisons achieved statistical significance. Therefore, there were no statistically significant drug-related neoplasms in this study.

### **Executive CAC Recommendations and Conclusions:**

Tg.ras H2 Mouse:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no statistically significant drug-related neoplasms.

- The Committee noted an increase in the incidence of benign and malignant pheochromocytomas of the adrenal medulla in high dose females although it was not statistically significant.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\n  
/Division File, DPP  
/Aisar Atrakchi, DPP  
/Elzbieta Chalecka-Franaszek, DPP  
/Kimberly Updegraff, DPP  
/ASeifried, OND IO

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/s/  
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ADELE S SEIFRIED  
06/13/2013

ABIGAIL C JACOBS  
06/13/2013

**Updegraff, Kimberly**

---

**From:** Updegraff, Kimberly  
**Sent:** Friday, May 17, 2013 11:29 AM  
**To:** Melina.Cioffi@frx.com  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370 - Cariprazine Information Request -- DMEPA

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we have the following request from the Division of Medication Error Prevention Analysis (DMEPA):

The Agency has preliminarily reviewed your proposed [redacted] (b) (4)  
You have proposed [redacted] (b) (4)  
[redacted] but did not provide a rationale regarding [redacted] (b) (4). We are  
concerned that the proposed [redacted] (b) (4)

[redacted]  
[redacted] If you still wish to seek approval of  
your proposed [redacted] (b) (4) please submit your rationale for the Agency to consider.  
Alternatively, you may submit an amendment requesting withdrawal of [redacted] (b) (4)  
previously submitted.

Let me know if you have any questions. We request a response by May 30, 2013.

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: Kimberly.Updegraff@fda.hhs.gov**

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/s/  
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KIMBERLY S UPDEGRAFF  
05/17/2013



NDA 204370

**MID-CYCLE COMMUNICATION**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine.

We also refer to the teleconference between representatives of your firm and the FDA on May 2, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, M.S.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication

## MID-CYCLE COMMUNICATION

**Meeting Date and Time:** May 2, 2013 (1:00 – 2:00 p.m.)  
**Application Number:** NDA 204370  
**Product Name:** Cariprazine  
**Indication:** Bipolar Disorder and Schizophrenia  
**Applicant Name:** Forest Laboratories, Inc.

**Meeting Chair:** Robert Temple, M.D.  
**Meeting Recorder:** Kimberly Updegraff, Regulatory Project Manager

### FDA ATTENDEES

Robert Temple, MD, Deputy Director for Clinical Science, Center for Drug Evaluation and Research (CDER)  
Mitchell Mathis, MD, Director (acting), Division of Psychiatry Products (DPP)  
Robert Levin, MD, Clinical Team Leader, DPP  
Francis Becker, MD, Clinical Reviewer, DPP  
Aisar Atrakchi, PhD, Nonclinical Supervisor, DPP  
Elzbieta Chalecka-Franaszek, PhD, Nonclinical Reviewer, DPP  
Chhagan Tele, PhD, Office of New Drug Quality Assessment (ONDQA) Team Leader  
Sherita McLamore-Hines, PhD, ONDQA Reviewer  
Sandra Suarez, PhD, ONDQA Biopharmaceutics Reviewer  
Hao Zhu, PhD, Office of Clinical Pharmacology (OCP) Team Leader  
Huixia Zhang, PhD, OCP Reviewer  
Venkatesh Atul Bhattaram, PhD, Team Leader, Pharmacometrics, OCP  
Joo-Yeon Lee, PhD, Reviewer, Pharmacometrics, OCP  
Peiling Yang, PhD, Biostatistics Team Leader  
Eiji Ishida, MS, Biostatistics Reviewer  
Wiley Chambers, MD, Deputy Division Director, Division of Transplant and Ophthalmology Products (DTOP)  
William Boyd, MD, Clinical Reviewer, DTOP  
Irene Z. Chan, PharmD, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)  
Loretta Holmes, BSN, PharmD, Reviewer, DMEPAR  
Reema Mehta, PharmD, Risk Management Team Leader, Division of Risk Management (DRISK)  
Jason Bunting, PharmD, Risk Management Analyst, DRISK  
Ida-Lina Diak, PharmD, Division of Pharmacovigilance I (DPV), Office of Surveillance and Epidemiology (OSE)  
Namita Kothary, PharmD, Reviewer, DPV, OSE  
Kimberly Taylor, Operations Research Analyst, Office of Planning and Informatics  
Mark Ritter, MD, Clinical Reviewer, DPP  
Terry Harrison, PharmD, Safety Regulatory Project Manager, DPP  
Kimberly Updegraff, RPh, MS, Senior Regulatory Project Manager, DPP

**INDEPENDENT ASSESSOR**

Patrick Zhou, Eastern Research Group (ERG)

**APPLICANT ATTENDEES**

Marco Taglietti, MD, Senior Vice President (SVP), Research and Development (R&D) and President, Forest Research Institute (FRI)

June Bray, RPh, MBA, SVP, FRI Regulatory Affairs

Gavin Cocoran, MD, Executive Vice President (EVP), R&D Clinical & Early Development

Willie Earley, MD, Sr. Director, Clinical Development Psychiatry

Michael Olchaskey, PharmD, Sr. Director, Regulatory Affairs

Melina Cioffi, PharmD, Associate Director, Regulatory Affairs

Alexander Bischoff, PhD, Associate Director, Regulatory Affairs

Patricia Jacala, PharmD, Manager, Regulatory Affairs

Amol Parekh, PharmD, Fellow, Regulatory Affairs

Suresh Durgam, MD, Sr. Director, Clinical Development

Denise Leclair, MD., Sr. Director, Pharmacovigilance & Risk Management, Global Drug Safety

Yih Lee, PhD., Sr. Principal Scientist, Clinical Pharmacology & Drug Dynamics

Antonia Periclou, Sr. Director, Clinical Pharmacology & Drug Dynamics

Tatiana Khariton, PhD, Sr. Principal Scientist, Modeling & Simulation

Shana Azri-Meehan, PhD, DABT, Sr. Principal Scientist, Toxicology

Kaifeng Lu, PhD, Directory, Biostatistics

Andreas Grill, PhD, Executive Director, DP & PR & D Project Management

Salvatore Iacono, MS, Sr. Director, Method Development

**1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

### Clinical:

#### Dosing and the long half-life of the didesmethyl-cariprazine metabolite:

The Division expressed concern about the proposed dosing recommendations, because the DD-CAR active metabolite has such a long half-life, and it comprises the majority of the active moiety soon after initiating treatment. The DD-CAR exposure is 3-fold the parent exposure, even before steady state has been achieved. In the dedicated PK study, DD-CAR had not reached steady state by Day 27 post-dose (the last PK assessment time point). Based on PK modeling, the sponsor calculated that the estimated terminal half-life for DDCAR is 4 to 10 weeks, and the functional half-life is 31 days.

The Division is concerned that there is no controlled efficacy or safety data beyond 6 weeks, well before the predominant active moiety (DD-CAR) has reached steady state. We discussed the possibility of reducing the cariprazine dose over time. The Division recommended that Forest examine the activity of all three active moieties over time. Forest will consider these and provide a response.

#### Safety Profile over Time:

The Division is interested in data on the safety profile over time, to address whether there may be differential safety profiles for cariprazine, DD-CAR, and D-CAR. The Division will request specific safety analyses.

#### Dose-Response Relationships:

We discussed the dose-response relationships in the cariprazine program. For both indications, the lower dose ranges were effective. In the schizophrenia program, there appears to be a modestly increased benefit with higher doses. However, in the bipolar disorder program the effects were quite similar between the low dose and high dose groups. It is possible that the maximum recommended dose would be 6 mg.

Forest has conducted PK/PD analyses using the PANSS in schizophrenia trials and YMRS in bipolar mania trials. Forest concludes that there is a positive dose-response relationship for doses up to (b) (4) mg for both indications. Forest will provide information on the contribution of each of the active moieties.

#### Maintenance Study:

Study RGH-MD-06 is an ongoing, randomized withdrawal maintenance study in schizophrenia. After the stabilization phase, subjects are randomized to fixed doses of cariprazine (3 mg, 6 mg, or 9 mg per day).

**Efficacy Results by Region:**

The Division requested that Forest perform efficacy analyses to assess potential regional differences in efficacy responses. It appears that there may be significant regional differences, particularly in the bipolar mania program (smaller efficacy in the U.S. compared to other regions).

**Study Site Observations:**

Forest stated that there were significant findings for a particular investigator involved in several cariprazine studies. It appears that one problem is under-reporting of adverse events. The investigator enrolled subjects in studies RGH-MD-4, 11, 16, 17, 31, and 32. Forest is in the process of conducting a complete audit of the investigator site. Forest will submit detailed information, and we will schedule a telecon to discuss findings.

**Office of Clinical Pharmacology (OCP):**

Forest concluded that all three moieties (cariprazine, and its two active metabolites DCAR and DDCAR) demonstrated linear PK. However, results from study RGH-MD-01 appear to only support this conclusion for cariprazine, not for the two active metabolites. DCAR and especially DDCAR demonstrated more than dose proportional increase in exposure. The determination of PK linearity affects the validity of the sponsor's assumption for the PopPK model. Please refer to our information request dated May 8, 2013.

**Division of Medication Error Prevention Analysis (DMEPA):**

The Agency has preliminarily reviewed the proposed [REDACTED] (b) (4)  
[REDACTED]. Forest has proposed [REDACTED] (b) (4)  
[REDACTED]. The  
Division will send additional comments as necessary.

**3.0 INFORMATION REQUESTS**

**Office of Clinical Pharmacology:**

Please refer to our information request dated May 8, 2013.

**Clinical:**

The Division will send specific information requests.

**Pharmacology/Toxicology:**

Please refer to our information request dated May 7, 2013.

**Office of New Drug Quality Assessment (ONDQA):**

The Office will send specific information requests.

**ONDQA-Biopharmaceutics:**

Please refer to our information request dated May 8, 2013.

**DMEPA:**

Please refer to our information request dated May 17, 2013.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

- **Clinical / Ophthalmology:** The Agency is actively reviewing the ocular data. At this point, we not have specific comments.
- **Preliminary thinking regarding risk management:** We are actively reviewing the submission. At this time, we are not prepared to address the need for risk management tools.

**5.0 ADVISORY COMMITTEE MEETING**

An advisory committee meeting is not anticipated at this time.

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

- 1) We plan to issue Discipline Review letters by: July 26, 2013
- 2) We plan to communicate proposed labeling, and if necessary, any post marketing commitment requests by: August 1, 2013 (if major deficiencies are not identified during the review)
- 3) A Late-Cycle Meeting (LCM) is scheduled on: August 16, 2013
- 4) We plan to send the Agency background package for the LCM by: August 2, 2013
- 5) We are on track with completing GCP and GMP inspections.
- 6) We plan to take an action on or before the PDUFA date: November 19, 2013

**7.0 APPLICANT QUESTIONS/CONCERNS**

- 1) A response to ONDQA's request dated March 5, 2013 regarding the DMF was submitted by the DMF holder, Gedeon Richter. (A representative from Gedeon Richter was present during the call). The applicant questioned whether the response was adequate. The FDA ONDQA team stated that the response is currently under review and had no additional comments.
- 2) The applicant referenced a recent inspection by the Office of Scientific Investigations which resulted in a Form 483 for a particular investigator with sites in several studies. The sponsor stated that they have responded to the Form 483 and are currently compiling data regarding sensitivity analysis and efficacy data. Additional information will be submitted as soon as possible.

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/s/  
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MITCHELL V Mathis  
05/17/2013

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Monday, April 01, 2013 4:20 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Clinical Request

Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we are requesting that you submit a complete clinical study report (CSR) for long-term study RGH-MD-11.

We request the CSR be submitted by April 23, 2013.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, MS, RAC**  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
04/02/2013



NDA 204370

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Forest Laboratories, Inc.  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

ATTENTION: Melina Cioffi, PharmD  
Associate Director, Regulatory Affairs

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received November 19, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Cariprazine Capsules, 1.5 mg, 3 mg, 4.5 mg (b) (4)

We also refer to your correspondence, dated and received January 17, 2013, requesting review of your proposed proprietary name, Vraylar. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Vraylar, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 17, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact Kimberly Updegraff, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
04/16/2013

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Monday, April 08, 2013 3:27 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Telecon (4/10/13)  
**Attachments:** NDA 204370 - Cariprazine Study-11 Requested Tables.doc

Hi Melina,

In preparation for our telcon scheduled for Wednesday, April 10, 2013 at 3:00 pm, please see the attached document. The attachment contains a preliminary list of information and tables that we would like to request regarding Study 11.

Thanks,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

## **NDA 204370, Trial RGH-MD-11, Requested Tables**

1. Figure (Flow Chart): Patient Populations and Dispositions – RGH-MD-11
2. Table: Patient Disposition by Country and By Lead-in Treatment – RGH-MD-11
3. Table: Patient Disposition by Week – RGH-MD-11
4. Table: Protocol Deviations – Enrolled Population (ie, updated line listing) – RGH-MD-11
5. Table: Cariprazine-treated Patients with Suicidality TEAEs in Group 1B – Safety Population (updated, ie line listing)
6. Updated table of Changes in Liver Biochemistries in Group 1B Over Time
7. Updated Overview of Changes in Metabolic Parameters During Treatment in Group 1B (include means and glucose parameters)
8. Updated Change from Baseline Over Time in CPK Levels in Group 1B – Safety Population

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/s/  
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KIMBERLY S UPDEGRAFF  
04/15/2013

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, March 21, 2013 2:59 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Information Request (NonClinical)  
**Attachments:** Carci Data Format and Stat Guidance Info Sheets 07-16-09.pdf

Dear Dr.Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We also refer to your report for study RGH-TX-34, entitled "2-year oral (gavage) carcinogenicity study in rats" and to the Pathology Working Group (PWG) review of proliferative changes involving the adrenal medulla, appended to this report.

Please submit the data set for the rat carcinogenicity study in the format submitted to the NDA, but with the adrenal tumor (Pheochromocytoma) data revised according to the incidence consistent with the PWG report. The new data set should indicate gender, dose group, animal identification number, time to death for each animal, (revised) tumor status, etc. In order to perform an additional statistical analysis with tumor incidence as reflected in the PWG report, we need these revised data set as soon as possible. Please see the attached document for additional information.

We request a response on or before COB on March 29, 2013.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation  
Phone: (301)796-2201

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/s/  
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KIMBERLY S UPDEGRAFF  
03/21/2013

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Tuesday, March 12, 2013 8:51 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370: Cariprazine - Information Request

Dear Dr.Cioffi,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing your application and we have the following requests:

- Long-term safety data: Please provide an integrated summary of safety for the long-term schizophrenia studies.
- Additional ocular narratives: Please provide detailed narratives for (1) new cases of ocular adverse events and (2) all cases in which there are abnormal ocular findings on ophthalmology exam or OCT scanning. This should include all cases with any ocular findings or terms such as (but not limited to): cataract, opacity, opalescence, macular degeneration, macular thickening or atrophy/thinning, drusen, separation of retinal layers, retinal pathology, retinal degeneration, epiretinal membrane, nerve degeneration or other pathology (e.g., thickening, thinning), abnormal color vision, decrease or change in color vision, pigment, pigmentation. Include cases in which there are findings at baseline.
- Previously submitted ocular narratives: Provide revised ocular narratives for patients who were in ongoing studies at the time of the previous data lock.
- All previous and new ocular narratives: Indicate whether patients in the long-term studies had been previously treated during the lead-in phase with cariprazine, placebo, aripiprazole, or risperidone, and indicate the duration of cariprazine exposure during the lead-in study. We acknowledge that most of the narratives address this point, but it is not clear in some cases. Indicate which patients had: 1) baseline OCT scanning before any exposure to cariprazine, 2) baseline OCT after exposure to cariprazine, and 3) no baseline OCT before the beginning of the long-term studies. For all ocular case narratives, indicate the reasons for unscheduled OCT scans or unscheduled ophthalmology exams. Some of the narratives for ocular adverse events narratives do not include a reason (e.g., adverse event) for the unscheduled visits.
- For patients who were in ongoing studies at the time of original data lock, please integrate all OCT scans, OCT data, and ophthalmological exam results in new files for each patient.
- Were OCT scans and OCT data submitted for all patients (n=172), including those with less than one year of cariprazine exposure, or were OCT scans and data submitted only for those exposed for > 1 year? Please provide the OCT information for all 172 subjects if this wasn't submitted.
- Please provide any reports from Dr. Laties and Dr. Serle. For all 3 independent ophthalmologists, please provide any documents regarding adjudication of cases or other ophthalmologic information.



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KIMBERLY S UPDEGRAFF  
03/12/2013

**Updegraff, Kimberly**

**From:** Updegraff, Kimberly  
**Sent:** Monday, February 11, 2013 3:58 PM  
**To:** Cioffi, Melina  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 204370- FDA Request in Day-74 letter - biopharmaceutics request

Hi Melina,

Please see the following responses to your questions below:

Response to request 6: your proposal is acceptable.

Response to request 7: the dataset needs to be stratified by time since the first dose and by each specific FINAL dose level (i.e., 1.5, 3, 4.5, 6, 7.5, and 9 mg), not by a dose range/treatment group (e.g., 6-9 mg). It is noted in your 12/18/2012 submission, there were patients reported on 12 mg. Data for those patients also need to be submitted. It is understood that some of the trials were under flexible dosing regimen, unless the doses were adjusted very frequently (e.g., less than a week) all the time for the whole study duration, data for each individual of those who have PK data need to be submitted as requested. You basically just need to summarize Figures 5-1 to 5-3 in your 12/18/2012 submission in the format as shown below (one for each moiety):

Time since first dose (weeks)	Number of subjects	Number of samples	Observed concentration (ng/mL)					Final Dose (mg)	Time post Last Dose (hours)	
			mean	SD	5 <sup>th</sup> percentile	median	95 <sup>th</sup> percentile		mean	sd
N								1.5		
N								3		
N								4.5		
N								6		
N								7.5		
N								9		
N								12		

Kim

**From:** Cioffi, Melina [mailto:Melina.Cioffi@frx.com]  
**Sent:** Thursday, February 07, 2013 1:35 PM  
**To:** Updegraff, Kimberly  
**Subject:** NDA 204370- FDA Request in Day-74 letter

Hi Kim,

Our team at Forest has some clarification/request for the reviewers in response to FDA Request #6 and #7 in the Day-74 Filing Letter for cariprazine. Can you please share these with the reviewers and let me know as soon as possible of their response?

For FDA Request #6, Forest will need to recreate the PK datasets, by study, to suit the format/scope requested by the reviewers.

We can provide the requested plasma concentration datasets for cariprazine clinical pharmacology studies in

healthy volunteers RGH-PK-04, 07, 10, 14, and RGH-188-001, 002, and 003 by February 14, 2013 as per the initial FDA request to provide within two weeks from the date of the Filing Letter.

For cariprazine efficacy, safety, and clinical pharmacology studies in patients, RGH-MD-01, 02, 03, 04, 05, 16, 17, 18, 32, 33, 36, we can provide the requested plasma concentration datasets by February 25, 2013.

For the recently completed RGH-MD-11 long term safety study, the clinical database was locked on February 4, 2013 (this Monday). We can provide the RGH-MD-11 requested plasma concentration dataset in the 120-day safety update.

Is this timeframe acceptable?

For FDA Request #7, Forest would just like to clarify that our plan is to create the requested dataset package using the dataset constructed for Population PK modeling; ALLC16.XPT dataset and corresponding data definition file included with Study RGH-MS-01 (2012). We will resubmit raw data with only the requested Phase 2 and Phase 3 studies and variables and will further split this dataset into 9 separate datasets corresponding to 9 cariprazine dose groups, as requested by February 14, 2013. We will also create separate summary tables and plots of concentrations vs. time since the first dose by dose groups. Forest would like to remind the agency the dose groups as defined by protocols were flexible thus, across 9 Phase 2/3 studies that collected PK sampling there were 9 different treatment groups (1.5, 1.5-4.5, 3, 3-6, 3-9, 4.5, 6, 6-12, 6-9 mg/day).

-----  
Kind regards,

Melina

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KIMBERLY S UPDEGRAFF  
02/21/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: Cariprazine -- Request  
**Date:** Friday, February 08, 2013 11:58:08 AM

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Dear Melina,

Please refer to your New Drug Application (NDA 204370) for cariprazine, dated and received on November 19, 2012. We are currently reviewing the labels and labeling, and note that you propose multiple starter pack and blister pack configurations. We request that you provide actual samples of all the proposed trade starter packs, sample starter packs, and sample blisters. Please provide *two* samples of each packaging configuration.

We request a response by COB on Friday, February 15, 2013.

Please send the samples directly to me at the following:

Kimberly Updegraff  
Division of Psychiatry Products  
Food and Drug Administration  
White Oak CDER Building 22, Office 4241  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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KIMBERLY S UPDEGRAFF  
02/08/2013



NDA 204370

## FILING COMMUNICATION

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for cariprazine capsules 1.5 mg, 3 mg, 4.5 mg, 6 mg (b) (4)

We also refer to your amendments dated December 13, 2012, December 18, 2012, and January 17, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is November 19, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 1, 2013. In addition, the planned date for our internal mid-cycle review meeting is April 12, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We remind you of your agreement, during our October 25, 2012 teleconference, to submit completed safety data for the long-term study, RGH-MD-11, with the 120 day safety update. As the long-term safety data is essential to the review of your application, we encourage you to submit the data as soon as possible.

We request that you submit the following information:

1. For the submitted efficacy studies (6 pivotal and 1 supportive), please provide a list of IND numbers with serial numbers and submission dates for the protocols, SAPs, amendments, and any relevant meetings. If it's already included in your original NDA submission, please specify its location.
2. Provide dissolution profile data (individual, mean, plots) for the batches used in PK studies RGH-PK-14, 2012 and RGH-PK-10, 2009.
3. To support the BA/BE waiver request for the 4.5 mg (b) (4) strengths, please submit multi-point dissolution profile comparison data in water, 0.1 N HCl, and USP buffer media at pH 4.5 and 6.8 for the proposed strengths. Include  $f_2$  statistical testing using the following strengths as the reference: 1.5 mg, 3 mg, and 6 mg.
4. Your proposed manufacturing (b) (4) changes implemented to the clinical trial formulation are within the limits defined by the FDA's *SUPAC-IR Guidance for Industry* (b) (4)  
(b) (4)
5. Your proposed dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at  $\frac{(b)}{(4)}$  minutes is not justified. Provide the following information to support the selection of the dissolution acceptance criterion:
  - a. Dissolution profile data (individual and mean in tabulated and graphical form) from the pivotal clinical batches and primary (registration) stability batches.
6. Please submit individual plasma concentration data for RGH-188, DCAR and DDCAR for each clinical pharmacology studies and those in efficacy and safety studies in SAS .xpt format. The dataset should include columns specifying the following variables: protocol number, subject ID, dose, analyte, day from first dose, scheduled PK time, actual PK time, and concentration. Please provide "define.pdf" file to define your variables. Please submit the data within two weeks from the date of this letter.
7. We acknowledge receipt of your submission on Dec.18, 2012. To make a better understanding of the PK information, please resubmit the datasets, summary tables and plots by weeks since first dose and by dose groups. Please submit the data within two weeks from the date of this letter.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights (HL) page must have ½ inch margins on all sides.
2. Initial U.S. Approval in HL must be placed immediately beneath the product title.
3. Revision Date must be in MM/YYYY or Month Year format and should not be bracketed.
4. The same title for the Boxed Warning that appears in the HL and Full Prescribing Information (FPI) must also appear at the beginning of the Table Of Contents (TOC) in upper-case letters and bolded.
5. Subsection title 9.2 should read “Abuse” and a new subsection, 9.3, titled “Dependence” should be created.
6. The entire contents of the Boxed Warning, including the referenced section(s), should be bolded.

We request that you resubmit labeling that addresses these issues within 2 weeks from the date of this letter. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver/deferral for pediatric studies for this application. Once we have reviewed your requests, we will notify you if the partial waiver/deferral request is denied.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Psychiatry Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director (acting)  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
01/31/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: cariprazine for bipolar disorder and schizophrenia  
**Date:** Friday, January 18, 2013 12:36:41 PM

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Dear Dr. Cioffi,

Please refer to your New Drug Application, NDA 204370, cariprazine for bipolar I disorder and schizophrenia, received on November 19, 2012. This communication is to confirm that your application will be considered filed, as of today, January 18, 2013.

We will issue a filing communication letter by day 74 which will include any comments/requests we have at this time.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
01/18/2013

**From:** [Updegraff, Kimberly](#)  
**To:** [Cioffi, Melina](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 204370: cariprazine - proprietary name request  
**Date:** Tuesday, January 15, 2013 8:17:37 PM

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Dear Dr. Cioffi,

Please refer to your New Drug Application (NDA) dated and received on November 19, 2012, for cariprazine capsules. We also refer to the trade name assessment document prepared by [REDACTED] (b) (4) located under section 1.12.4 of your submission.

In order to evaluate the information in the document and your request for a review of the name Vraylar, we are requesting that you submit a cover letter requesting a Proprietary Name review.

The cover letter should reference the location of labels and labeling in the NDA submission (date and sequence) as well as reference the safety/trade name assessment prepared by [REDACTED] (b) (4).

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF  
01/16/2013



NDA 204370

**NDA ACKNOWLEDGMENT**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cariprazine capsules (1.5mg, 3mg, 4.5mg, 6mg (b) (4))

Date of Application: November 19, 2012

Date of Receipt: November 19, 2012

Our Reference Number: NDA 204370

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 18, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, M.S.  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KIMBERLY S UPDEGRAFF  
12/03/2012



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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IND 71958  
IND 77726

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cariprazine (RGH-188).

We also refer to the teleconference between representatives of your firm and the FDA on October 25, 2012. The purpose of the meeting was to discuss and document certain elements of "The Program" under PDUFA V.

A copy of the official minutes of the telecom is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Post PreNDA (PDUFA V Discussion)  
**Meeting Category:** Type C  
**Meeting Date and Time:** October 25, 2012  
10:00 AM – 11:00 AM EST  
**Meeting Location:** Teleconference  
**Application Number:** 71958; 77726  
**Product Name:** Cariprazine  
**Indication:** Schizophrenia; Bipolar disorder  
**Sponsor/Applicant Name:** Forest Labs, Inc  
**Meeting Chair:** Thomas Laughren, M.D.  
**Meeting Recorder:** Kimberly Updegraff

### FDA ATTENDEES

Thomas Laughren, Division Director  
Mitchell Mathis, Deputy Division Director  
Robert Levin, Clinical Team leader  
Francis Becker, Clinical Reviewer  
Aisar Atrakchi, Pharmacology/Toxicology Supervisor  
Elzbieta Chalecka-Franaszek, Pharmacology/Toxicology Reviewer  
Hao Zhu, Office of Clinical Pharmacology Team Leader  
Huixia Zhang, Office of Clinical Pharmacology Reviewer  
Peiling Yang, Statistics Team Leader  
George Kordzakhia, Statistics Reviewer  
Andrejus Parfionovas, Statistics Reviewer  
Valerie Gooding, Specialist - Electronic Submission Support  
Doug Warfield, Electronic Data Support  
(b) (6), Student  
Kim Updegraff, Project Manager

### SPONSOR ATTENDEES

Melina Cioffi, Associate Director, Regulatory Affairs  
Alexander Bischoff, Associate Director, Regulatory Affairs  
Patricia Jacala, Manager, Regulatory Affairs  
Amol Parekh, PharmD Fellow, Regulatory Affairs  
Michael Olchaskey, Senior Director, Regulatory Affairs  
June Bray, Senior Vice President, Regulatory Affairs  
Suresh Durgam, Senior Director, Clinical Development  
Anjana Bose, Executive Director, Clinical Development  
Anne Gilson, Principal Scientist, Toxicology  
Yih Lee, Senior Principal Scientist, Clinical Pharmacology and Drug Dynamics  
Tatiana Khariton, Principal Scientist, Modeling and Simulation  
Antonia Periclou, Senior Director, Clinical Pharmacology and Drug Dynamics  
Denise Leclair, Senior Director, Global Drug Safety

## 1.0 BACKGROUND

On May 24, 2012, FDA met with representatives from Forest to discuss the proposed New Drug Application (NDA) for cariprazine for the treatment of schizophrenia and bipolar I disorder. The Sponsor plans to submit the application on or after October 1, 2012, thus it will be subject to "The Program" under PDUFA V.

Under "The Program", applicants are strongly encouraged to discuss the planned content of their application with the appropriate FDA review division at a pre-submission (pre-NDA or pre-BLA) meeting to 1) reach agreement on the content of a complete application, including preliminary discussions on the need for risk evaluations and mitigation strategies (REMS) or other risk management actions, and 2) reach agreement on submission of a limited number of minor application components (components of the type that would not be expected to materially impact the ability of the review team to begin its review) not later than 30 calendar days after submission of the original application.

This teleconference, scheduled for October 25, 2012, was scheduled to discuss and document certain elements of "The Program".

## 2. DISCUSSION

If an application for a new molecular entity or an original biologic is submitted on or after October 1, 2012, the application will be subject to "The Program" under PDUFA V. Therefore, during this teleconference, be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements on the content of a complete application will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and "The Program" is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

### 2.1. PDUFA V Discussion

***Discussion Point 1:*** Discuss and agree upon the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions.

**FDA Comments:** *Agreement regarding the contents of a complete application was reached during the May 24, 2012 Pre-NDA meeting (refer to meeting minutes dated June 8, 2012).*

*The Division does not believe a REMS is necessary at this time, however, the issue will be considered in more detail during the review cycle. If you feel a REMS is warranted, we request that you present your concerns to us.*

*We request that you submit the report with the results of the electroretinogram study conducted in dogs and the datasets for the rat carcinogenicity and transgenic mouse carcinogenicity studies in the proper format for statistical analysis prior to or with the NDA submission.*

**Discussion at Meeting:** *Both parties acknowledged the agreements made during the May 24, 2012 PreNDA meeting as documented in the June 8, 2012 meeting minutes. The Sponsor also acknowledged receipt of our request for carcinogenicity datasets and they shared their plan to submit the datasets to IND 71958. In addition, they plan to submit the results of the electroretinogram prior to the NDA submission.*

*We stated that we do not believe a REMS is necessary at the time of NDA filing and asked the Sponsor if they had any concerns regarding safety that may require risk mitigation tools. The Sponsor did not have any such concerns and stated that they did not feel a REMS is necessary for this product. We added a reminder that the need for a REMS would be revisited during the review cycle.*

**Discussion Point 2:** *Discuss and agree upon, if appropriate, submission of a limited number of application components not later than 30 calendar days after the submission of the original application. The submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review.*

**FDA Comments:** *No agreement regarding late submissions was reached during the May 24, 2012 meeting.*

**Discussion at Meeting:** *The Sponsor acknowledged our request for the summary statistics and plots for sparse PK samples collected during the Phase 3 trials [see Section 2.2 Additional Discussion(s)/Requests(s)]. They offered to submit the requested information as a minor amendment no later than 30 calendar days after the submission of the NDA. We agreed with the approach.*

**Post Meeting Comment:**

*We also request that you provide the original dataset used to generate the plots in SAS.xpt format. The dataset should include columns specifying the following variables: protocol number, subject ID, dose (at time of sample collection), time (from the 1<sup>st</sup> dose), and concentration for each of the three moieties (i.e. cariprazine, desmethylcariprazine, and didesmethylcariprazine), separately. Please provide "define.pdf" file to define your variables.*

**Discussion Point 3:** We remind you that all applications are expected to be complete (as agreed upon at presubmission meeting) at the time of original submission. All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application. Since applications are expected to be complete at the time of submission, unsolicited amendments are expected to be rare and not contain major new information of analyses.

**Discussion at Meeting:** We reminded the Sponsor that we expect the application to be complete as per the agreements made during the PreNDA meeting and this teleconference, as well as be in compliance with 21 CFR 314.50. They acknowledged understanding and stated that they plan to comply with all previous agreements made during the May 24, 2012, PreNDA meeting and the February 16, 2012 CMC PreNDA meeting. This includes the submission of a 120 day safety update that will include completed safety data for the completed long-term study, RGH-MD-11.

## 2.2 Additional Discussion(s)/Request(s)

**Office of Clinical Pharmacology:** Please provide the dataset and plots for sparse PK samples collected in the Phase 3 trials. Plots should be provided for cariprazine, desmethyl cariprazine, and didesmethyl cariprazine, separately, with time (in weeks since the first dose) on the x-axis, and concentration on the y-axis. Please also provide summary statistics including mean, median, 5% and 95% percentile for the concentrations stratified by weeks since the first dose, and number of subjects.

**Discussion at Meeting:** See "Discussion at Meeting" comments under the second discussion point in Section 2.1 (PDUFA V Discussion).

**Electronic Submission Support (ESUB):** In response to your June 15, 2012 submission requesting feedback regarding the size limitations for Module 2.7, we have the following comments:

- 1) The size limitation applies to the entire 2.7 Clinical Summary section, not just for single-indication NDA. However, it is acceptable in occasions wherein, the entire 2.7 clinical summary section exceeds the 400 page limitation guidelines, because of information to be conveyed.
- 2) For content related information regarding 2.7 (Clinical Summary), please refer to the ICH M4 Guidance, located at:  
[http://www.ich.org/fileadmin/PublicWeb\\_Site/ICH\\_Products/CTD/M4\\_R1\\_Efficacy/M4E\\_R1\\_.pdf](http://www.ich.org/fileadmin/PublicWeb_Site/ICH_Products/CTD/M4_R1_Efficacy/M4E_R1_.pdf).

**Discussion at Meeting:** The Sponsor reported that Module 2.7 will be approximately 660 pages upon completion. We agreed that 660 pages would be acceptable to the Division.

### **Post Meeting Comment:**

Instead of providing the actual synopsis in m2.7.6, you could provide a list of synopsis (in tabular format) in m2.7.6. and hyperlink from m2.7.6. to the actual synopsis in m5.

### **3.0 Other Important Information**

#### **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

#### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

#### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

#### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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THOMAS P LAUGHREN  
11/02/2012



IND 071958

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cariprazine (RGH-188).

We also refer to the meeting between representatives of your firm and the FDA on May 24, 2012. The purpose of the meeting was to discuss the proposed New Drug Application (NDA) for cariprazine for the treatment of schizophrenia and bipolar I disorder.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Kimberly Updegraff, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING

IND 071958 Cariprazine (RGH-188)  
Forest Research Institute, Inc.  
Type B Pre-NDA Meeting  
May 24, 2012

**Objective:** To discuss the proposed New Drug Application (NDA) for cariprazine for the treatment of schizophrenia and bipolar I disorder.

### Participants –

#### **FDA**

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Robert Levin, MD	Medical Team Leader
Frank Becker, MD	Medical Reviewer
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor
Elzbieta Chalecka-Franaszek, PhD	Pharmacology/Toxicology Reviewer
George Kordzhakia, PhD	Statistics Team Leader
Andrejus Parfionovas, PhD	Statistical Reviewer
Huixia Zhang, PhD	Clinical Pharmacology Reviewer
Akm Khairuzzaman, PhD	Chemistry, Manufacturing, and Controls Reviewer
Doug Warfield	Office of Business Informatics (OBI)
Valerie Gooding	Office of Business Informatics (OBI)
John Lee, MD	Office of Scientific Investigations (OSI)
Kimberly Updegraff, MS	Regulatory Project Manager

#### **Sponsor**

Melina Cioffi, PharmD	Regulatory Affairs
Michael Olchaskey, PharmD	Regulatory Affairs
June Bray, MBA	Regulatory Affairs
Patricia Jacala, PharmD	Regulatory Affairs
Gavin Corcoran, MD	Research and Development
Anjana Bose, PhD	Clinical Development
Suresh Durgam, MD	Clinical Development
Dayong Li, PhD	Biostatistics
Maureen Toulon, PhD	Toxicology
Anne Gilson, MS	Toxicology
Salvatore Iacono, MS	CMC
Herta Palfine Goots	Regulatory Affairs (Gedeon Richter)
Gyorgy Nemeth, MD	Medical Affairs (Gedeon Richter)
Alexander Bischoff, PhD	Regulatory CMC

## **Background:**

Cariprazine (RGH-188) is a potent dopamine D<sub>3</sub> preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist. Cariprazine is under development by FRI, Gedeon Richter Plc, and Mitsubishi Pharma Corporation for the treatment of schizophrenia, bipolar mania and depression, and major depressive disorder.

Forest is planning to submit a New Drug Application for the treatment of patients with schizophrenia and for the treatment of manic and mixed episodes associated with bipolar I disorder during the fourth quarter of 2012.

The Division held a End-of-Phase 2 meeting with Forest on January 14, 2010 to discuss the clinical, non-clinical and pharmacokinetics program. On March 18, 2010, the Office of New Drug Quality Assessment I met with the sponsor to discuss the overall Chemistry, Manufacturing, and Controls (CMC) development program. On September 19, 2011, the Division held a telecon to discuss ocular issues and on November 15, 2011, another telecon to discuss clinical pharmacology issues was held. Most recently, FDA met with Forest on February 16, 2012 for a Pre-NDA CMC discussion.

The NDA will include data from a total of 21 studies in patients with schizophrenia or bipolar mania (10 phase 2/3 studies and 11 PK/pharmacology studies). For the phase 2/3 program, data will be included from 1921 cariprazine-treated patients (1309 patients with schizophrenia and 612 patients with bipolar mania) in short-term, placebo-controlled studies, and 1025 cariprazine-treated patients (622 patients with schizophrenia and 403 patients with bipolar mania) in long-term, open-label studies.

The schizophrenia program includes a total of 6 Phase 2/3 clinical studies:

- 3 pivotal short-term (6 weeks of treatment), placebo-controlled studies: RGH-MD-04 (cariprazine 3 and 6 mg/day), RGH-MD-16 (cariprazine 1.5, 3, and 4.5 mg/day), and RGH-MD-05 (cariprazine flexible doses [range 3-6 and 6-9 mg/day]): demonstrated positive results for the protocol-defined primary efficacy parameter (change from baseline in PANSS total score at end of Week 6) to support efficacy of cariprazine 1.5 to 9 mg/day for (b) (4) treatment of schizophrenia, according to the sponsor.
- (b) (4)
- 2 long-term (48 weeks of treatment), open-label studies: RGH-MD-17 (extension study of RGH-MD-16; cariprazine flexible doses [range 1.5-4.5 mg/day], and RGH-MD-11 (extension of RGH-MD-04 and RGH-MD-05, plus newly enrolled patients; cariprazine flexible-doses [range 1.5-9 mg/day]. In the 2 studies, 302 cariprazine-treated patients completed the 24-week visit and 134 cariprazine-treated patients completed the 48-week clinical visit. For the NDA, data from

Study RGH-MD-11, which is ongoing, will include long-term safety analysis using an interim safety database that will include all patients exposed for at least 6 months and patients who prematurely discontinued from the study as of the cutoff date of March 16, 2012.

The bipolar mania program includes a total of 4 Phase 2/3 clinical studies:

- 3 pivotal short-term (3-weeks of treatment) placebo-controlled studies: RGH-MD-31 (cariprazine flexible doses [range: 3-12 mg/day]), RGH-MD-32 (cariprazine flexible doses [range 3-12 mg/day]), and RGH-MD-33 (cariprazine fixed-flexible doses [range: 3-6 and 6-9 mg/day]): demonstrated positive results for the protocol-defined primary efficacy parameter (change from baseline in YMRS total score at end of Week 3) to support efficacy of cariprazine 3-12 mg/day for the treatment of manic and mixed episodes associated with bipolar I disorder, according to the sponsor.
- 1 long-term (16 weeks of treatment) open-label study: RGH-MD-36 (cariprazine flexible doses [range 3-12 mg/day]): 132 cariprazine-treated patients completed the 16-week clinical visit.

The integrated safety database of cariprazine will include data from the 10 short-term and long-term Phase 2/3 studies in patients with schizophrenia or bipolar mania, 7 PK/pharmacology studies in healthy subjects, 4 PK/pharmacology studies in patients with schizophrenia, 2 studies in patients with depression, and 4 studies conducted in Japan by Mitsubishi-Tanabe (3 PK studies in healthy subjects and 1 MTD study in patients with schizophrenia).

Patient exposure and SAEs for the 4 ongoing studies (1 major depressive disorder, 1 bipolar depression, 1 relapse prevention in schizophrenia, and 1 receptor occupancy in schizophrenia) reported as of April 30, 2012 will be included in the NDA submission. Three of the 4 ongoing studies will be blinded at the time of submission (the receptor occupancy study is open-label). A safety update will be provided 4 months after the NDA submission and will include updated patient exposure and any new SAEs reported during the period of April 30, 2012 to October 30, 2012 for all studies.

The most common treatment-emergent adverse events ( $\geq 10\%$  of patients in any cariprazine treatment group and at least twice the incidence of patients in the placebo group) were insomnia, extrapyramidal disorder, akathisia, restlessness, and constipation in the schizophrenia studies, and akathisia, extrapyramidal disorder, constipation, dyspepsia, vomiting, and tremor in the bipolar studies.

**Question 1:** Does the Division concur that positive results from the 3 pivotal studies (RGH-MD-16, RGH-MD-04, and RGH-MD-05) (b) (4) can support the NDA for cariprazine at doses of (b) (4) mg/day for the treatment of patients with schizophrenia?

**Preliminary Comments:** We agree.

**Discussion at Meeting:** *No further discussion.*

**Question 2:** Does the Division concur that positive results from the 3 studies (RGH-MD-31, RGH-MD-32, and RGH-MD-33) can support the NDA for cariprazine at a dose range of (b) (4) mg/day for the treatment of manic and mixed episodes associated with bipolar I disorder?

**Preliminary Comments:** *We concur.*

**Discussion at Meeting:** *No further discussion.*

**Question 3:** Does the Division concur with the proposed structure and statistical analyses for the Integrated Summary of Effectiveness (ISE) for schizophrenia?

**Preliminary Comments:** *We concur. We request that you provide efficacy analyses by dose for the fixed-dose studies.*

*Because the purpose of the subgroup analyses is to explore consistency of treatment effects across subgroups, we will evaluate the results from individual studies rather than pooled studies. We would not be interested in p-values from pooled results.*

**Discussion at Meeting:** *The sponsor stated that they plan to perform efficacy analyses by dose group and overall efficacy analyses for each individual study. In addition, they will provide descriptive statistics for subgroup analysis of the primary efficacy endpoint for each individual study.*

**Question 4:** Does the Division concur with the proposed structure and statistical analyses for the ISE for manic and mixed episodes associated with bipolar I disorder?

**Preliminary Comments:** *We concur. We request that you provide an analysis by dose range for the fixed, flexible dose study. Also, we request that you conduct an exploratory efficacy analysis regarding manic vs. mixed episodes.*

*Refer to the comments above regarding the subgroup analyses.*

**Discussion at Meeting:** *The sponsor confirmed that the fixed-flexible dose study (RGH-MD-33) will be analyzed by dose group. In addition, the sponsor will provide descriptive statistics for subgroup analysis of the primary efficacy parameter for each individual study, and they will include a subgroup analysis regarding manic and mixed episodes.*

**Question 5:** Does the Division concur that the estimated exposure data (including long-term safety) is adequate to support the NDA?

**Preliminary Comments:** *We concur that the estimated exposure database is adequate. You have stated that for ongoing Study RGH-MD-11, you will submit an interim safety database that will include all patients exposed for at least 6 months and patients who prematurely discontinued from the study as of the cut-off date of March 16, 2012. Please clarify your plan for submission of the final safety database for Study –MD-11 this study after the study is complete.*

**Discussion at Meeting:** *The sponsor stated that they plan to submit the NDA in the 4<sup>th</sup> quarter of 2012 and will submit the 120-day safety update in the 1<sup>st</sup> quarter of 2013. The 120-day safety update will include the complete safety data for the completed long-term study, RGH-MD-11.*

**Question 6:** Does the Division concur with the proposed structure, study groupings, and statistical analyses for the Integrated Summary of Safety (ISS)?

**Preliminary Comments:** *We concur.*

**Discussion at Meeting:** *No further discussion.*

**Question 7:** Does the Division concur with the proposed special safety analyses for the NDA?

**Preliminary Comments:** *Generally, we concur.*

***Metabolic Parameters (Changes in Weight, Glucose Concentration, and Lipid Concentration):***

*Provide an outlier analysis for weight changes, as outlined below. In addition, provide an outlier analysis of the proportion of patients with weight gain  $\geq 7\%$  of baseline body weight.*

	<u>6 weeks</u>		<u>24 weeks</u>		<u>48 weeks</u>	
<i>Weight change (kg)</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
<i>&gt;0 to 5 kg</i>						
<i>&gt; 5 to 10 kg</i>						
<i>&gt; 10 to 15 kg</i>						
<i>&gt; 15 to 20 kg</i>						
<i>&gt;20 to 25 kg</i>						
<i>&gt; 25 to 30 kg</i>						
<i>&gt;30 to 35 kg</i>						

>35 to 40 kg						
>40 kg						

***Lipid Analyses:** For the analyses of lipid changes, in addition to the analyses you have proposed, provide analyses for each of the following groups: 1) All subjects, 2) Subjects with at least 12 weeks of exposure, and 3) Subjects with at least 24 weeks of exposure. Include the median duration of exposure at the time of lipid measurement. For the categorical lipid analyses, report the mean or median baseline, post-baseline, and change in lipid values for each analysis. Include the following subgroup analyses for the proportion of subjects with changes of interest at any time post-baseline in each category, as outlined in the table below:*

***Treatment-Emergent Changes in Lipids: Based on NCEP-based Classifications for Adults:***

	Baseline	Postbaseline
Total Cholesterol (Fasting and Non-Fasting)*		
Normal to High	<200 mg/dL	≥240 mg/dL
Borderline to High	≥200 and <240 mg/dL	≥240 mg/dL
Normal/Borderline to High	<240 mg/dL	≥240 mg/dL
Normal to Borderline/High	<200 mg/dL	≥200 mg/dL
LDL Cholesterol (Fasting)		
Normal to High	<100 mg/dL	≥160 mg/dL
Borderline to High	≥100 and <160 mg/dL	≥160 mg/dL
Normal/Borderline to High	<160 mg/dL	≥160 mg/dL
Normal to Borderline/High	<100 mg/dL	≥100 mg/dL
HDL Cholesterol		
Normal to Low	≥40 mg/dL	<40 mg/dL
Triglycerides (Fasting)		
Normal to High	<150 mg/dL	≥200 mg/dL
Normal to Very High	<150 mg/dL	≥500 mg/dL
Borderline to High	≥150 and <200 mg/dL	≥200 mg/dL
Borderline to Very High	≥150 and <200 mg/dL	≥500 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Normal/Borderline to Very High	<200 mg/dL	≥500 mg/dL
Normal to Borderline/High/Very High	<150 mg/dL	≥150 mg/dL

***Glucose Analyses:** Provide an analysis of the mean and median changes in serum glucose from baseline to endpoint (last measurement) and from baseline to the*

highest measurement. Provide an analysis of the mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks, using the mean change in glucose from baseline to the highest post-baseline measurement for all subjects who completed the study time up to the time point specified.

Include an outlier analysis for categorical shifts of interest, as outlined in the table below:

***Serum Glucose: Criteria for Clinically Significant Changes:***

	Baseline	Post-Treatment
<b>Fasting Serum Glucose</b>		
Normal to High	<100 mg/dL	≥126 mg/dL
Impaired Fasting Glucose to High	100-125 mg/dL	≥126 mg/dL
Normal/Impaired Fasting Glucose to High	<126 mg/dL	≥126 mg/dL
Change in fasting serum glucose ≥10 mg/dL at any time post-baseline*	Any value	Fasting glucose increased ≥10 mg/dL
<b>Non-Fasting Serum Glucose</b>		
Normal to High	<140 mg/dL	≥200 mg/dL
Borderline to High	140-199 mg/dL	≥200 mg/dL
Normal to Borderline/High	<140 mg/dL	≥140 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Change in non-fasting serum glucose ≥20 mg/dL at any time post-baseline*	Any value	Non-fasting glucose increased ≥20 mg/dL

***Ophthalmologic Assessments***

*In the original NDA submission, you must submit adequate ocular coherence tomography data. You are required to submit complete results on at least 60 patients with one year of cariprazine exposure. The data must include the source documents from the ophthalmologists' assessments including electronic copies of the OCT scans. This will be a filing issue.*

***Discussion at Meeting:*** *The sponsor agreed to perform the metabolic analyses as requested. The sponsor will perform weight analyses at 6, 24, and 48 weeks, using the post-baseline maximum weight within each time frame. For lipid and glucose analyses, the sponsor will provide data on the mean and median change from baseline. For the glucose analysis, the sponsor will use the highest value within each time frame. The sponsor noted that metabolic data at 48 weeks would only be available for the schizophrenia program, because only this program included 48-week studies.*

*The sponsor clarified that in the original NDA they will submit the required OCT data for at least 60 patients treated with cariprazine for at least one year. This will include OCT scans using a standard OCT (3<sup>rd</sup> generation or higher), tabular listings, and narratives for cases in which there are OCT abnormalities. The sponsor requested clarification regarding the acceptable resolution limits for the OCT scans. The sponsor agreed to submit their questions and plan regarding the submission of OCT scans and data.*

**Additional Post-Meeting Comments:**

*We would expect that a third generation (or newer) OCT machine would provide acceptable resolution. We request that you provide scans in the highest resolution possible.*

*For the initial NDA submission, we request that you provide patient narratives, tabular listings, and CRFs for all patients with ophthalmic adverse events in any of the studies (not only for those patients studied with OCT).*

**Question 8:** Does the Division concur that case report forms (CRFs) and narratives would be submitted only for subjects who discontinued due to an adverse event (AE) or experienced a serious adverse event (SAE) (including death)?

**Preliminary Comments:** *Generally, we concur. It is possible that we would request CRFs for particular patients of interest.*

**Discussion at Meeting:** *No further discussion.*

**Question 9:** Does the Division concur with the proposal for reporting safety information from ongoing blinded studies?

**Preliminary Comments:** *We agree.*

**Discussion at Meeting:** *No further discussion.*

**Question 10:** Does the Division concur with the proposed safety cut-off date for the original NDA ISS and 120-day safety update?

**Preliminary Comments:** *We concur.*

**Discussion at Meeting:** *No further discussion.*

**Question 11:** Does the Division concur with the scope of the 120-day safety update?

**Preliminary Comments:** *We concur.*

**Discussion at Meeting:** *No further discussion.*

**Question 12:** Does the Division concur with the organization of the Electronic Common Technical Document (eCTD) NDA submission for a dual-indication NDA?

**Preliminary Comments:** *We concur; however, correct use of the 'indication' attribute under Module 2 summaries and Module 5 study reports is essential for information to be organized correctly for the review team. It would be helpful if the leaf title included shortened name of both indications. Please note that m3 was not provided in the proposed table of content for the NDA.*

**Discussion at Meeting:** *No further discussion.*

**Question 13:** Does the Division concur that the proposed content of the eCTD NDA submission is adequate for filing the cariprazine NDA?

**Preliminary Comments:** *From a technical standpoint (not content related), yes, the proposed format for the planned NDA is acceptable. However, please see the comments below:*

- *Please include technical point of contact in your cover letter.*
- *Providing a linked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, would be helpful to reviewers.*
- *The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.*
- *Please make sure that non-allowable characters are not used when naming files and folders. Also, to avoid truncation, the length of the entire path of the file should not exceed 230 characters.*
- *All modules should use descriptive leaf titles which are short, meaningful and indicative of the document's content.*

**Discussion at Meeting:** *No further discussion.*

**Question 14:** Does the Division concur with the proposal for presenting data in the 2 Summaries of Clinical Effectiveness (SCEs) and the Summary of Clinical Safety (SCS), assuming the size limitations are met?

**Preliminary Comments:** *Yes, we concur.*

**Discussion at Meeting:** *The sponsor asked if it would be acceptable to exceed the 400-page limit because the NDA will contain two indications (bipolar I disorder and schizophrenia). We requested that the sponsor submit their request in writing so that we can consult the eDATA team prior to responding.*

**Question 15:** Does the Division concur with Forest's plan for submitting study-level data sets in the NDA?

**Preliminary Comments:** *The study-level datasets described in 12.1.4 of the Pre-NDA Meeting Briefing Book generally conform to the requirements of the [Study Data Specifications](#) guidance. However, the FDA expects the sponsor to follow the current [Study Data Specifications](#) guidance for all study data when submitting the application.*

*Clinical trials research study designs should define the protocol for data collection. The Agency's methodology and submission structure supports research study design, as indicated in the [Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#) and the [Study Data Specifications](#). In addition, the Agency's methodology and submission structure supports integrating study data collection for Safety and Efficacy study submission.*

*The Agency requires implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency requires each study submitted to be complete and evaluated on its own merits. The Agency prefers studies be maintained independently in the SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)).*

*The sponsor should submit program files in ASCII format, consistent with the [Study Data Specifications](#) (pg. 5). The sponsor should locate the files under the [m3, m4, or m5]\datasets\[studyname]\analysis\programs directory, again per the [Study Data Specifications](#) (pg. 8). SAS program (.sas) files that are viewable as ASCII formatted files are acceptable.*

**Discussion at Meeting:** *The representative from eDATA clarified that the sponsor should indicate where the data will be placed in the submission. The sponsor expressed understanding.*

**Question 16:** Does the Division concur that the potential impurities of the cariprazine HCl drug substance should be considered adequately qualified regarding their genotoxic potential and that these impurities can be controlled per ICH Q3A and Q3B?

**Preliminary Comments:** *No, we do not concur. You were able to maintain low levels of these impurities in previous clinical batches, therefore, it seems reasonable and doable that they are controlled at similar low levels in the current and future clinical batches. Alternatively, these impurities should be qualified by testing for gene mutation in bacteria and in cytogenetic test for chromosomal damage in mammalian cells. Note that one of these impurities*

is [REDACTED] (b) (4) that was tested positive in human lymphocyte chromosomal aberration test. In addition, impurities [REDACTED] (b) (4) contain alerting functional groups other than the [REDACTED] (b) (4) group you refer to as [REDACTED] (b) (4).

*Additional Comments:* We again remind you to submit human steady state PK data for [REDACTED] (b) (4) as soon as possible. This information is needed to compare exposure in humans to that in animals in order to determine adequate safety assessment of [REDACTED] (b) (4) one of the drug substance impurities.

**Discussion at Meeting:** The agency stated that the level of the impurities containing [REDACTED] (b) (4) should be maintained at or below the qualification threshold as previously achieved (slightly higher levels may be justified) or these impurities will need to be tested for genotoxicity. We acknowledged that the sponsor has already agreed to this approach during the End of Phase 2 CMC meeting in March 2010 and that the drug substance impurities of interest have not been qualified in any of the batches used in pivotal toxicology studies.

Forest will be submitting information from the literature and NCTR to show that some of these impurities are qualified for genotoxicity and/or carcinogenicity; we agreed and will review the information when submitted and respond in writing.

Forest confirmed that a steady state for [REDACTED] (b) (4) will be presented in the upcoming NDA submission. The agency reminded Forest that additional nonclinical studies may be needed pending review and evaluation of the clinical results.

**Division's clarification comment added after the meeting:**  
Human/transgenic mice [REDACTED] (b) (4) exposure ratio will be calculated based on the steady state clinical levels of this metabolite when become available and the TK data from the transgenic mice (Tg.rasH2) carcinogenicity study, which appears to be negative. If margins of exposure are adequate, the API and the metabolites containing [REDACTED] (b) (4) may be considered qualified for carcinogenicity.

**Additional Statistical Comments:**

In the original NDA submission, include the following items for the trials intended to support efficacy claims:

- 1) SAS programs by which the derived (primary and key secondary) variables were

- produced from the raw variables;*
- 2) *SAS programs that produced the (primary and key secondary) efficacy results;*
  - 3) *A list of IND numbers with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

**Discussion at Meeting:** *No further discussion.*

**Comments from the Office of Clinical Pharmacology:**

*We request that you provide a completely elucidated human metabolic pathway scheme in the original NDA submission.*

**Discussion at Meeting:** *No further discussion.*

**Comments from the Office of Scientific Investigations:**

*Please see attached document entitled, “NDA Information and Format: OSI Request to Sponsor”.*

**Discussion at Meeting:** *The sponsor requested a contact in OSI in case they have questions regarding the request. Dr. John Lee, with the Office of Scientific Investigations, stated that Forest may contact him directly if needed. Dr. Lee’s information: office phone (301)796-1396; email [John.Lee@fda.hhs.gov](mailto:John.Lee@fda.hhs.gov)*

**Post-Meeting Comment:** *Please refer to the document entitled, “NDA Information and Format: OSI Request to Sponsor” which was attached to the preliminary comments.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Forest Research Institute is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, RPh, MS  
Senior Regulatory Project Manager

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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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THOMAS P LAUGHREN  
06/08/2012

**INDs 71,958 and 77,726 (Cariprazine HCl)  
Type B, Pre-NDA CMC Meeting on February 16, 2012  
Sponsor's Meeting Minutes**

**Meeting Information**

Meeting type: Type B, Pre NDA CMC  
Meeting date and time: February 16, 2012, 11:00 a.m.  
Meeting location: FDA, White Oak Campus, Bldg 22 Rm. 1417, Silver Spring, MD  
Application number: INDs 71,958 and 77,726  
Product name: Cariprazine HCl  
Indication: Schizophrenia, Bipolar disorder  
Sponsor/applicant: Forest Laboratories, Inc.

**FDA Attendees**

Ramesh Sood, Ph.D., Branch Chief  
Chhagan Tele, Ph.D., CMC Lead  
Akm Khairuzzaman, Ph.D., Chemistry Reviewer  
Teshara G. Bouie, Regulatory Health Project Manager

**Sponsor Attendees**

Alexander Bischoff, PhD, Associate Director, Regulatory Affairs CMC	Forest
Ranajoy Sarkar, PhD, Manager, Development Pharmaceuticals	Forest
Salvatore Iacono, MS, Senior Director, Method Development PR&D	Forest
Andreas Grill, MBA, Executive Director, Development Pharmaceuticals	Forest
Náray Zsófia, MS, Manager, API Research and Development	Gedeon Richter
Maureen Toulon, PhD, Executive Director, Toxicology	Forest
Yih Lee, PhD, Senior Principal Scientist, Clinical Pharmacology & Drug Dynamics	Forest

**Background**

- The purpose of the meeting was to discuss critical CMC issues of the cariprazine HCl program with the Office of New Drug Quality Assessment. The sponsor sought to gain the Agency's agreement on chemistry, manufacturing and controls data to support the NDA for cariprazine HCl.
- The meeting was requested by the Sponsor on December 9, 2011 (SN0328, SN0214).
- FDA granted the meeting request on January 6, 2012.
- The briefing package was submitted by the Sponsor on January 13, 2012 (SN0333, SN0219).
- The Sponsor received the preliminary meeting comments letter responding to the questions in the briefing package in advance of the meeting on February 14, 2012.

## Meeting Minutes

**Question 1:** *Does the Agency agree that these potential impurities of the cariprazine HCl drug substance should be considered adequately qualified regarding their genotoxic potential, and that these impurities can be controlled per ICH Q3A and Q3B?*

FDA Preliminary Response: The impurities with (b) (4) as the only structural alert (b) (4) would require additional review in consultation with pharmacology/toxicology discipline reviewer within the agency to evaluate their genotoxic potential. This would be determined during the NDA review. However, the impurities containing additional structural alerts that are not present in the drug substance structure should be evaluated for their potential genotoxicity and controlled accordingly.

### Discussion:

- The Sponsor considered the potential impurities adequately qualified through their structural (b) (4). The Sponsor asked whether the supporting data for Question 1 were shared with the FDA pharm/tox colleagues prior to the meeting for review and feedback.
- FDA indicated that the supporting data were not shared with the FDA pharm/tox reviewers.
- The Sponsor asked if the data could be forwarded to the pharm/tox reviewers in order to provide the Sponsor with feedback in a foreseeable time frame.
- FDA indicated that the CMC review team will forward the information to the FDA pharm/tox reviewer's for feedback. FDA also stated that the Sponsor is to follow up with a request for feedback to the IND.
- The Sponsor acknowledged FDA's commitment to forward the supporting data to the FDA pharm/tox reviewers and the recommendation to submit a request for feedback to the IND.

**Question 2:** *Does the Agency agree that further monitoring of these potential impurities in the commercial drug substance is not required?*

FDA Preliminary Response: In your April 9, 2009 meeting minutes, you have stated that the residual levels of (b) (4) are < (b) (4) % and < (b) (4) %, respectively. In the current briefing package you have stated that these two impurities are too reactive to detect analytically. Please clarify. We agree that the levels of (b) (4) impurities are consistently low in the batches made at the current site and hence, may not be needed to be monitored routinely. The remaining impurities with structural alerts that are being detected in the batches following their introduction will need to be controlled either in the final drug substance or at the appropriate (b) (4) level.

### Discussion:

- To part 1 of FDA's response (levels of (b) (4)):
  - The Sponsor indicated that a (b) (4) study in the reaction media demonstrated that (b) (4)
  - FDA was satisfied with the provided clarification.
- To part 2 of FDA's response (b) (4)
  - The Sponsor acknowledged FDA's response.
- To part 3 of FDA's response (remaining impurities with structural alerts):

- The Sponsor indicated that the batch analysis data were generated for 7 commercial scale batches, and the process demonstrated capability to remove potential impurities. (b) (4)  
Because (b) (4) are not compounds of toxicological concern, the Sponsor asked if the agency agreed that further monitoring of these compounds in the commercial drug substance is not required.
- FDA stated that the levels for (b) (4) are too close to the TTC. However, the non-genotoxic compounds, (b) (4), may not need to be included in the drug substance specification, if the levels to be seen were consistently low by either the API impurities release method or via another method.

**Question 3:** *Does the Agency agree that the quality attributes of the specification adequately control the drug substance to ensure its quality, strength, purity and identity?*

**FDA Preliminary Response:** You have mentioned about (b) (4) identification in page 96 of 223 of your meeting package but in the proposed specification you are referring to USP< (b) (4)> for identification. Clarify if your current IR method for identification in the specification is capable of identifying the desired (b) (4).

**Discussion:**

- The Sponsor confirmed that the IR method does discriminate between (b) (4) and that the method is a (b) (4) method. The Sponsor will provide detailed information for methodology in the NDA.
- FDA was satisfied with the Sponsor's clarification.

**Question 4:** *Does the Agency agree that the tests, studies, analytical procedures, and acceptance criteria described in the comparability protocol are sufficient to demonstrate equivalence of the identity, strength, quality, purity, and potency of the drug substance batches manufactured at different sites?*

**FDA Preliminary Response:** The final determination for the acceptability of the comparability protocol will be done during the NDA review. However, the approach appears to be reasonable. However, we recommend that you monitor all the impurities that you have listed in 7.1.2.2-3 in the new site as well. The equivalence will be determined upon receiving the data. Note that if your proposed site of manufacturing for the API is not in compliance with cGMP for the intended operations, then proposed reporting category would be a PAS (Prior Approval Supplement). Please note that when you submit the supplement, we will request an inspection. For further details, please refer to the draft "Guidance for Industry: Comparability Protocols - Chemistry, Manufacturing, and Controls Information (2003)".

**Discussion:** There was no further discussion of this question during the meeting.

**Question 5a:** *Does the agency agree that Cariprazine Capsule of 1.5, 3.0, 6.0, (b) (4) strengths are (b) (4) in the preliminary comments on Question 3 in FDA's official meeting minutes issued December 1, 2011 for the type C meeting held on November 15, 2011, to support a request for a biowaver for the 4.5 (b) (4) mg strength?*

**FDA Preliminary Response:** Yes, we agree. However, to support the biowaiver you still need to demonstrate that Cariprazine has linear elimination kinetics over the proposed therapeutic range.

Discussion: There was no further discussion of this question during the meeting.

**Question 5b:** *Does the Agency agree that dissolution profile comparison data and f2 values generated in one media using the same dissolution testing procedure is acceptable, and therefore fulfills the dissolution requirement, that is Criterion (4) in the preliminary comments on Question 3 in FDA's official meeting minutes issued December 1, 2011 for the type C meeting held on November 15, 2011, to support a request for a biowaiver for the 4.5 (b) (4) mg strength?*

FDA Preliminary Response: No, we do not agree. You should provide the dissolution profile comparison data and f2 values at the recommended pH media. If there is any reason that the dissolution testing can not be conducted, you should provide a justification. Additionally, from the given f2 data, we noted that, i) the dissolution testing conditions (apparatus, medium, etc.) and dissolution data (individual, mean) used to generate the reported f2 values were not included, and ii) (b) (4)

Discussion:

- The Sponsor acknowledged FDA's recommendation to generate dissolution profiles in multiple dissolution media. (b) (4)  
Sponsor proposed to generate dissolution profiles in dissolution media of pH (b) (4) 5.0, (b) (4) the 4.5 (b) (4) mg strength. to support a request for a biowaiver for the
- FDA indicated that their major concern was not the diminished solubility (b) (4) at pH 6.8, but that the dissolution profiles should be comparable at pH 6.8 using the similarity factor calculation.
- The Sponsor indicated that the %RSDs were (b) (4). f2 values (b) (4).
- FDA asked about the f2 values in Table 8-5 of the briefing package (p. 56) and the method used, as well as time points tested.
- The Sponsor responded that pH 5.0 (proposed regulatory dissolution method) was used to generate the f2 values in Table 8-5 at pulled time points of 15, (b) (4) minutes.
- FDA indicated that they will re-review the data provided in the briefing package and committed to providing feedback as an addendum to the official FDA meeting minutes.

**Question 6:** *Does the Agency agree that the quality attributes of the specification adequately control the drug product to ensure its quality, strength, purity, identity, and potency?*

FDA Preliminary Response: For the drug product identification, you have proposed an HPLC method in specification. Identification solely by retention time is not regarded as specific as per the ICH Q6A. Therefore, we recommend that you either include specific test such as IR, or a combination of tests into a single procedure, such as HPLC/UV diode array and HPLC/MS.

Discussion: There was no further discussion of this question during the meeting.

**Question 7:** *Does the Agency agree with the Sponsor's proposal to amend the application with 24 months stability no later than 120 days after the submission date of the NDA?*

FDA Preliminary Response: Not provided prior to meeting.

Discussion:

- The Sponsor ask if the Agency agreed with the Sponsor's proposal to amend the application with 24 months stability no later than 120 days after the submission date of the NDA.
- FDA agreed to the proposed timeline to amend the NDA with additional stability data.



IND 71,958 and 77,726

**MEETING REQUEST GRANTED**

Forest Laboratories, Inc.  
Attention: Alexander Bischoff, Ph.D., Assistant Director, Regulatory Affairs CMC  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Bischoff:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for caripazine (RGH-188).

We also refer to your December 9, 2011, correspondence requesting a Pre-NDA CMC meeting to discuss the following:

- Impurities qualification
- Discontinuation of monitoring of potential drug substance impurities
- Critical quality attributes of the commercial drug substance and product
- Comparability protocol for alternate drug substance manufacturing sites
- Composition and dissolution criteria to support a biowaiver request
- Amendment of the NDA with additional stability data after the submission of the NDA

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

**Date:** February 16, 2012  
**Time:** 11:00 am – 12:00 pm EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1417  
Silver Spring, Maryland 20993

**CDER participants:**

Ramesh Sood, Ph.D., Branch Chief  
Chhagan Tele, Ph.D., CMC Lead  
Akm Khairuzzaman, Ph.D., Chemistry Reviewer  
Teshara G. Bouie, Regulatory Health Project Manager

Please e-mail me any updates to your attendees at [Teshara.Bouie@fda.hhs.gov](mailto:Teshara.Bouie@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Teshara G. Bouie 301-796-1649, or the division secretary, Monet Rogers 301-796-3881.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 5 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 19, 2012, we may cancel or reschedule the meeting.

Submit the 5 desk copies to the following address:

Teshara G. Bouie  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 21, Room: 2661  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20903

If you have any questions, call me, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Teshara G. Bouie, MSA, OTR/L  
CDR, USPHS, Regulatory Health Project Manager  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

### FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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TESHARA G BOUIE  
01/06/2012



IND 071958

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cariprazine (RGH-188).

We also refer to the teleconference between representatives of your firm and the FDA on November 15, 2011. The purpose of the teleconference was to discuss the proposed Clinical Pharmacology package intended to support a future New Drug Application (NDA) for the use of cariprazine in the treatment of schizophrenia and bipolar mania.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Kimberly Updegraff, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURES:  
Meeting Minutes  
Clinical Pharmacology Summary Template

**MEMORANDUM OF MEETING**  
IND 071958 Cariprazine (RGH-188)  
Forest Research Institute  
Type C Teleconference  
November 15, 2011

**Objective:** To reach agreement regarding the proposed Clinical Pharmacology package intended to support a future New Drug Application (NDA) for the use of cariprazine in the treatment of schizophrenia and bipolar mania.

Participants –

**FDA**

Thomas Laughren, M.D.	Division of Psychiatry Products Director
Mitchell Mathis, M.D.	Deputy Director
Robert Levin, M.D.	Medical Team Leader
Francis Becker, M.D.	Medical Reviewer
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor
Aisar Atrackhi, Ph.D.	Pharmacology/Toxicology Team Leader
Elzbieta Chalecka-Franaszek, Ph.D.	Pharmacology/Toxicology Reviewer
Chhagan Tele, Ph.D.	Office of New Drug Quality Assessment Lead
Elsbeth Chikhale, Ph.D.	Office of New Drug Quality Assessment Biopharmaceutics Reviewer
Hao Zhu, Ph.D.	Office of Clinical Pharmacology Team Leader
Huixia Zhang, Ph.D.	Office of Clinical Pharmacology Reviewer
Kimberly Updegraff, M.S.	Regulatory Project Manager

**Sponsor**

Melina Cioffi, Pharm.D.	Assistant Director, Regulatory Affairs
Michael Olchaskey, Pharm.D.	Senior Director, Regulatory Affairs
June Bray, R.Ph., M.B.A.	Vice President, Regulatory Affairs
Patricia Jacala, Pharm.D.	Associate, Regulatory Affairs
Suresh Durgam, MD	Director, Clinical Development
Parviz Ghahramani, Ph.D.	Executive Director, Clinical Pharmacology & Drug Dynamics
Antonia Periclou, Ph.D.	Director, Clinical Pharmacology & Drug Dynamics
Yih Lee, Ph.D.	Senior Principal Scientist, Clinical Pharmacology & Drug Dynamics
Andreas Grill, Ph.D.	Executive Director, Drug Product and Pharmaceutical Research & Development
Ranajoy Sarkar, Ph.D.	Manager, Product Development Pharmaceutics & Clinical Packaging
Fuxing Tang, Ph.D.	Senior Manager, Exploratory Pharmaceutics
Alexander Bischoff, Ph.D.	Assistant Director, Regulatory Affairs-CMC
Anne Gilson, M.S.	Principal Scientist, Toxicology & Operations

**Background:**

Cariprazine (RGH-188) is a potent dopamine D<sub>3</sub> preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist. Cariprazine is under development by FRI, Gedeon Richter Plc, and Mitsubishi Pharma Corporation for the treatment of schizophrenia, bipolar mania and depression, and major depressive disorder. Several important events in the development program were as follows:

- In October 2007, FRI submitted a “Mass Balance” briefing document that presented data on a quantitative whole-body autoradiography study in pigmented rats using [<sup>14</sup>C] RGH-188.
- The Agency issued a letter on August 17, 2010 addressing questions posed by Forest concerning cariprazine metabolism.
- The Division held a End-of-Phase 2 meeting with Forest on January 14, 2010 to discuss the clinical, non-clinical and pharmacokinetics program.
- On March 18, 2010, the Office of New Drug Quality Assessment I met with the sponsor to discuss the overall Chemistry, Manufacturing, and Controls (CMC) development program.

In support of a future NDA, the sponsor has conducted numerous clinical pharmacology studies, including studies of bioavailability, mass balance, protein binding, hepatic and drug metabolism, P-glycoprotein inhibitory activity, and PK and tolerability in healthy subjects and patients. For the studies with PK data analyzed, the maximum-tested regimens were 2.5 mg single-dose (Study RGH-188-001) and 1.0 mg/day for 21 days (Study RGH-188-001) in healthy subjects; and 12.5 mg/day for 30 days (including the titration period) in schizophrenic patients (Study RGH-MD-01). The sponsor has also conducted *in vitro* multi-point dissolution profiles to demonstrate bioequivalence between the Phase 3 clinical trial and to-be-commercial formulations.

Based on PK data from 3 patients in a double-blind, placebo-controlled, escalating-dose (maximum dose 12.5 mg for 30 days) safety and tolerability study (RGH-MD-01) in male schizophrenic patients (N=30), the sponsor concludes that cariprazine is extensively metabolized and that renal excretion is not the major route of elimination for cariprazine or its two active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). The sponsor plans to further investigate the potential effect of decreased renal function on the PK of cariprazine, DCAR, and DDCAR in population PK analyses using the collective data from all clinical studies.

In a single-dose (2 mg) food effect study (RGH-PK-10) in healthy subjects (N=42), a high-fat breakfast lowered C<sub>max</sub> (by ~6%), delayed absorption (median T<sub>max</sub> 8 hr vs. 4 hr) and increased AUC (~27%).

The effects of hepatic impairment on the PK of cariprazine were evaluated in healthy subjects and patients with impaired hepatic function (Study RGH-PK-04, final study

report in progress). The sponsor reports that, compared to healthy subjects, patients with either mild to moderate hepatic impairment had similar  $C_{max}$  and AUC for cariprazine and 20-40% lower  $C_{max}$  and AUC for DCAR and DDCAR following a single dose of 1 mg of cariprazine and following 0.5 mg/day dosing of cariprazine for 14 days.

The effect of the CYP3A4 inhibitor, ketoconazole, on the PK of cariprazine, DCAR, and DDCAR was evaluated in healthy subjects (Study RGH-PK-07). According to the sponsor, the data suggest that CYP3A4 is the major enzyme responsible for the metabolism of cariprazine and the contribution of CYP2D6 is relatively small, consistent with the data from *in vitro* metabolism studies using recombinant CYP isozymes. The sponsor plans to further investigate the contribution of CYP2D6 to the metabolism of cariprazine in a subset of patients in upcoming Phase 3 clinical studies using CYP2D6 genotype as a covariate in the population PK analysis.

Results of *in vitro* studies (Studies PKD-RPT-EXP-00064 to 00069) demonstrated that cariprazine, DCAR, and DDCAR are not P-glycoprotein (P-gp) substrates and are weak P-gp inhibitors. The sponsor plans to conduct *in vitro* transporter studies for cariprazine, DCAR, and DDCAR to evaluate OATP 1B1/1B3 and BCRP inhibition and substrate potential.

### **Questions:**

#### **Question 1:**

**Does the Division agree that an *in vivo* renal impairment study for Cariprazine is not required?**

***Preliminary Comments:*** *We understand that cariprazine and its two active metabolites are minimally excreted unchanged in the urine. However, there are examples of drugs that are extensively metabolized, where renal impairment significantly affects drug exposure (e.g., duloxetine and tadalafil). Thus, we recommend that you evaluate the effect of varying degrees of renal impairment on the PK of cariprazine and its two active metabolites. Using PopPK analyses to assess the effect(s) of renal impairment is acceptable. However, you are reminded that you will need a sufficient number of patients with varying degrees of renal function in the trials. Please refer to “Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling” and “Guidance for Industry: Population Pharmacokinetics” for details in trial design and data analysis related issues. You are encouraged to submit your PK sampling and data analysis plans for review prior to conducting the study.*

***Discussion at Meeting:*** *The sponsor reiterated that the effect of renal impairment on the PK of cariprazine and its two active metabolites will be evaluated using a PopPK approach. Patients with mild and moderate renal impairment are enrolled in the ongoing phase 3 study. We stated that the approach is acceptable. We encouraged the sponsor to use simulation to aid in trial design (e.g., sampling schedule and sample size) so that the study results can be properly interpreted.*

## Question 2

**Does the Division agree that the effect of hepatic impairment on the PK profile of Cariprazine has been adequately characterized to support a future NDA?**

**Preliminary Comments:** *Since cariprazine is extensively metabolized in the liver, decreased liver function would be expected to affect drug exposure. Even though your study results have shown that mild to moderate hepatic impairment does not have a significant impact on the exposure of cariprazine and its two active metabolites, the results can not be extrapolated to severe hepatic impairment. The effect of severe hepatic impairment on the PK of cariprazine and its two active metabolites needs to be evaluated at some point.*

**Discussion at Meeting:** *No further discussion.*

## Question 3

**Does the Division concur that bioequivalence between the Phase 3 clinical trial and the to-be-commercial formulations has been established to support a future NDA?**

**Preliminary Comments:** *Your comparative dissolution data are sufficient to support the manufacturing site change between the phase 3 clinical trial batches (made in NY) and the to-be-marketed batches (made in Ireland). We note, however, that you are proposing to market the following strengths 1.5, 3.0, 4.5, 6.0 (b)(4) mg, whereas the Phase 3 trial included only the 1.5, 3.0, and 6.0 mg strengths. Please clarify whether or not you have characterized the bioavailability (BA) of all the proposed strengths. If you have not, you may request a biowaiver for the strengths for which you do not have the BA data. The biowaiver request should be supported with the following: (1) clinical safety and/or efficacy data covering the proposed therapeutic range, (2) a demonstration of linear elimination kinetics information over the therapeutic dose range, (3) information showing that (b)(4) and (4) dissolution profile comparison data and f<sub>2</sub> values in three media (pH (b)(4)) using the same dissolution testing procedures.*

**Discussion at Meeting:** *The sponsor stated that they will request a bioavailability (BA) waiver and will provide support for items 1 through 4 to include qualitative and quantitative composition for the 4.5 (b)(4) mg strengths and proof of linear kinetics. The sponsor stated that a previous agreement regarding the dissolution profile was reached; however, we noted that the dissolution data are sufficient to support the manufacturing site change, but for the BA waiver we will need to review the dissolution comparison data using three media (pH (b)(4)). If dissolution in pH 6.8 medium cannot be evaluated, a justification for omitting this information must be provided.*

#### Question 4

**Does the Division agree that the effect of food on the absorption of Cariprazine has been adequately characterized to support a future NDA?**

**Preliminary Comments:** *No. The effect of food needs to be evaluated in vivo using the highest dose of the final product. In vitro dissolution similarity for food effect cannot be extrapolated using different formulations.*

**Discussion at Meeting:** *The sponsor stated that the tablet and capsule have (b) (4) We reiterated that in vitro similarity in dissolution cannot replace an in vivo food study.*

*We clarified that in general, the food effect needs to be evaluated in vivo using the highest strength (not dose) of the final product. However, since tolerability is an issue in healthy volunteers (maximal tolerated dose is 2 mg), we agreed that the food effect could be assessed at the 1.5 mg strength in healthy volunteers using the to-be-marketed formulation.*

#### Question 5

**Does the Division agree with FRI's proposal for characterizing the effect of extrinsic factors on the PK of Cariprazine to support a future NDA?**

**Preliminary Comments:** *The information provided suggests that CYP3A plays a significant role in the metabolism of cariprazine. A study designed to evaluate the effect of strong CYP3A inducers (e.g., rifampin) will be needed to guide future dosing recommendations for patients who take cariprazine and CYP3A inducers concomitantly. In addition, a worst case scenario analysis will be needed for those patients taking strong CYP3A and CYP2D6 inhibitors along with cariprazine or for patients who are poor metabolizers (PMs) of CYP2D6 and take strong CYP3A inhibitors.*

*The two active metabolites, DCAR and DDCAR in particular, circulate at significant levels in the body. The inhibition and induction potential of the metabolites on major CYP enzymes needs to be evaluated.*

**Discussion at Meeting:** *The sponsor stated that recruitment of an adequate number of patients receiving strong CYP3A inducers may be difficult. They feel that they may not be able to provide adequate data for that group of patients, and they propose to address the issue in labeling.*

*We stated that, although the effect of CYP3A inducers on the PK of parent and the two active metabolites need to be evaluated at some point, it would not be considered a filing issue.*

**Additional Comments:**

1) *We request that you submit human PK data for the active metabolite didesmethyl cariprazine at steady state as soon as possible. We note that accumulation of this metabolite is likely in humans due to its very slow elimination with a prolonged terminal elimination half-life ( $T_{1/2}$ ) of several weeks. Moreover, the  $T_{1/2}$  in all toxicology species tested is significantly shorter; therefore, steady state levels achieved in humans may exceed the highest exposure levels observed in toxicology studies.*

2) *We request that you provide a completed Clinical Pharmacology Summary (copy attached) with the NDA package. Should you have any questions regarding the document, please contact the Regulatory Project Manager.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Forest Research Institute is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, R.Ph., M.S.  
Senior Regulatory Project Manager

# CLINICAL PHARMACOLOGY SUMMARY

## 1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

## 2. Question Based Review

### 2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

### 2.2 General Attributes of the Drug

#### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for

all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

**2.2.3 What are the proposed dosages and routes of administration?**

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

**2.3 General Clinical Pharmacology**

**2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

**2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

**2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal  $t_{1/2}$  and AUC.

## **2.4 Exposure-Response**

### **2.4.1 Does the exposure-response relationship support evidence of effectiveness?**

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from pivotal and other appropriate trials. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

### **2.4.2 What are the characteristics of the exposure-response relationships for safety?**

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints.

Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C<sub>max</sub> and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

### **2.4.3 Does this drug prolong QT/QTc Interval?**

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

### **2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the pivotal trials. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

## **2.5 What are the PK characteristics of the drug?**

### **2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C<sub>max</sub>, t<sub>max</sub>, AUC, C<sub>max,ss</sub>, C<sub>min,ss</sub>, C<sub>max,ss</sub>/C<sub>min,ss</sub>, t<sub>max,ss</sub>, AUC<sub>0-τ</sub>, CL/F, V/F and t<sub>1/2</sub> (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

**2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

**2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C<sub>max</sub>, C<sub>min</sub>, CL/F and t<sub>1/2</sub> of the parent drug and relevant metabolites after single doses and at steady-state.

**2.5.4 What are the characteristics of drug absorption?**

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, t<sub>max</sub>, t<sub>max,ss</sub>, C<sub>max</sub>, C<sub>max,ss</sub> and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

**2.5.5 What are the characteristics of drug distribution?**

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

**2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

**2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**

Provide identification for  $\geq 90\%$  of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

### **2.5.8 What are the characteristics of drug metabolism?**

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

### **2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?**

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

### **2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?**

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

### **2.5.10 What are the characteristics of drug excretion in urine?**

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

### **2.5.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C<sub>max</sub> and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

### **2.5.12 How do the PK parameters change with time following chronic dosing?**

Indicate whether the mean ratio of AUC<sub>0-τ</sub> at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

### **2.5.13 Is there evidence for a circadian rhythm of the PK?**

Indicate whether C<sub>max</sub> and C<sub>min</sub> of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

## **2.6 Intrinsic Factors**

### **2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C<sub>max</sub>, clearance, volume of distribution and t<sub>1/2</sub> for pairs studied: elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

### **2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and

exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

#### **2.6.2.1 Severity of Disease State**

#### **2.6.2.2 Body Weight**

#### **2.6.2.3 Elderly**

#### **2.6.2.4 Pediatric Patients**

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

#### **2.6.2.5 Race/Ethnicity**

#### **2.6.2.6 Renal Impairment**

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC and C<sub>max</sub> of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C<sub>max</sub> and CL/F on Cl<sub>r</sub> for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

#### **2.6.2.7 Hepatic Impairment**

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC and C<sub>max</sub> of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C<sub>max</sub>, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

#### **2.6.2.8 What pregnancy and lactation use information is available?**

#### **2.6.3 Does genetic variation impact exposure and/or response?**

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

#### **2.6.4 Immunogenicity (NOT applicable to small molecule drugs)**

**2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

**2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

**2.6.4.3 Do the anti-product antibodies have neutralizing activity?**

#### **2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?**

#### **2.6.4.5 What is the impact of anti-product antibodies on clinical safety?**

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

### **2.7 Extrinsic Factors**

#### **2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

#### **2.7.2 Is the drug a substrate of CYP enzymes?**

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to  $K_m$ , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

#### **2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?**

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for  $K_i$ ,  $IC_{50}$  and  $V_{max}$  for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ( $[I]$ ). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the  $[I]/K_i$  ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

**2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

**2.7.5 Are there other metabolic/transporter pathways that may be important?**

**2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

**2.7.7 What are the drug-drug interactions?**

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and C<sub>max</sub> of each of the co-administered drugs in the presence and absence of the drug of interest.

- 2.7.8 Does the label specify co-administration of another drug?**
- 2.7.9 What other co-medications are likely to be administered to the target population?**
- 2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

## **2.8 General Biopharmaceutics**

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C<sub>max</sub> after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

### **IR Product**

- 2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?**
  - 2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**
  - 2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**
- 2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

- 2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?**
- 2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

**MR product (if an IR is already marketed)**

- 2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?**

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C<sub>max</sub>, AUC and C<sub>min</sub> of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

- 2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?**
- 2.8.8 What is evidence that MR formulation displays less variability in C<sub>max</sub>, AUC and C<sub>min</sub> than IR formulation?**
- 2.8.9 Does the MR product show dose dumping *in vivo*?**

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

- 2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?**

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

- 2.8.11 Are the MR and IR products marketed simultaneously?**

If the intention is to market both the MR and IR products, indicate how patients

are converted from the IR to the MR product and vice versa.

**2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?**

**2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?**

## **2.9 Analytical Section**

**2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?**

List all assays used and briefly describe the individual methods.

**2.9.2 Which metabolites have been selected for analysis and why?**

**2.9.3 For all moieties measured, is free, bound, or total measured?**

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

**2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?**

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

**2.8.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?**

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

**2.9.5.1 What are the lower and upper limits of quantitation?**

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted

and diluted samples.

**2.9.5.2 What are the accuracy, precision, and selectivity at these limits?**

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

**2.9.5.3 What is the sample stability under conditions used in the study?**

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at  $\leq -20^{\circ}\text{C}$ .

**2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?**

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

**Applicable to therapeutic proteins only**

**2.9.5.5 What bioanalytical methods are used to assess therapeutic protein concentrations?**

Briefly describe the methods and summarize the assay performance.

**2.9.5.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies?**

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

**2.9.5.7 What is the performance of the neutralizing assay(s)?**

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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  
12/01/2011

THOMAS P LAUGHREN  
12/01/2011



IND 071958

**MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cariprazine (RGH-188).

We also refer to the meeting between representatives of your firm and the FDA on September 19, 2011. The purpose of the meeting was to discuss the nonclinical and clinical assessment of the potential for retinal toxicity with cariprazine as well as the timing of data.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Kimberly Updegraff, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING**  
IND 071958 Cariprazine (RGH-188)  
Forest Research Institute  
Type C Meeting  
September 19, 2011

**Objective:** To reach an agreement regarding the nonclinical and clinical assessment of the potential for retinal toxicity with cariprazine as well as an agreement on the timing of the data.

Participants –

**FDA**

Thomas Laughren, M.D.	Division of Psychiatry Products Director
Mitchell Mathis, M.D.	Deputy Director
Robert Levin, M.D.	Medical Team Leader
Francis Becker, M.D.	Medical Reviewer
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Team Leader
Elzbieta Chalecka-Franaszek, Ph.D.	Pharmacology/Toxicology Reviewer
Wiley Chambers, M.D.	Division of Transplant and Ophthalmology Products Deputy Director
William Boyd, M.D.	Division of Transplant and Ophthalmology Products Team Leader
Varun Vasudeva	Student, Division of Psychiatry Products
Kimberly Updegraff, M.S.	Regulatory Project Manager

**Sponsor**

Michael Olchaskey	Senior Director, Regulatory Affairs, Forest Research Institute (FRI)
Suresh Durgam	Director, Clinical Development, FRI
Anjana Bose	Clinical Development, FRI
Denise Leclair	Senior Director, Pharmacovigilance and Risk Management, Global Drug Safety, FRI
Anne Gilson	Principal Scientist, Toxicology and Operations, FRI
Maureen Toulon	Executive Director, Toxicology and Operations, FRI
Yih Lee	Senior Principal Scientist, Clinical Pharmacology and Drug Dynamics, FRI
(b) (4)	Ophthalmologist, External Expert
(b) (4)	Ophthalmologist, External Expert
Krisztian Nagy	Clinical Scientist, Clinical Development, Gedeon Richter
June Bray	Vice President, Regulatory Affairs, FRI
Melina Cioffi	Assistant Director, Regulatory Affairs, FRI

### **Purpose of the Meeting:**

The Mass Balance Briefing Book from October 2007 was referenced in an Advice Letter, dated March 28, 2011, containing several comments and suggestions based on the reported findings of: 1) accumulation of cariprazine and/or metabolites in the eye of pigmented rats, and 2) melanin binding of cariprazine in the retina. This meeting was requested as a follow-up to the Division's March 28, 2011 Advice Letter as a means of discussing the responses to the comments in the letter.

### **Background:**

Cariprazine (RGH-188) is a potent dopamine D<sub>3</sub> preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist. Cariprazine is under development by FRI, Gedeon Richter Plc, and Mitsubishi Pharma Corporation for the treatment of schizophrenia, bipolar mania and depression, and major depressive disorder.

In October 2007, FRI submitted a "Mass Balance" briefing document that presented data on a quantitative whole-body autoradiography study in pigmented rats using [<sup>14</sup>C] RGH-188. This study indicated that the highest concentration of radioactivity in the choroid layer of the eye observed at 24 hours post-dose was approximately 100-fold higher than the C<sub>max</sub> of radioactivity in plasma. It was also reported that the elimination of radioactivity in the choroid layer of the eye proceeded with a T<sub>1/2</sub> of 28 days. Furthermore, FRI reported the finding of melanin binding of cariprazine and/or metabolites in the rat retina.

### **Advice Letter**

On March 28, 2011, the Division issued an advice letter regarding the concerns about ocular toxicity. The letter stated the following:

Because of the potential for ocular toxicity in humans, we have the following requests and comments:

1. To collect necessary data regarding the finding of melanin binding in the eye, we request that you conduct electroretinogram (ERG) testing in a pigmented species such as rabbit or dog.
2. Based on the finding of accumulation of cariprazine and/or metabolites in the eye, we request that you perform Ocular Coherent Tomography (OCT) testing of the retina on at least a portion of the patients (at least 60 patients) in the 48-week cariprazine study to assess whether there is drug and/or metabolite deposition in the retina. If the animal ERGs or human OCT testing is abnormal, we would request additional human testing in subsequent clinical trials.
3. The use of pseudoisochromatic plates in clinical trials with cariprazine should specify the inclusion of plates which test for Blue-Yellow confusion. The more common acquired color which test Red-Green confusion (i.e., Ishihara plates) are used.

4. We recommend that distance visual acuity be a “best-corrected distance visual acuity” in all clinical trials with ophthalmological assessments.
5. We request that you report visual adverse events, such as decreased visual acuity, decreased light perception, decreased color perception, and related adverse events, as expedited reports.
6. For a subsequent NDA filing, you must conduct these studies and adequately address the concerns about ocular toxicity.

#### Forest’s Response to the Advice Letter

Forest has addressed the Division’s requests in the current briefing book:

1. FRI agrees to conduct the ERG study in dogs to fully assess the nonclinical potential for retinal toxicity with cariprazine. FRI seeks the Division’s concurrence on the nonclinical ERG study design, duration, and species selection.
2. FRI agrees to include plates which test for Blue-Yellow confusion when using pseudoisochromatic plates for color vision testing. This was communicated to all sites in the United States (US) by 07 Jul 2011 and to non-US sites by 29 Jul 2011.
3. Best-corrected visual acuity (BCVA) is currently used for visual acuity assessment in all ongoing clinical trials with ophthalmological assessments.
4. In response to FDA’s request for expedited reports of visual adverse events, FRI proposes to submit all serious adverse events (SAEs) which code to a preferred term within the MedDRA Eye Disorders SOC (system organ class) as expedited reports (i.e., within a 15 day timeline), regardless of causal relationship or expectedness. Additionally, all non-serious AEs, regardless of expectedness or causality, that code to a PT in the Eye Disorders SOC will be sent to FDA as line listings on a quarterly basis.
5. In response to FDA’s request for Ocular Coherence Tomography (OCT) testing in a subset of patients (at least 60) in the 48-week, open-label cariprazine study (RGH-MD-11) to “assess whether there is drug and/or metabolite deposition in the retina”, FRI believes that OCT is not warranted at this time. This opinion is based on the following:
  - Binding of drugs to melanin in the eye, especially in the retina, is not predictive of ocular toxicity.
  - Cariprazine nonclinical subchronic and chronic data to date has not demonstrated retinal toxicity.
  - All ocular treatment-emergent adverse events in the 5 completed short-term, placebo-controlled studies in patients with schizophrenia or bipolar mania (N = 870 cariprazine-treated patients) were non-serious, and none suggested retinal toxicity. The most frequent ocular AE seen was “vision blurred” (2.53% versus 0.48% on placebo). Blurred vision is a non-specific term and is seen commonly in antipsychotic medications,

including risperidone, aripiprazole, ziprasidone, and olanzapine which include either blurred vision or abnormal vision in their United States package inserts at incidences of 3%, 3%, 3% and 2% respectively.

- In one 48-week long-term, open-label, extension study in patients with schizophrenia (N = 93), “vision blurred” was reported at an incidence of 1.1%, with no other visual AEs reported that may suggest retinal pathology. Ophthalmological examinations in this study revealed no clinically significant changes in color discrimination (n = 11) and visual acuity (n = 9).
- Following the previous FDA recommendation (05 Jun 2007), ophthalmology evaluations were added to all cariprazine clinical studies with treatment duration of more than 8 weeks. The current ocular tests in the cariprazine clinical development program include BCVA and color vision testing, which are subjective tests of visual function that are sensitive detectors of early retinal damage [Vu et al, 1999].
- The enrollment in the 48-week study (RGH-MD-11) is near completion and the majority of patients will not have an OCT baseline assessment, making interpretation of the OCT results difficult. Also patients with confounding conditions such as diabetes and hypertension are not excluded in this study. Based on these reasons, OCT testing in Study RGH-MD-11 is not feasible.

Therefore, FRI proposes to reevaluate the request to perform OCT on a subgroup of patients after results from the ERG dog study and the ophthalmological assessments in the ongoing clinical studies, which include an estimated 1650 patients, are available.

In summary, FRI states that cariprazine has exhibited melanin binding in the eyes in rats; however, no signal for retinal toxicity has been observed in the cariprazine nonclinical data. FRI also states that the correlation of melanin binding with ocular toxicity has not been established with the majority of drugs showing melanin binding not exhibiting retinal toxicity. Apparently in the completed clinical studies, there have been no adverse event reports indicative of retinal toxicity, and the results of visual acuity and color vision testing were essentially normal. Forest will conduct the requested ERG testing in dogs and proposes to continue to assess for functional changes (color vision testing and best-corrected visual acuity) in the ongoing cariprazine studies that include an estimated 1650 patients.

## **Questions:**

### **Question 1**

Does the Division agree with the proposed study design of the nonclinical ERG study, including use of the dog as the species, study duration of 3 months, recovery period duration of 3 months, and dose selection consistent with other cariprazine dog studies?

***Preliminary Comments:*** *Yes. Dogs should be dosed at final dose levels for 13 weeks (in addition to the planned 2-4 week adaptation period).*

***Discussion at Meeting:*** *The sponsor proposed, and we agreed to, a 2 month recovery period.*

## **Question 2**

- a) Does the Division agree that the best corrected visual acuity and color vision (including blue-yellow confusion) testing implemented in the ongoing studies will be adequate in assessing functional changes related to retinal toxicity with cariprazine treatment?

***Preliminary Comments:*** *No. We have continuing concerns about the apparent ocular accumulation of the drug product in animals. Based on the finding of accumulation of cariprazine and/or metabolites in the eye, we continue to recommend that Ocular Coherent Tomography (OCT) testing of the retina be performed on at least a portion of the human patients (at least 60 patients) in the 48-week cariprazine study to assess whether there is drug and/or metabolite deposition in the retina. The studies performed to date have not been adequate to satisfactorily answer the question of whether there is drug deposition or retinal toxicity with cariprazine in humans. The non-invasive OCT procedure should not be substantially confounded by subjects with diabetes or hypertension.*

*If the animal ERGs or human OCT testing is abnormal, we would recommend additional human testing in subsequent clinical trials.*

***Discussion at Meeting:*** *We reiterated that the sponsor will be required to submit OCT results for at least 60 patients at one year of exposure. This will be a requirement for filing an NDA. These should be standard OCT examinations of the retina. The primary objective of OCT testing would be to assess whether there is deposition of drug/metabolites in any retinal layer and whether there is separation in any retinal layer. We clarified that such changes would appear on OCT before there would be clinical changes.*

*We agreed that the population may include patients who are already enrolled in or have already completed a study. The sponsor acknowledged our request for data on an additional 60 patients, and they agreed with the request. They agreed to submit a protocol amendment for review and comment. The protocol amendment will include: 1) OCT assessments with a standard OCT (3<sup>rd</sup> generation or higher) of the macula, 2) electronic copies of scans and ophthalmologist assessments, and 3) 1-year assessments. The current schedule of ophthalmologic testing at 4, 8 and 12 months is acceptable.*

- b) Does the Division agree that the request for OCT testing can be reevaluated following the results of the completed ERG dog study and the ophthalmological assessments in the ongoing clinical studies?

**Preliminary Comments:** *No. See response to 2a.*

**Discussion at Meeting:** *See comments under Question 2a.*

### **Question 3**

Does the Division agree to quarterly (every 3 months) reporting of all non-serious adverse events coded to the MedDRA Eye disorders SOC and expedited (i.e., 15-day) reporting of all serious adverse events coded with one of the preferred terms in the MedDRA Eye disorders SOC?

**Preliminary Comments:** *Yes.*

**Discussion at Meeting:** *No further discussion.*

### **Question 4**

Does the Division agree to FRI's proposed timing of submission of the nonclinical data to assess possible retinal toxicity?

**Preliminary Comments:** *We recommend the final report for the nonclinical ERG data be submitted prior to or included in the original NDA submission (August 2012) and not in the 120 day safety update (December 2012).*

**Discussion at the Meeting:** *The sponsor stated that the final report for the nonclinical ERG data will be included in the NDA submission.*

### **Addendum:**

#### ***Additional nonclinical request for information:***

*In the Division Advice Letter dated August 17, 2010, we requested that you assess the potential genotoxicity of the major human metabolite didesmethyl cariprazine in two in vitro assays (Ames and in another assay that detects chromosomal aberrations). We also indicated that evaluation of the genetic toxicity potential of didesmethyl cariprazine must be conducted to support Phase 3 clinical trials. Please inform the Division when final reports of these studies will be submitted.*

### **Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Forest Research Institute is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, R.Ph., M.S.  
Senior Regulatory Project Manager

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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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THOMAS P LAUGHREN  
09/29/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 77,726/71,958/ (b) (4)

MEETING MINUTES

Forest Laboratories, Inc.  
Attention: Sejal A. Parikh, PharmD,  
Assistance Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Parikh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RGH-188 (cariprazine).

We also refer to the meeting between representatives of your firm and the FDA on March 18, 2010. The purpose of the meeting was to discuss the overall Chemistry, Manufacturing, and Controls (CMC) development program.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry  
Regulatory Project Manager  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure – meeting minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

<b>Sponsor Name:</b>	Forest Laboratories, Inc.
<b>Application Number:</b>	IND 71,958 / 77,726 / (b) (4)
<b>Product Name:</b>	Cariprazine (RGH-188)
<b>Meeting Type:</b>	Type B
<b>Meeting Category:</b>	Chemistry, Manufacturing and Controls, End of Phase 2 Meeting
<b>Meeting Date and Time:</b>	Thursday, March 18, 2010, 12:00 – 13:00 ET
<b>Meeting Location:</b>	Food and Drug Administration, White Oak Campus, Silver Spring, MD
<b>Received Briefing Package</b>	February 17, 2010

**FDA ATTENDEES**

Ramesh Sood, Ph.D., Branch Chief  
Thomas Oliver, Ph.D., Chemistry Lead  
Prafull Shiromani, Ph.D., Chemistry Reviewer  
John Duan, Ph.D., Biopharmaceutics Reviewer  
Don Henry, Regulatory Project Manager

**FOREST LABORATORIES ATTENDEES**

Charlene Ganser, MS - Manager, Regulatory Affairs CMC,  
Andreas Grill, MBA - Executive Director, Pharmaceutical Research & Development  
Mary B. Hooper, MS - Associate Director, Project Management  
Salvatore Iacono, MS - Senior Director, Analytical Method Development  
Sejal Parikh, PharmD - Assistant Director, Regulatory Affairs  
Ranajoy Sarkar, PhD - Assistant Manager, Development Pharmaceuticals  
Satyam Upadrashta, PhD, RAC - Executive Director, Regulatory Affairs CMC

## 1. DISCUSSION

### 1.1. Drug Substance

- 1.1.1. **Briefing Package Question 1:** Does the Agency agree with the designation (b) (4), as regulatory starting materials for the synthesis of the cariprazine HCl drug substance?

**FDA Response:** We agree with your starting material designations. You will need to add an appropriate specification for (b) (4) and possibly other related (b) (4) derivatives to ensure that the (b) (4) level of these compounds in the drug product each do not exceed (b) (4) µg/day exposure.

**Meeting Discussion:** There was no further discussion on this topic.

- 1.1.2. **Briefing Package Question 2a:** Does the Agency agree that sufficient data has been generated to demonstrate the absence of (b) (4) intermediate and (b) (4) impurity in the API?

**FDA Response:** Your approach seems reasonable. We recommend that you continue to monitor for these compounds through drug development to the commercial scale/process. Based on data collected (development and commercial batches), you may consider providing a justification for eliminating the testing in the NDA.

**Meeting Discussion:** There was no further discussion on this topic.

- 1.1.3. **Briefing Package Question 2b:** If yes, does the Agency agree that the (b) (4) intermediate, (b) (4) do not require future monitoring in the API?

**FDA Response:** Your approach seems reasonable. We recommend that you continue to monitor for these compounds through drug development to the commercial scale/process. Based on data collected (development and commercial batches), you may consider providing a justification for eliminating the testing in the NDA.

**Meeting Discussion:** There was no further discussion on this topic.

- 1.1.4. **Briefing Package Question 3:** Does the Agency agree that sufficient data has been provided to demonstrate that the levels of (b) (4) in the API are negligible and do not warrant continued monitoring during the API synthesis?

**FDA Response:** *Your approach seems reasonable. We recommend that you continue to monitor for these compounds through drug development to the commercial scale/process. Based on data collected (development and commercial batches), you may consider providing a justification for eliminating the testing in the NDA.*

**Meeting Discussion:** There was no further discussion on this topic.

- 1.1.5. **Briefing Package Question 4a:** Does the Agency agree with the proposed regulatory specification for the cariprazine HCl drug substance?

**FDA Response:** *In addition to the attributes already listed, your drug substance specification should include:*

- a. *a specification for the (b) (4) to ensure that the level does not exceed (b) (4) ug/day exposure in the drug product.*
- b. *a limit for residual (b) (4).*
- c. *a limit for the control of fines (D10). The particle size data should be presented in a graphical form.*

*Additionally, provide information on how residual amounts of (b) (4) are controlled. If multiple polymorphs can be formed, you may need to demonstrate how you control the levels of the undesired forms. Refer to ICH Q6A.*

**Meeting Discussion:** Forest Lab clarified that (b) (4) is identified as (b) (4) during the synthesis process (see attachment I). The Agency emphasized the need for code names for each of the intermediates in the drug substance synthesis. Forest Lab indicated that the (b) (4) process is used for (b) (4) the material. The sponsor indicated that two additional (b) (4) (b) (4) have been observed. In addition, the sponsor stated that no (b) (4) material has been observed. Information on particle size, (b) (4) will be included in the NDA.

- 1.1.6. **Briefing Package Question 4b:** Does the Agency agree that the stability plan for the registration lots of drug substance supports the NDA?

**FDA Response:** *The Agency agrees with the approach*

**Meeting Discussion:** There was no further discussion on this topic.

- 1.1.7. **Briefing Package Question 5:** Does the Division agree that the Sponsor's assessment strategy is appropriate?

**FDA Response:** *In general your approach is acceptable. However, we refer you to the draft Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches; December 2008 for more details and specifically to Table 2 and Appendix A. In addition to an Ames test, a test for chromosomal aberration will need to be conducted to qualify the impurity.*

**Meeting Discussion:** There was no further discussion on this topic.

## 1.2. Drug Product

- 1.2.1. **Briefing Package Question 6:** Does the Agency agree that the regulatory specifications adequately control the quality of the drug products?

**FDA Response:** *The acceptance criteria for the unspecified impurities (for all dosage strengths) should be based on the maximum daily dose and not the individual strength. You should include a specification for microbial contamination (refer to ICHQ6A). With respect to the dissolution test, the dissolution conditions are not specified and the justification for the setting of the dissolution specification is not provided. Therefore, the adequacy of the dissolution specification can not be evaluated. Provide the dissolution method-report as an amendment to the IND. This report should include all the multi-point dissolution profile data generated during the development and validation of the proposed dissolution method (i.e., individual, mean, standard deviation, plots). For each test, clearly specify the testing conditions. The justification for the selection of the proposed dissolution specification should be also included.*

**Meeting Discussion:** Forest Lab agreed to provide a specification for microbials. The sponsor will also provide the dissolution method report as an amendment to the IND. The Agency noted that the active content is approximately (b) (4)% (1.5 mg strength), and therefore (b) (4) and content uniformity control will be

critical to the product quality. The test methods employed and the sampling plans will need to be closely evaluated.

- 1.2.2. **Briefing Package Question 7:** Does the Agency agree that the proposed stability testing plan for the NDA registration drug product batches is supportive of the NDA and the proposed 24 month shelf-life?

**FDA Response:** *You need to evaluate the drug product for color fading as part of the stability plan. Regarding the dissolution test, we recommend testing at multiple time points so that a scientifically justified single point limit can be determined during the NDA review based on the collected data. The drug product expiry will be based on the quality and quantity of data submitted and will be determined as part of the NDA review.*

**Meeting Discussion:** Forest Lab is currently monitoring color fading during stability. The Agency indicated that the proposed stability bracketing strategy is acceptable.

- 1.2.3. **Briefing Package Question 8:** Does the Agency agree with the proposed comparability approach?

**FDA Response:** *The proposed approach is appropriate. However, the multi-point dissolution testing should be conducted using an acceptable dissolution test. Therefore, as mentioned in our response for Question 6, provide the dissolution method-report showing that the proposed test has adequate discriminating power.*

**Meeting Discussion:** Forest Lab will provide the dissolution method report as an amendment to the IND.

**2. ADDITIONAL COMMENTS/ISSUES REQUIRING FURTHER DISCUSSION**

*2.1. Develop code names for each of the intermediates in your drug substance synthesis.*

**3. CONCURRENCE:**

*{See appended electronic signature page}*

Don Henry  
Regulatory Health Project Manager for Quality  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

**4. ATTACHMENT:**

Attachment I

**Flow Diagram for the Synthesis of Cariprazine HCl**

(b) (4)



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-71958	GI-1	FOREST LABORATORIES INC	RGH-188 HCL
IND- (b) (4)	GI-1	FOREST LABORATORIES INC	RGH-188 (cariprazine)
IND-77726	GI-1	FOREST LABORATORIES INC	RGH188

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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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DON L HENRY  
04/13/2010

THOMAS F OLIVER  
04/13/2010



IND 71,958

MEETING MINUTES

Forest Research Institute  
Attention: Sejal Parikh, PharmD  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Parikh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cariprazine (RHG-188).

We also refer to the telecon between representatives of your firm and the FDA on January 14, 2010. The purpose of the meeting was to discuss the sponsor's questions regarding End of Phase 2 issues.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager at (301) 796-0240.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B  
Meeting Category: End of Phase 2

Meeting Date and Time: January 14, 2010 at 3:00 PM  
Meeting Location: Telecon

Application Number: IND 71,958  
Product Name: Cariprazine (RGH-188)  
Indication: Schizophrenia  
Sponsor/Applicant Name: Forest Research Institute

**FDA Attendees:**

Thomas Laughren, M.D., Division Director, DPP  
Mitchell Mathis, M.D., Deputy Division Director, DPP  
Robert Levin, M.D., Medical Team Leader, DPP  
Frank Becker, M.D., Medical Reviewer  
Peiling Yang, Ph.D., Statistical Team Leader  
Barry Rosloff, Ph.D., Supervisory Pharmacologist  
Elzbieta Chalecka-Franaszek, Ph.D., Pharmacology/Toxicology Reviewer  
Aisar Atrakchi, Ph.D., Pharmacology, Team Leader  
Raman, Baweja, Ph.D., Pharmacology, Team Leader  
Huixia Zhang, Ph.D., Pharmacology Reviewer  
Janet Cliatt, Sr. Project Manager, DPP

**Forest Research Institute Attendees:**

Anjana Bose, Ph.D. – Clinical Development  
Nicole Bradley, Pharm.D – Regulatory Affairs  
June Bray, RPh, MBA – Regulatory Affairs  
Theresa Fico, Ph.D. – Project Management  
Parvis Ghahramani, PhD, PharmD, MSc, MBA – Clinical Pharmacology  
Andreas Grill, PhD – Pharmaceutical Research and Development  
Dayong Li, Ph.D – Biostatistics  
Charles Lindamood III, Ph.D., D.A.B.T. – Toxicology and Clinical Pharmacology  
Michael Olchaskey, PharmD – Regulatory Affairs  
Sejal Parikh, PharmD – Regulatory Affairs  
Serge Stankovic, MD – Clinical Development  
Maureen Toulon, Ph.D. – Toxicology  
Hongjie Zheng, PhD – Biostatistics

Gedeon Richter Plc. Attendees

Krisztian Nagy, MD – Clinical  
Istvan Laszlovszky, Ph.D. – Clinical  
Krisztian Gorog, MD – Clinical

**Background**

Cariprazine (RGH-188) is an orally (PO) active and potent dopamine D3 preferring D3/D2 receptor antagonist-partial agonist currently in development for the treatment of schizophrenia, bipolar disorder, and adjunctive treatment of major depressive disorder. This drug is being co-developed by Gedeon Richter Plc., Budapest, Hungary, and Forest Research Institute.

At present, twelve studies have been completed: seven in healthy volunteers and five in patients. A total of 175 healthy subjects, 752 subjects with Schizophrenia, and 118 subjects with Bipolar Disorder have received cariprazine in the completed studies. It is estimated that upon completion of all planned Bipolar Mania and Schizophrenia studies, approximately 2695 subjects will have been exposed to cariprazine.

In the Schizophrenia program, four studies have been completed, and one is ongoing.

-Study RGH-MD-01 was a double-blind, placebo-controlled study in male schizophrenic subjects, evaluating the safety, tolerability, and pharmacokinetics of multiple escalating doses (0.5-12.5 mg/day) of cariprazine during a 22-30 day dosing period.

-Study RGH-MD-03 was a 6-week, randomized, double-blind, placebo-controlled, fixed dose-range study of the safety and efficacy of cariprazine (fixed dose ranges of 1.5-4.5 mg/day or 6-12 mg/day) in acute Schizophrenia.

-Study RGH-MD-14 was an open-label clinical pharmacology study in 8 male subjects with Schizophrenia, assessing striatal and extrastriatal dopamine receptor D2/D3 occupancy after multiple doses of cariprazine.

-Study RGH-MD-16 was a six-week, randomized, double-blind, placebo- and active-controlled, fixed-dose study in subjects with acute exacerbation of Schizophrenia (placebo, n=148; risperidone 4 mg/day, n=138; cariprazine 1.5mg/day, n=140; cariprazine 3.0 mg/day, n=141; and cariprazine 4.5 mg/day, N=144).

-The ongoing study, RGH-MD-17, is a 48-week, open-label, extension study of cariprazine (1.5 to 4.5 mg/day) in eligible patients completing Study RGH-MD-16.

Three additional studies are planned for the Schizophrenia indication. Two acute studies (RGH-MD-04 and RGH-MD-05) will evaluate the safety and efficacy of cariprazine in acute exacerbation of Schizophrenia.

- Study RGH-MD-04 will be a 6-week, randomized, double-blind, placebo - and active-controlled, parallel group fixed dose study (placebo, n=150; aripiprazole 10 mg/day; n=150; cariprazine 3 mg/day, n=150; cariprazine 6 mg/day, n=150).
- Study RGH-MD-05 will be a randomized, double-blind, placebo-controlled, fixed, flexible dose study (placebo, n=150; cariprazine 3-6 mg/day, n=159; cariprazine 6-9 mg/day, n=150).

- Patients completing 6 weeks of double-blind treatment in the two acute studies will be eligible to enroll in Study RGH-MD-11, a 48-week, open-label, flexible-dose (1.5 to 9.0 mg/day), extension study in the treatment of Schizophrenia (N≈600).

**Questions:**

**Question 1-** Does the Division concur that the proposed nonclinical pharmacology package for cariprazine provides sufficient nonclinical profiling, efficacy, and safety to support an NDA?

**Preliminary Comments:** Yes.

**Discussion at Meeting:** There was no further discussion.

**Question 2-** Does the Division concur that the proposed cariprazine toxicology package, as outlined above, is sufficient to support the Phase 3 clinical program and a subsequent NDA filing?

**Preliminary Comments:**

Yes, provided that no new safety issues are identified in clinical or nonclinical studies, which may require further assessment. Please re-submit the chromosomal aberration study report (Serial No. 025). The previously submitted report could not be reviewed because some tables were missing a column, allowing only partial review of the study results.

**Discussion at Meeting:**

The Division stated that any major metabolites identified in humans would require further safety evaluation in nonclinical studies.

**Additional pharmacology/toxicology comments:**

In submission Serial No. 079, you included a summary of metabolic profiling in rats and dogs. According to this submission, relevant studies RGH-TX-28 and RGH-TX-30 were in preparation. Please provide a table listing all studies conducted to date containing animal metabolic profiling data, and submit complete study reports as soon as possible, since the summaries are not sufficient to allow independent review.

**Question 3-** Does the Division concur that the proposed population PK would provide adequate information to characterize PK of cariprazine, DCAR and DDCAR?

**Preliminary Comments:**

The proposed approach is acceptable. The analysis of the data will be a matter of review. We request that you collect sparse samples during the Phase 3 studies, in order to characterize the exposure-response relationship.

**Discussion at Meeting:**

The sponsor stated that they will collect sparse samples during the phase 3 studies in order to characterize the exposure-response relationship.

**Question 4-** Does the Division concur that the proposed approach would be sufficient to characterize the contribution of CYP2D6 in the metabolism of cariprazine?

**Preliminary Comments:**

The following is a reiteration of comments that we conveyed after our recent teleconference regarding mass balance and metabolite characterization:

- 1) Recovery was very low, and this remains an important concern. Further studies may be needed to increase the recovery of RGH-188 (for example, studying 12 mg in 6-8 patients).
- 2) A completely elucidated human metabolic pathway scheme including Phase II reactions must be provided.
- 3) It will be necessary to define precisely the circulating species in plasma, with detailed data. Our current understanding is that you have only monitored the following 3 circulating species: cariprazine, desmethylcariprazine, and didesmethyl-cariprazine. From the in vitro study results, it appears that you have identified 7 species. Thus, we recommend that you monitor for these species in plasma.
- 4) You have stated that the 4-hydroxy RGH-188 metabolite, and possibly all three of the hydroxy metabolites, are “probably or likely” excreted as glucuronide or sulfate conjugates. It will be necessary to ascertain analytically the presence of these terminal metabolites. Furthermore, you should identify more metabolites (e.g. amide, and hydrolysis metabolites). This will probably also help with increasing recovery.
- 5) We recommend that you analyze all available chromatograms to identify additional peaks/metabolites.

- 6) Furthermore, you can conduct a full-spectrum scan of plasma, urine, and fecal samples that might be available from the previous studies.

**Discussion at Meeting:**

The sponsor stated that they are preparing their response to the above-mentioned comments, and they will submit them by the end of next week.

**Question 5 -** Does the Division concur that, in conjunction with other in vitro and in vivo studies, the in-vivo data generated from patients treated at the projected therapeutic dosage (12.5 mg/d using the nonradiolabeled drug to approximately steady state) provide sufficient information regarding cariprazine metabolism and that no additional studies are needed to support the registration of the compound?

**Preliminary Comments:** Please refer to the comments for Question 4 above.

**Discussion at Meeting:**

The sponsor requested an additional meeting/telecon to discuss the mass balance and metabolite profiling issues. They plan to submit information next week for us to review. We stated that we will need time to review the information. They will have a response regarding final results of human, dog, and rat metabolism studies. We reminded the sponsor that they will have to consider additional studies, if there are human metabolites that do not occur in animals.

**Question 6 -** Does the Division concur that the proposed clinical program would be adequate to support an NDA for cariprazine in the schizophrenia indication?

**Preliminary Comments:**

On face, the proposed clinical program appears adequate to support filing of an NDA for cariprazine in the Schizophrenia indication. As noted in our Type C meeting minutes (February 11, 2009), you would be required to submit the results of at least two positive, adequate, and well-controlled studies in order to file an application for the indication of Schizophrenia.

On face, studies RGH-MD-04, RGH-MD-05, and RGH-MD-11 appear adequately designed. We note that the planned dose range for these studies is different than the dose range utilized in the recently completed study RGH-MD-16 and that you have provided a rationale for this change. Whether or not you have adequately addressed dose response for efficacy will be a review issue.

**Discussion at Meeting:** There was no further discussion.

**Question 7-** Does the Division concur that the proposed safety database for the schizophrenia studies along with the exposure in the acute mania studies with cariprazine would be adequate to support an NDA for cariprazine in the schizophrenia indication?

**Preliminary Comments:**

The proposed safety database outlined in the briefing package appears adequate to support an NDA for cariprazine for the Schizophrenia indication. Whether or not the data obtained would be sufficient would be a matter of review. As noted in the Type C meeting minutes, it will be important that the doses of cariprazine used to evaluate safety are the same doses that have been demonstrated to be effective in Schizophrenia trials.

**Discussion at Meeting:** There was no further discussion.

**Question 8-** Does the Division concur that the proposed TQT study plan for cariprazine would be adequate to support an NDA?

**Preliminary Comments:**

We have consulted the Cardiorenal QT Interdisciplinary Review Team to review the proposed thorough QT protocol and provide feedback. The Division will convey the consult results and specific recommendations for the protocol once we have received them.

**Discussion at Meeting:**

The sponsor requested feedback on the proposed study synopsis for the planned MTD study, which will be conducted before the dedicated QT study. The Division stated that the plan generally appears acceptable. The sponsor will submit the final protocol, and the Division will provide formal feedback.

**Question 9-** Does the Division concur that the statistical approach for the primary efficacy parameter is acceptable?

**Preliminary Comments:**

In principle, we have no objection to your proposed closed testing procedure to control the overall type I error rate. However, it may not be optimal to use LOCF ANCOVA as the primary

analysis. The response profiles in Studies RGH-MD<sup>(b) (4)</sup> and -16 revealed an upward trend immediately prior to discontinuation for the majority of dropouts (Appendix 4). This suggests that the missingness mechanism is unlikely to be MCAR (missing completely at random). The MMRM approach, which relies on a less rigorous assumption (MAR), may be less problematic. In fact, one cannot determine from the response profiles whether the MAR assumption would be adequate. Therefore, you should plan sensitivity analyses to deal with the scenario for which the MAR assumption is violated.

**Discussion at Meeting:**

There was some discussion about which missingness mechanism (between MCAR and MAR) appears more reasonable based on the response profiles from those two completed studies. We iterated that the MCAR assumption is more rigorous, and if it is satisfied, the MAR assumption will also be satisfied. The sponsor agreed to our suggestions, i.e., using MMRM as the primary analysis and proposing sensitivity analysis to deal with the situation where the MAR assumption is violated. They will consider the LOCF ANCOVA as an additional sensitivity analysis.

**Question 10-** Does the Division concur with Forest's intent to request a deferral for conducting studies required under the Pediatric Research and Equity Act (PREA) in pediatric patients until safety and efficacy has been demonstrated in adults?

**Preliminary Comments:** The plan to request a deferral for pediatric studies is acceptable.

**Discussion at Meeting:** The plan to request a deferral for pediatric studies is acceptable.

**Additional Comments:**

We encourage you to submit future NDA data (efficacy and safety) using the CDISC (Clinical Data Interchange Standards Consortium), such as SDTM (Study Data Tabulation Model), and ADaM (Analysis Data Model) standards. Standardization of data structures and terminology will facilitate a more efficient and comprehensive data review. Please refer to <http://www.cdisc.org> for more information.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-71958

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GI-1

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FOREST  
LABORATORIES  
INC

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RGH-188 HCL

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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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THOMAS P LAUGHREN  
01/22/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 71958  
IND 77726

Forest Laboratories, Inc.  
Attention: Jana D. Weinberger, M.P.H.  
Senior Associate, Regulatory Affairs  
Harborside Financial Center  
Plaza Three, Suite 602  
Jersey City, NJ 07311

Dear Ms. Weinberger:

Please refer to your Investigational New Drug Application (IND), submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cariprazine (RGH-188).

We also refer to the meeting between representatives of your firm and the FDA on February 11, 2009. The purpose of the meeting was to provide feedback to Forest regarding the Schizophrenia and Bipolar I Disorder development programs for cariprazine.

The official minutes of our meeting are attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301)-796-2260.

Sincerely,

*{See appended electronic signature page}*

Thomas P. Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure -- Meeting Minutes

**Preliminary Comments / Minutes of Meeting**  
IND 71958 [schizophrenia], IND 77726 [bipolar]: RGH-188 (cariprazine)  
Forest Laboratories, Inc.  
Type C Guidance meeting  
Premeeting: 30JAN09; Meeting: 11FEB09

**Purpose of Meeting:** Forest has requested this Type C meeting in order to obtain Division feedback on the schizophrenia and bipolar I disorder development programs for cariprazine.

**Participants:**

**FDA [30JAN2009 - present or contributing]:**

Director, Division of Psychiatry Products	Thomas P. Laughren, M.D.
Deputy Director, DPP	Mitchell Mathis, M.D.
Clinical Team Leader	Robert Levin, M.D.
Statistical Team Leader	Peiling Yang, Ph.D.
Team Leader, Nonclinical Pharmacology and Toxicology	Barry Rosloff, Ph.D.
Team Leader, Nonclinical Pharmacology and Toxicology	Aisar Atrakchi, Ph.D.
Team Leader, Office of Clinical Pharmacology	Raman Baweja, Ph.D. [contributing]
Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment	Thomas Oliver, Ph.D.
Clinical Reviewer	Francis Becker, M.D.
Nonclinical Pharmacology Reviewer	Elzbieta Chalecka-Franaszek, Ph.D.
Statistical Reviewer	George Kordzakhia, Ph.D. [contributing]
Regulatory Project Manager	Doris J. Bates, Ph.D.

**FDA [11FEB2009]:**

Director, Division of Psychiatry Products	Thomas P. Laughren, M.D.
Deputy Director, DPP	Mitchell Mathis, M.D.
Clinical Team Leader	Robert Levin, M.D.
Statistical Team Leader	Peiling Yang, Ph.D.
Team Leader, Nonclinical Pharmacology and Toxicology	Aisar Atrakchi, Ph.D.
Clinical Reviewer	Francis Becker, M.D.
Clinical Reviewer	Christina Burkhart, M.D.
Nonclinical Pharmacology Reviewer	Elzbieta Chalecka-Franaszek, Ph.D.
Statistical Reviewer	George Kordzakhia, Ph.D.
Regulatory Project Manager	Doris J. Bates, Ph.D.

**Forest Laboratories, Inc. [11FEB2009]:**

Vice President, Regulatory Affairs	June Bray
Senior Associate, Regulatory Affairs	Jana D. Weinberger
Executive Director, Clinical Development	Anjana Bose
Director, Clinical Development	Kelly Papadakis
Principal Scientist, Toxicology	Anne Gilson
Executive Director, Biostatistics	Hongjie Zheng
Director, Biostatistics	Dayong Li
Executive Director, Clinical Pharmacology	Parviz Ghahramani
Senior Scientist, Clinical Pharmacology	Bei Yu
Associate Director, Pharmacovigilance. Risk Management	Eddy Nkwepo

**Gedeon Richter, Ltd. [11FEB2009]:**

Medical Director	Gyorgy Nemeth
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Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

**Background:**

RGH-188 (cariprazine) is an atypical antipsychotic drug (dopamine D2 and D3 and 5HT receptor antagonist) in development for the treatment of Schizophrenia (IND 71-958) and Bipolar Disorder (IND 77-726). As of November 28, 2008, eleven studies have been completed (7 in healthy volunteers and four in patients). Two studies in patients are ongoing.

In the **Schizophrenia program**, three studies have been completed:

-**Study RGH-MD-01** was a double-blind, placebo-controlled study in male schizophrenic subjects, evaluating the safety, tolerability, and pharmacokinetics of multiple escalating doses (0.5-12.5 mg/day) of cariprazine during a 22-30 day dosing period.

-**Study RGH-MD-03** was a 6-week, randomized, double-blind, placebo-controlled, fixed dose-range study of the safety and efficacy of cariprazine in subjects with an acute exacerbation of Schizophrenia. The fixed dose ranges of cariprazine were 1.5-4.5 mg/day or 6-12 mg/day.

-**Study RGH-MD-14** was an open-label clinical pharmacology study in 8 male subjects with Schizophrenia. The study assessed striatal and extrastriatal dopamine receptor D2/D3 occupancy after multiple doses of cariprazine.

Two studies are ongoing in the Schizophrenia program:

-**RGH-MD-16** is a six-week, randomized, double-blind, placebo- and active-controlled (risperidone), fixed-dose study in subjects with an acute exacerbation of Schizophrenia. The fixed-doses of cariprazine include 1.5, 3.0, and 4.5 mg/day. The risperidone dose is 4.0 mg/day.

-**Study A002-A3** is a proof of concept study ongoing in Japan. No further information is available.

The sponsor plans 5 additional studies in Schizophrenia (3 acute trials and 2 open-label, long-term extension studies):

-**Studies RGH-MD-04, -05, -12** will be randomized, double-blind, placebo-controlled, 6-week studies in subjects with Schizophrenia.

-**Study 17** will be a 12-month, open-label extension study of subjects from Study 16. The cariprazine dose range will be 1.5-4.5 mg/day.

-**RGH-MD-11** will be a 48-week open-label, flexible-dose, extension study of subjects who have completed studies RGH-MD-04, RGH-MD-05, or RGH-MD-12.

The **Bipolar Mania development program** consists of one completed study and three planned studies:

-**RGH-MD-31** was an acute, 3-week, randomized, double-blind, placebo-controlled, flexible-dose (1.5-12 mg/day) efficacy and safety study of cariprazine in the treatment of subjects with Bipolar Disorder, acute manic or mixed episodes.

-**Studies RGH-MD-32 and RGH-MD-33** will also be acute, 3-week, randomized, double-blind, placebo-controlled, flexible-dose (1.5-12 mg/day) efficacy and safety studies of cariprazine in acute mania.

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

-**RGH-MD-36** will be a 12-week, open-label, extension study of subjects who have completed study RGH-MD-32 or RGH-MD-33.

Thus far, the safety profile of cariprazine appears to be similar to those of other atypical antipsychotic drugs. Commonly reported adverse reactions have been sedation, akathisia, extrapyramidal symptoms, and orthostatic hypotension. Please see the briefing package submitted on December 26, 2008 for further details.

The purpose of this meeting is to discuss the proposed clinical development program in both indications and obtain Division feedback on specific issues set forth in the questions following.

**Questions:**

**Schizophrenia**

**Question 1.** Based on our completed proof-of-concept study (RGH-MD-03) and ongoing dose-finding study (RGH-MD-16) and our planned pivotal studies, would this be adequate to support a schizophrenia indication?

**Preliminary Comments:** *You would be required to submit results of at least two positive, adequate and well-controlled studies in order to file an application for the indication of Schizophrenia. On face, ongoing study RGH-MD-16 appears adequately designed. The other three proposed, fixed-dose, controlled, acute trials (studies RGH-MD-04, RGH-MD-05, and RGH-MD-12) also appear to be adequately designed. We note that you plan to determine the dose levels for these 3 studies based on the results of Study RGH-MD-16. Whether or not you meet the above criteria for a schizophrenia indication will depend on the Division's review of the submitted data and statistical analysis plan.*

**Discussion at Meeting:** *The sponsor discussed ongoing considerations regarding selection of doses for future trials in Schizophrenia; the decision about particular doses for future trials will be based on the results from ongoing study RGH-MD-16. The sponsor asked about possibly seeking approval for a dose range, e.g., if two trials were positive for a low dose, and two trials were positive for a higher dose. The Division stated that this would be possible, but expressed a preference for studies looking at fixed doses within the same study.*

*The Division inquired about specific features of the Schizophrenia trials. The topics included: 1) use of an active comparator for assay sensitivity; 2) the need for titration of cariprazine; and 3) recommendation to consider mixed models repeated measures (MMRM) as the primary statistical analysis model in future trials. The sponsor noted that the current study uses risperidone as an active comparator. At least some of the future trials will include an active comparator. The Division encouraged using active controls in all trials, in order to establish assay sensitivity. When asked if cariprazine requires titration, the sponsor stated that titration is necessary in order to improve tolerability and*

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

*reduce the risk of adverse events (including hypotension/orthostatic hypotension and other unspecified adverse events). Cariprazine dosing begins with 1.5 mg/day and is titrated to 12 mg/day by day 5. The active comparator, risperidone was titrated similarly in previous and ongoing studies. Due to the need for cariprazine titration and the possibility of relatively delayed onset of efficacy, the Division suggested that the sponsor might consider MMRM as the primary statistical model for future studies, so that all information can be included in the analysis. The sponsor stated that they have been planning to consider an MMRM approach as the primary analysis, depending on the results of Study RGH-MD-16. Study RGH-MD-16 will be analyzed using an LOCF approach as the primary analysis.*

**Question 2.** Is the statistical approach for the primary efficacy parameter including imputation of missing data acceptable?

**Preliminary Comments:** *Yes. On face, the statistical methods appear acceptable. We request that you submit detailed statistical analysis plans in advance for pivotal studies, to allow sufficient time for us to review them and for you to finalize the protocols before data unblinding.*

**Discussion at Meeting:** *As above, the Division recommended that the sponsor consider using an MMRM analysis as the primary analysis for future trials. The sponsor plans to consider using an MMRM analysis, depending on the results from the ongoing trial.*

**Question 3.** Based on the proposed safety database, would this be adequate to support an approval for this indication?

**Preliminary Comments:** *The estimated exposure for Schizophrenia subjects based on the information that you have provided in this briefing package appears acceptable. However, this determination would be contingent on the Division's review of the submitted safety data. In addition, it is important that the dosages of cariprazine used to evaluate safety are the doses that have demonstrated efficacy in the Schizophrenia trials.*

**Discussion at Meeting:** *There was no further discussion at the meeting on this question.*

## **Acute Mania**

**Question 1.** Forest has completed Study RGH-MD-31. Based on the study design, could Study RGH MD-31 be considered 1 of 2 pivotal studies for this indication?

**Preliminary Comments:** *Yes. On face, Study RGH-MD-31 appears adequately designed as a potential pivotal efficacy trial for acute mania. In order to make a final determination, the Division would need to review the design, statistical analysis plan, and efficacy data in detail.*

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

**Discussion at Meeting:** *No further discussion.*

**Question 2.** Based on the draft protocol synopsis for the second pivotal study (Study RGH-MD-32), would this study, in addition to Study RGH-MD-31, be adequate to support an approval for the indication of Acute Mania?

**Preliminary Comments:** *Yes, assuming that you demonstrate efficacy in these two trials. On face, the study design appears adequate. Please see comments for Question 1. We have, however, noted that both of your intended pivotal studies, RGH-MD-31 and RGH-MD-32, utilize a flexible dosing regimen. The dosing range, from 3 to 12 mg, is relatively wide. If these studies demonstrate efficacy, it may not be clear a priori what dose range is most effective; thus it may be difficult to write appropriate dosing recommendations in product labeling. We ask that you conduct at least one fixed dose study for this indication.*

**Discussion at Meeting:** *The sponsor discussed plans to narrow the dosing range in Study RGH-MD-32, compared to the dose range in Study RGH-MD-31. In flexible-dose study RGH-MD-31, the planned dose range was 3-12 mg/day. More than 90% of subjects were treated with doses of 6-12 mg/day. Therefore, the sponsor plans to use a dose range of 6-12 mg/day in the flexible dose study.*

*The sponsor asked whether it would be sufficient to demonstrate efficacy in two flexible-dose studies in mania, as opposed to one fixed-dose study and one flexible-dose study. The Division emphasized the importance of establishing the minimal effective dose; a fixed-dose study would be the ideal study design to meet this objective. We also discussed the possibility of a fixed-flexible dose study using fixed ranges of doses. We agreed that it would be acceptable for the sponsor to conduct one flexible dose study in mania and one fixed-flexible dose study in mania.*

**Question 3.** Is the statistical approach for the primary efficacy parameter including imputation of missing data acceptable?

**Preliminary Comments:** *On face, the statistical methods appear acceptable. As indicated above, we request that you submit detailed statistical analysis plans in advance for all studies, in order to allow sufficient time for us to review them and for you to finalize the protocols before data unblinding.*

**Discussion at Meeting:** *There was no further discussion at the meeting on this question.*

**Question 4.** Based on the anticipated safety database, would this be adequate to support a bipolar indication?

**Preliminary Comments:** *The proposed subject exposure for the Bipolar Disorder safety database appears acceptable, assuming that dosages used for the safety evaluation are the clinically relevant doses that have demonstrated efficacy in the mania trials.*

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

**Discussion at Meeting:** *There was no further discussion at the meeting on this question.*

**Other**

**Question 1.** Does the Division agree that population PK modeling using the sparse sampling proposed in the phase II/III studies is an acceptable approach to characterize the PK of didesmethyl-cariprazine?

**Preliminary Comments:** *The approach is reasonable. We request that you also discuss your rationale for the approach in the NDA. The assessment of pharmacokinetics of cariprazine and its metabolites will be a matter of review when the NDA is submitted.*

**Discussion at Meeting:** *The sponsor discussed plans to conduct pharmacogenomics studies specifically regarding CYP26 status in subjects in the clinical trials, along with the population pharmacokinetic assessments. The Division agreed that this is acceptable. For the population PK analysis, the sponsor plans to examine covariates such as weight, age, and possibly others. The Division stated that, in principle, this would be acceptable. However, we could provide detailed feedback once the sponsor has submitted specific protocols for review.*

**Additional Questions From Forest Relevant to IND submissions for Bipolar and MDD:**

The following two questions were submitted to FDA on November 13, 2008 in a separate Meeting Request. We are addressing these questions here as well, to provide you with consolidated information in a single document.

**Question 1.** Is it acceptable to cross-reference IND 77,726 Acute Mania Associated with Bipolar I Disorder (b) (4)

**FDA Response:** *Our electronic mail message dated December 9, 2008, provided the following response to this question, which we include here for ease of reference:*

*"... we consider Bipolar Disorder to be an 'overall' indication. An IND opened for any bipolar sub-indication, such as acute mania, (b) (4)*

*For specific marketing claims under the bipolar indication, however, we do differentiate, based upon the extent to which specific clinical data are analyzed to support the*

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

*individual claim.*

(b) (4)

**Post Meeting Note:** *The above cited electronic mail also clarified that*

(b) (4)

**Question 2.** Reference is made to a June 5, 2007 email from Dr. Doris Bates, Ph.D., Regulatory Project Manager, Division of Psychiatry Products to Michael Macalush, former Director, Regulatory Affairs, Forest Laboratories, Inc. The above-referenced email (provided in Attachment 1) enumerated the Division's comments and requests following the review of the initial IND 77,726. Please refer to Request #6, which reads as follows:

*6. We consider cataractogenesis to be a serious potential safety concern for patients taking RGH-188. Patients should be screened for a history of cataracts. Patients who have a prior history of cataracts should be excluded from Study RGH-MD-31. For all studies using RGH-188 for 8 weeks or more, long-term ocular testing should be conducted (up to 18-24 months) and monitoring should occur at 4 to 6 month intervals.*

RGH-MD-52 is a Phase II multicenter, randomized, double-blind, placebo-controlled, flexible-dose study comparing cariprazine (RGH-188) to placebo in outpatients 18 to 65 years of age meeting DSM-IV-TR criteria for bipolar I or II disorder who are currently experiencing a major depressive episode. The study will consist of a 1-week no drug screening period followed by 8 weeks of double-blind treatment and a 1-week safety follow-up period. Patients meeting the entry criteria will be randomized (1:1:1:1) to one of 4 treatment groups (placebo, cariprazine 0.1-0.2 mg/d, 0.5-1.0 mg/d, or 2.0-4.0 mg/d). A total of 240 patients are planned to be randomized in this study.

RGH-MD-71 is a Phase II multicenter, randomized, double-blind, placebo-controlled study in outpatients 18 to 65 years of age meeting DSM-IV-TR criteria for major depressive disorder (MDD) with 1-2 historical failures to antidepressant therapy (ADT). The study will consist of a 1-week no drug screening period, followed by 8 weeks of prospective treatment with a new ADT, followed by 8 weeks of double-blind adjunctive treatment with ADT plus (cariprazine or placebo), and 1-week safety follow-up period. At the end of 8 weeks of ADT, non-responders to the ADT are planned to be randomized (1: 1: 1) to one of 3 treatment groups (placebo, cariprazine 0.1-0.3 mg/d, or cariprazine 1-2 mg/d) plus ADT.

Forest hereby requests an exemption from conducting the aforementioned ocular testing in these two depression studies given the planned low range of cariprazine doses (0.1 mg/d to 4 mg/d) that provide estimated safety margins of at least 13 (13-week dog study) and 9 (1 year dog study) and the short duration of exposure to cariprazine (8-weeks).

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

**FDA Response:** *This proposal is acceptable, given the short duration of exposure planned, and the estimated safety margins based on the findings of cataracts in dogs. However, if subjects entering the short-term controlled trials have the potential to continue treatment with cariprazine beyond 8 weeks in an extension study, then all subjects must undergo ophthalmological testing before beginning the controlled, short-term studies.*

*In any future studies in which cariprazine exposure has the potential to exceed 8 weeks, ophthalmological examinations would be required at baseline and at 4 month intervals for 18-24 months from the time of first dose. Patients with a prior history of cataracts or who are found to have cataracts at baseline examination should be excluded from the studies. The following ophthalmological examinations will be required:*

- *Assessment of distance visual acuity.*
- *Slit-lamp assessment using the Lens Opacities Classification System III (LOCS III). This must be performed by ophthalmologists trained and certified as LOCS III graders. Each ophthalmologist will remain masked as to his/her own prior LOCS III grades for each eye. The same ophthalmologist will perform both baseline and follow-up examinations.*
- *The ophthalmologist must also perform an examination of the vitreous, retina, macula, and optic nerve after completion of the above lens examination.*
- *Intra-ocular pressure must be measured at the end of each exam.*

**Discussion at Meeting:** *As discussed above, the Division requests that the sponsor conduct ophthalmologic studies on every subject exposed to cariprazine for more than 8 weeks.*

*The sponsor proposed conducting ophthalmological testing for [REDACTED] (b) (4) [REDACTED]. The Division stated that this plan would not be acceptable. We request that investigators conduct ophthalmologic testing for 100% of U.S. subjects who would potentially be exposed to cariprazine for more than 8 weeks. For subjects outside the U.S., we strongly recommend the same appropriate ophthalmologic testing.*

*We discussed two primary reasons for conducting ophthalmologic testing in relevant subjects:*

- 1) *For an NDA submission, the sponsor will have to provide an adequate database for the Division to make a definitive assessment of the potential ophthalmologic toxicity; and*
- 2) *the sponsor must address the ophthalmologic safety of individual subjects.*

*The sponsor agreed to try to make arrangements for ophthalmologic testing at all U.S. sites.*

Preliminary Responses, 30JAN2009  
Meeting with Firm, 11FEB2009

**Additional Comment From FDA: Suicidality [Policy Information]**

All clinical protocols for this product need to include prospective assessments for suicidality. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development.

An acceptable instrument would be one that maps to C-CASA (Columbia Classification Algorithm for Suicide Assessment). The C-SSRS (Columbia Suicide Severity Rating Scale) would be an acceptable instrument. You can obtain information about the C-SSRS from Dr. Kelly Posner at Columbia University ([posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)).

You may propose alternatives, but you would then need to justify that the alternative instrument would meet this need, and you would need to obtain DPP's prior approval of the instrument. There will likely be several different approaches to administering the C-SSRS, including investigator administered or self report (phone, computer, etc). Any could be acceptable as long as the method is validated.

***Discussion at Meeting:*** *The sponsor agreed to use the C-SSRS for assessment of suicidality in several indications. For the depression program, the sponsor is considering using the STS for assessing suicidality. The Division recommended that the sponsor submit a rationale for using the STS. Two main questions to address are:*

- 1) How well does the STS map to C-CASA?*
- 2) How well does the STS protect individual subjects from the standpoint of detecting suicidality?*

***General Comments:***

***These are the official minutes of our February 11, 2009 meeting. If you have any questions or disagree with the content of these minutes in any particular, it is your responsibility to bring these points to our attention.***

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 71958

-----  
FOREST  
LABORATORIES INC

-----  
RGH-188 HCL

IND 77726

FOREST  
LABORATORIES INC

RGH188

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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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THOMAS P LAUGHREN  
02/20/2009

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 204370

**LATE-CYCLE MEETING MINUTES**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Associate Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for cariprazine.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 16, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Senior Regulatory Project Manager at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Robert Levin, MD  
Medical Team Leader  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** August 16, 2013  
**Meeting Location:** FDA/Building 22/Room 1315

**Application Number:** NDA 204370  
**Product Name:** Cariprazine  
**Applicant Name:** Forest Laboratories, Inc.

**Meeting Chair:** Robert Levin, MD  
**Meeting Recorder:** Kimberly Updegraff, MS

**FDA ATTENDEES**

Ellis Unger, MD	Director, Office of Drug Evaluation I
Robert Temple, MD	Deputy Director, Office of Drug Evaluation I and Deputy Center Director for Clinical Science
Mitchell Mathis, MD	Division Director (acting), Division of Psychiatry Products (DPP)
Colleen Locicero, RPh	Associate Director for Regulatory Affairs, Office of Drug Evaluation I
Robert Levin, MD	Medical Team Leader, DPP
Francis Becker, MD	Clinical Reviewer, DPP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, DPP
Elzbieta Chalecka-Franaszek, PhD	Pharmacology/Toxicology Reviewer, DPP
Kimberly Updegraff, MS	Senior Regulatory Project Manager, DPP
Terry Harrison, PharmD, MBA	Safety Project Manager, DPP
Wiley Chambers, MD	Deputy Director, Division of Transplant & Ophthalmology Products (DTOP)
Chhagan Tele, PhD	Division Liaison, Office of New Drug Quality Assessment (ONDQA)
Sherita McLamore-Hines, MD	Chemistry Reviewer, ONDQA
Peiling Yang, PhD	Biostatistics Team Leader, Office of Biometrics (OB)
Eiji Ishida, MS	Biometrics Reviewer, OB
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Irene Chan, PharmD	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Loretta Holmes, BSN, PharmD	Safety Evaluator, DMEPA
Amy Taylor, MD, MHS	Medical Officer, Pediatric and Maternal Health Staff
Vicki Moyer, MS	Project Manager, Pediatric and Maternal Health Staff
Susan Leibenhaut, MD	Office of Scientific Investigations

Jason Bunting, PharmD	Risk Management Analyst, Division of Risk Management (DRISK)
Ida-Lina Diak, PharmD	Team Leader, Division of Pharmacovigilance (DPV)
Louis, Flowers, PharmD, MS	Project Manager, Office of Surveillance and Epidemiology (OSE)
Shawna Hutchins	Patient Labeling
Susannah O'Donnell	Reviewer, OPDP
Anastasiya Shakurova	Intern, Division of Epidemiology (DEPI)

#### **EASTERN RESEARCH GROUP ATTENDEES**

Patrick Zhou Independent Assessor

#### **APPLICANT ATTENDEES**

June Bray	Senior Vice President, Regulatory Affairs
Michael Olchaskey	Senior Director, Regulatory Affairs
Melina Cioffi	Associate Director, Regulatory Affairs
Gavin Corcoran	Executive Vice President, Global Medicines Development
Stephen Barat	Senior Director, Toxicology
Zsolt Szombathelyi	Research Director, Gedeon Richter, Plc.
Suresh Durgam	Senior Director, Clinical Development
Willie Early	Senior Director, Clinical Development
Shana Azri-Meehan	Senior Principal Scientist, Toxicology
Kaifeng Lu	Director, Biostatistics
Tatiana Khariton	Senior Principal Scientist, Modeling & Simulation
Antonia Periclou	Senior Director, Clinical Pharmacology & Drug Dynamics
Yih Lee	Senior Principal Scientist, Clinical Pharmacology & Drug Dynamics
George Nemeth	Medical Director, Gedeon Richter, Plc.
Hui-Talia Zhang	Pharmacovigilance & Risk Management, Global Drug Safety

### **1.0 BACKGROUND**

NDA 204370 was submitted on November 19, 2012 for cariprazine.

Proposed indications: Treatment of Bipolar I Disorder and Schizophrenia

PDUFA goal date: November 19, 2013

FDA issued a Background Package in preparation for this meeting on August 1, 2013.

### **2.0 DISCUSSION**

#### **1. Introductory Comments**

Welcome, Introductions, Ground rules, Objectives of the meeting

**Discussion:** *The meeting started at 1:00 pm EST with:*

- 1) Welcome
- 2) Background information on application and meeting  
(NDA #; proposed indications; time allotted for meeting; purpose of LCM);
- 3) Materials referenced for meeting (LCM briefing document; DR letter; previously sent PMR/PMCs/Labeling; information request dated 8-9-13; PDUFA date);
- 4) Statement indicating the a need for a REMS has not been identified at this point;
- 5) Statement indicating that there is not an Advisory Committee scheduled for this product;
- 6) Introductions of attendees from FDA, Eastern Research Group, and Forest.

## 2. Discussion of Substantive Review Issues

### A) Dosing

**Discussion:** *We began the discussion by stating that there appears to be a modest dose-response relationship for efficacy within some of the schizophrenia studies; however, there does not appear to be a dose-response relationship for efficacy in the mania studies. The Division stated that there are several significant safety findings that appear to be dose-related. These include akathisia and other extrapyramidal symptoms, CPK elevation, transaminase elevation, and blood pressure elevation. The sponsor claimed that [REDACTED] <sup>(b) (4)</sup> in bipolar mania based on their PK/PD model. However, FDA's PK/PD analysis demonstrated no added benefit at doses greater than 4.5 mg/day, which is consistent with the clinical trial results. We asked if there were any studies that assessed doses less than 1.5mg; it is possible that lower doses could be effective. The sponsor stated that there are no studies with doses less than 1.5 mg. They understand our questions with regard to the long-term dosing.*

### B) Long Half-life, Accumulation, and Reversibility of Adverse Reactions

#### 1) Adverse Reactions

**Discussion:** *We expressed concern that, because of the long half-life of cariprazine and its active metabolites, adverse events including akathisia, EPS, and rhabdomyolysis may persist for weeks after drug discontinuation. We noted that we requested additional information regarding adverse events via email on August 9, 2013. The sponsor stated that a full response was planned for August 19, 2013.*

**Hepatic concerns:** *We expressed concern regarding the potential for liver injury with the use of cariprazine. There appear to be significant dose-related increases in transaminases. In addition, there appear to be cases of increased bilirubin and transaminases that persist after discontinuation of cariprazine. We are currently working with our hepatic specialists to further assess the risk.*

*CPK: There are significant increases in serum CPK, which may be dose-related. In addition, there appears to be at least one case of rhabdomyolysis associated with renal failure. The Division acknowledged that a significant proportion of subjects in all treatment groups had CPK elevations, and some were present at baseline. Forest acknowledged that CPK elevations occurred with cariprazine, but they have not identified a specific mechanism. Forest also noted that CPK elevations are not uncommon in patients treated with antipsychotics. The Division expressed interest in analyses examining associations between CPK elevations and increases in creatinine.*

*Blood Pressure: The Division expressed concern regarding increased blood pressure, which may be dose-related. We inquired about the sponsor's assessment of the increases in blood pressure. Forest responded that they do not believe cariprazine has an effect on blood pressure. We recommended that the sponsor perform further blood pressure analyses.*

## **2) Long Half-Life, Accumulation**

*Discussion: Forest's analysis of the half-life relied on modeling and simulation. According to their analysis, the sponsor claimed that didesmethylcariprazine, the major active metabolite, has a half-life of 7-8 days. They believe that steady state is reached by Week 6. In addition, the sponsor indicated that the population PK model describes Phase 1 clinical trial data well. Our interpretation of Phase 1 trial data showed that cariprazine and didesmethylcariprazine have longer half-lives than 1 and 7-8 days, respectively, so that 6 weeks is not long enough to reach real steady state for didesmethylcariprazine, the major active moiety after multiple dosing. We do not agree with the PK parameters (i.e., half-life) derived from the population PK model because of inconsistency between the model prediction and observed concentrations stratified by different dose groups. Furthermore, the modeling results do not appear to sufficiently explain the observations from Phase 1 clinical trials. Both parties agreed that this difference in interpretation is critical to the review and that additional discussion will be necessary.*

## **C) Potential for Clinical Adrenal Toxicity**

*Discussion: The Division asked if there are data available on endocrine function from the clinical program. Forest stated that such information was not available. From a nonclinical perspective, Forest stated that there is a 3-fold safety margin for the findings in the adrenals in nonclinical studies. We stated that two types of toxicity were observed in dogs: reversible vacuolation/vesiculation and hypertrophy/hyperplasia of the adrenal cortex, with a 2-3-fold margin of safety, and irreversible phospholipidosis of the adrenal cortex with no margin of safety. Forest responded that the lack of changes in pituitary weights could indicate no endocrine effects of cariprazine and that they consider phospholipidosis to be not a safety finding but rather an adaptive response.*

## **D) (b) (4)**

*Discussion: We acknowledged the sponsor's August 15, 2013, response to our July 30, 2013 Discipline Review letter. The submission is currently under review by the Division*

*of Medication Error Prevention and Analysis (DMEPA). We will follow-up with a response when the review is complete.*

### **3. Information Requests**

**Discussion:** *We acknowledged the sponsor's statement that a response to our August 9, 2013 Information Request will be submitted on August 19, 2013. We plan to request additional information related to CPK elevation, increased blood pressure, increased akathisia and psychosis, and the activating properties of cariprazine. We also plan to meet internally to discuss next steps regarding the half-life discussion and will contact the sponsor after the team's discussion.*

### **4. Postmarketing Requirements/Postmarketing Commitments**

**Discussion:** *The sponsor plans to provide written responses to the preliminary Postmarketing Requirements and Commitments communicated on August 1, 2013. They requested feedback on the following:*

*a) PREA Studies (schizophrenia and mania): Forest asked if it would it be acceptable to include pediatric schizophrenia and mania subjects in a single long term safety study?*

*This may be acceptable to the Division.*

*b) Maintenance Study: There is currently a maintenance study underway (150 patients currently enrolled, plan to enroll a total of 180 patients). The study began in 2011. Would it be possible to use this study to satisfy the requirement?*

*The Division may request an additional randomized withdrawal maintenance study in which patients stabilized on cariprazine are randomized to various fixed doses, including cariprazine doses lower than those used for stabilization.*

*c) Juvenile Animal Study: Why did we request that the study be conducted in the dog?*

*We stated that the dog has a metabolic profile similar to that of humans, with high levels of the metabolite DDCAR (rats produce small amount of this metabolite). We also acknowledged that it is difficult to assess learning and memory in dogs; therefore, it may be necessary to perform two juvenile animal studies in separate species if an acceptable testing strategy is not feasible in the juvenile dogs. The protocol should be submitted to the Division for review prior to study initiation.*

*d) Drug-drug Interaction Study (cariprazine and proton pump inhibitor): Why did we request this study?*

*Cariprazine seems to undergo a marked change in solubility with changes in pH.*

## 5. Major Labeling Issues

***Discussion:*** *The sponsor plans to provide written responses to the preliminary labeling communicated on August 1, 2013. In preparation for the submission, they requested to briefly discuss the following:*

*a) Long term Adverse Event lipid table in Section 5*

The sponsor expressed concern over our addition of a table in labeling regarding shifts in lipid parameters in long-term, open-label schizophrenia trials, because this table is not present in other antipsychotic labeling. We stated that this was an attempt to more accurately describe the metabolic safety profile of cariprazine, but we can discuss this further with the sponsor.

*b) Dose Categorizations for the Adverse Reactions Tables in Section 6.*

The sponsor asked for clarification regarding categorizations of dose groups. We asked the sponsor to submit a proposal.

*c) Warning in label for long half-life*

*The Division discussed the recommendation to include in Warnings and Precautions section regarding the long half-lives. We referred to the warning for fluoxetine.*

## 6. Wrap-up and Action Items

***Discussion:*** *On August 19, 2013, we will receive a response to our August 9, 2013, Information Request and a response to the proposed Postmarketing Requirements/Commitments and Labeling will be submitted shortly thereafter. We will send additional information requests for adverse events. We will have an internal discussion regarding the half-life and will follow-up with the sponsor with additional information needs or discussion.*

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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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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ROBERT L LEVIN  
09/13/2013



NDA 204370

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Forest Laboratories, Inc.  
Attention: Melina Cioffi, Pharm.D.  
Assistant Director, Regulatory Affairs  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cariprazine.

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 16, 2013. Attached is our background package, including our agenda for this meeting.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director (acting)  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** August 16, 2013  
**Meeting Location:** FDA/Building 22/Room 1315

**Application Number:** NDA 204370  
**Product Name:** Cariprazine  
**Indication:** Bipolar Disorder and Schizophrenia  
**Sponsor/Applicant Name:** Forest Laboratories, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### OVERVIEW OF ISSUES IDENTIFIED TO DATE

In addition to the contents of this background document, please refer to the following Discipline Review letter already provided to you:

Division of Medication Error and Analysis (DMEPA) – July 30, 2013

**The current substantive review issues are as follows:**

#### CLINICAL

Dosing Recommendations: We are in the process of examining the dose-response and exposure-response data. Another important consideration is the pharmacokinetic profile of cariprazine and the two major active metabolites, particularly the long half-life of didesmethyl-cariprazine and the large contribution of DDCAR to the total active moiety. It is possible that we will

recommend [REDACTED] <sup>(b) (4)</sup>. At this point, we have not reached a conclusion about the recommended doses. We acknowledge that you have provided the requested information to address the dose-response and exposure-response considerations.

Potential for Clinical Adrenal Toxicity: Based on the significant adrenal toxicity findings observed in nonclinical studies, we request that you address the potential for clinical adrenal toxicity with cariprazine. Provide any relevant clinical data regarding cortisol assessments or other hypothalamic-pituitary-adrenal axis assessments in the cariprazine program. Address whether there are potential cases of adrenal insufficiency or adverse events related to the HPA axis. To identify potential cases, we request that you search the existing cariprazine clinical database for adverse events terms and relevant vital sign and clinical laboratory findings including (but not limited to) the following: cortisol abnormalities, adrenal insufficiency, adrenal suppression, weakness, fatigue, malaise, depression, nausea, vomiting, anorexia, weight loss, hyperpigmentation, hypotension, hyponatremia, hyperkalemia, electrolyte abnormality, and eosinophilia. It would be useful to search for cases in which such events co-occur in individual patients. You may propose relevant analyses to address these concerns. It would be useful to provide patient profiles and narratives for potential cases.

Transaminase Elevations: Cariprazine treatment was associated with increases in serum transaminases. There were mean increases in transaminases, as well as cases of transaminase elevations >3, > 5, >10, and >20 times the upper limit of normal. We are continuing to review this issue in consultation with our hepatologists.

Ocular Safety Findings: We are in the process of reviewing the ocular safety data in consultation with the ophthalmology division. We have not reached conclusions on the issues.

## **CLINICAL PHARMACOLOGY**

Long Half-Life of the DDCAR Metabolite and Reversibility of Adverse Events: One potential concern is that toxicity will not resolve rapidly after discontinuing treatment with cariprazine. We request that you address this concern by providing information about the timing of resolution of significant adverse events. These would include (but are not limited to): akathisia, extrapyramidal symptoms, sedation, nausea, vomiting, hypertension, and orthostatic hypotension.

## **PHARMACOLOGY/TOXICOLOGY**

We are concerned about toxicity findings in the adrenal cortex in dogs and the extent of drug-induced phospholipidosis observed in the lungs and/or adrenal cortex of rats, dogs, and mice. Because of the severity and/or frequency of these findings and occurrence in multiple animal species, these effects will be described in the label under Section 13.2 Animal Toxicology and/or Pharmacology.

**ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

We have not identified the need for REMS or other risk management actions to date.

## LATE-CYCLE MEETING AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 60 minutes

Each issue will be introduced by FDA and followed by a discussion.

1. Recommended Dosing
2. Long Half-life, Accumulation, and Reversibility of Adverse Reactions
3. Potential for Clinical Adrenal Toxicity
4. (b) (4)

3. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical

1. PREA requirements:

A deferred pediatric study in patients 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.

A deferred pediatric study for the treatment of schizophrenia in patients ages 13 to 17. A placebo-controlled study of the efficacy and safety of cariprazine in the relevant pediatric population.

A deferred pediatric study for the treatment of bipolar disorder, manic episode in patients ages 10 to 17 years. A placebo-controlled study of the efficacy and safety of cariprazine in the relevant pediatric population.

A long-term, open-label safety study in pediatric patients with schizophrenia (ages 13 to 17).

A long-term, open-label safety study in pediatric patients with bipolar disorder, recent manic episode (ages 10 to 17 years).

## 2. Maintenance Study in Schizophrenia:

A placebo-controlled, randomized withdrawal study in schizophrenia to assess the efficacy 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. The main objective is to determine the minimum effective dose required for maintenance treatment.

### Pharmacology/Toxicology

A juvenile animal study to be conducted in the dog at the appropriate age that corresponds to children age 10 years. The study protocol should be submitted for review and the study must be completed prior to initiation of pediatric clinical studies in children 10 years of age.

### Clinical Pharmacology

1. An *in vivo* drug-drug interaction study to assess cariprazine exposure when cariprazine is coadministered with a proton pump inhibitor.
  2. *In vitro* evaluation of cariprazine and its two major metabolites on inhibition potential toward CYP2C8.
  3. *In vitro* evaluation of cariprazine and its two major metabolites on induction potential toward CYP2B6.
  4. *In vitro* evaluation of cariprazine on induction potential toward CYP3A4 and CYP1A2.
  5. *In vitro* evaluation of desmethyl-cariprazine and didesmethyl-cariprazine on inhibition potential toward CYP2B6 and CYP2C19 .
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4. Major labeling issues – 10 minutes
  
  5. Wrap-up and Action Items – 5 minutes

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/s/  
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MITCHELL V Mathis  
08/01/2013