



NDA 204370/Original 1  
NDA 204370/Original 2

**NDA APPROVAL**

Forest Laboratories, LLC  
Attention: Melina Cioffi, PharmD  
Director, Regulatory Affairs  
Morris Corporate Center III  
400 Interpace Parkway  
Parsippany, NJ 07054

Dear Dr. Cioffi:

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

We also refer to our approval letter dated September 17, 2015, which contained the following error: timetables for trial completion and final report submission for postmarketing requirements 2947-9 and 2947-10 are incorrect.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain September 17, 2015, the date of the original approval letter.

We acknowledge receipt of your amendments dated February 14, 2014, March 18, 2014, April 9, 2014, April 17, 2014, July 11, 2014, July 28, 2014, December 17, 2014, January 14, 2015, January 22, 2015, January 29, 2015, February 26, 2015, March 16, 2015, April 21, 2015, May 6, 2015, June 8, 2015, June 12, 2015, July 21, 2015, July 27, 2015, September 3, 2015, September 11, 2015, and September 15, 2015.

The December 17, 2014, submission constituted a complete response to our November 19, 2013, action letter.

NDA 204370 provides for the use of Vraylar (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

The subject of this action letter is NDA 204370/Original 1 and NDA 204370/Original 2.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE-CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on September 15, 2015 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 204370.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **ADVISORY COMMITTEE**

Your application for VRAYLAR was not referred to an FDA advisory committee because the clinical trial designs are similar to previously approved products for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the treatment of schizophrenia and the safety profile is similar to that of other drugs approved for these indications.

### **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 are waiving the pediatric study requirement for ages 0 to 9 years for the treatment of manic or mixed episodes associated with bipolar I disorder and 0 to 12 years for the treatment of schizophrenia because necessary studies are impossible or highly impractical due to the low incidence of these disease states in these age ranges.

We are deferring submission of your pediatric studies for ages 10 to 17 years for the treatment of manic or mixed episodes associated with bipolar I disorder and 13 to 17 years for the treatment of schizophrenia because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2947-1      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:    11/2016  
Study Completion:                09/2017  
Final Report Submission:        03/2018

2947-2      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 a definitive toxicity/TK study. TK assessment should include cariprazine and the metabolites DCAR and DDCAR.

Final Protocol Submission:    11/2016  
Study Completion:                10/2017  
Final Report Submission:        03/2018

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

Final Protocol Submission:    07/2016  
Study Completion:                12/2018  
Final Report Submission:        06/2019

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

Final Protocol Submission: 06/2018  
Study Completion: 11/2022  
Final Report Submission: 05/2023

2947-5 Deferred pediatric study under PREA for the treatment of bipolar I 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 Completion: 10/2022  
Final Report Submission: 03/2023

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

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

Submit the protocols to IND 71958 or IND 77726, depending upon the indication, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

#### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of toxicity or adverse outcomes due to treatment failure precipitated by drug interactions, including co-medication with proton-pump inhibitors or major CYP enzymes, resulting in non-therapeutic levels of cariprazine or its active metabolites.

The new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on September 15, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2016  
Study Completion: 09/2017  
Final Report Submission: 03/2018

2947-8 *In-vitro* evaluation of:

- 1) inhibition potential of cariprazine, and the metabolites DCAR and DDCAR toward CYP2C8;
- 2) inhibition potential of DCAR and DDCAR toward CYP2B6 and CYP2C19;
- 3) induction potential of cariprazine, DCAR and DDCAR toward CYP2B6;
- 4) induction potential of cariprazine toward CYP3A4 and CYP1A2.

The timetable you submitted on September 15, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2016  
Study Completion: 12/2016  
Final Report Submission: 04/2017

Finally, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to assess the signals of serious risks of adrenal dysfunction, tardive dyskinesia, akathisia, and extrapyramidal symptoms.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on September 15, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2017  
Trial Completion: 12/2020  
Final Report Submission: 08/2021

2947-10 Conduct a placebo-controlled, randomized withdrawal, dose-response trial in adult patients with bipolar I disorder to assess the long-term, dose-related serious adverse effects of cariprazine, including tardive dyskinesia, akathisia, adrenal dysfunction, and extrapyramidal symptoms. The trial will also assess both 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 timetable you submitted on September 15, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/2016
Trial Completion:	06/2020
Final Report Submission:	12/2020

Submit the protocols to IND 71958 or IND 77726, depending upon the indication, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **SPECIAL REPORTING REQUIREMENTS**

We request 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)).

Every effort should be made to obtain 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.

We remind you of your agreement dated September 14, 2105, regarding obtaining follow-up information for case assessments of these findings as outlined in our letter dated September 11, 2015.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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

Sincerely,

*{See appended electronic signature page}*

Robert Temple, MD  
Deputy Director, Office of Drug Evaluation I and  
Deputy Center Director for Clinical Science  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling  
Carton and Container Labeling

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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 TEMPLE  
09/17/2015