CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1Orig2s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Division Director Summary Review
NDA/BLA #	204370
Applicant Name	Forest Pharmaceuticals, Inc.
Date of Submission	December 17, 2014
PDUFA Goal Date	September 17, 2015 (Extended Goal Date)
Proprietary Name / Established (USAN) Name	Vraylar / (cariprazine)
Dosage Forms / Strength	Capsules/1.5 mg, 3 mg, 4.5 mg, and 6 mg
Proposed Indication(s)	1. Treatment of Schizophrenia 2. Acute treatment of manic or mixed episodes associated with bipolar I disorder
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Francis Becker, MD Lucas Kempf, MD
Team Leader Review	Robert Levin, MD Lucas Kempf, MD
Statistical Review	Eiji Ishida, MS
Pharmacology Toxicology Review Supervisory Tertiary Review	Elzbieta Chalecka-Franaszek, PhD Aisar Atrakchi, PhD Paul Brown, PhD
Senior Science and Policy Staff, CFSAN (animal histology review)	Sabine Francke, D.V.M., PhD, FIATP Steven Mog, D.V.M., DACVP
Office of Pharmaceutical Quality (OPQ) Tertiary Review	Sherita McLamore-Hines, PhD Sandra Suarez Sharp, PhD Ramesh Sood, PhD David Claffey, PhD
Microbiology Review	-----
Clinical Pharmacology Review Pharmacometrics	Huixia Zhang, PhD Atul Bhattaram, PhD Joo-Yeon Lee, PhD Kevin Krudys, PhD Hao Zhu, PhD
OPDP	Susannah O'Donnell, MPH
DSI	Jong Hoon (John) Lee, MD
OSE/DMEPA	Loretta Holmes, PharmD Deborah Myers, RPh, MBA
OSE/OPE	John Senior, MD

OSE/DRISK	Jason Bunting, PharmD Leah Hart-Banks, PharmD
Other	
Pediatrics Maternal Health	Amy Taylor, MD Carrie, Ceresa, PharmD, MPH Hari Sachs, MD
QT-IRT	Moh Jee Ng
DCRP	Preston Dunnmon, MD
DMEP	Smita Abraham, MD
DPARP	Sally Seymour, MD Timothy W. Robison, Ph.D., D.A.B.T.
DTOP	Wiley Chambers, MD
CSS	Katherine Bonson, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

I. Introduction

This new drug application is for cariprazine, an oral atypical anti-psychotic, and was submitted by Forest Laboratories. Much of the important information about its safety and effectiveness in the treatment of acute schizophrenia and manic and mixed episodes associated with bipolar I disorder has been described in the initial review of the application that resulted in a complete response letter on Nov 19, 2013, citing an increasing frequency of important drug-related toxicities over the course of the 6-week controlled studies, a finding suggesting that the long half-life DDCAR metabolite might represent a problem as it accumulates. The major effectiveness and safety issues are discussed in the Division Director, Medical Officer (Drs. Kempf and Becker), Team Leader (Dr. Levin) reviews, and my previous Deputy Office Director review, so these will not be repeated here. Dr. Mathis's Division Director review summarizes them well. My previous Deputy Division Director Memo (included as Appendix I, dated Nov 19, 2013) discussed effectiveness at some length, noting the difficulties associated with the unusual presence of 3 active moieties: parent cariprazine, desmethylcariprazine (DCAR), and didesmethylcariprazine (DDCAR), the last with a very long half-life (1-3 weeks), compared with a half-life of about 2-4 days for the cariprazine parent. The memo strongly suggested that in such a case (long half-life drug or, in this case, metabolite) use of a loading dose made good sense and that studies using such a design should be conducted. They have not been conducted and the previous effectiveness conclusions and issues remain.

A. There is clear effectiveness and a dose-response over a range of 1.5 mg to 9 mg seen in essentially every steady in both schizophrenia and bipolar disease, although in bipolar disease, there was no further increase in effect beyond 6 mg. Adverse effects also showed a D/R and there was some increase in important effects, notably akathisia, over time, perhaps suggesting an effect of accumulating DDCAR.

B. Despite the delayed accumulation of DDCAR, (e.g., concentration at a week was less than half of steady state levels), effectiveness was seen relatively early (see my previous memo showing a clear effect at 2 weeks and a more or less full effect by 4 weeks in schizophrenia and 2 weeks in bipolar), with the 6 mg dose. The treatment effect became apparent as rapidly as with aripiprazole, suggesting that the accumulated DDCAR might not be critical to effectiveness. Moreover, doses of 1.5 and 3 mg per day were effective.

C. All this led us to suggest in our CR letter that this was a situation in which a loading dose made sense, which would allow a lower maintenance dose than was studied. (b) (4) [redacted] It was noted that akathisia rates rose with time.

   The specific study we suggested, and that I endorsed in my complete response memo, (b) (4) [redacted] For reasons I will describe below, we are prepared to approve doses of 1.5-6 mg daily, with a starting dose of 1.5 mg, increase to 3 mg on day 2, and further increases in 1.5-3 mg increments to 4.5-6 mg daily doses as appropriate.

D. Several safety issues have arisen and have been resolved.

1. As noted, [redacted] (b) (4) the excess incidence of akathisia with cariprazine compared to control agents is smaller, as is also the case for extrapyramidal symptoms.
2. BP elevations at doses ≤ 6 mg are small, < 2 mmHg and creatinine phosphokinase CPK elevations no longer are a concern. (See reviews of Drs. Kempf and Mathis).
3. During review a new concern arose related to animal findings, specifically a finding of phospholipidosis in the lungs of mice, rates, and dogs. Phospholipidosis has led rarely to severe pulmonary damage (amiodarone is the classic case), but in many other cases it does not appear to lead to damage. In the present case, the histopathology report of the dog study described a lung finding as "subacute, chronic, inflammation/fibrosis." It was the fibrosis finding that triggered important concern. The applicant was asked about this and slide review by 4 veterinary pathologists did not find fibrosis. Their data were reviewed by our expert veterinary pathologists, Drs. Francke and Mog at CFSAN, who agreed with the applicant (Aug 12, 2015 memo). Dr. Atrachi, the pharm-toxicology supervisory reviewer describes these events in her August 24, 2015 Supervisory Memo and notes that the primary pharm-tox reviewer, Dr. Chalecka-Franaszek also recommended approval in her August 24, 2015 amendment to her review.
4. Adrenal cortical hypertrophy (reversible) was also observed in mice and rats. The dose needed to cause this was above the maximum recommended human dose.

II. Effectiveness

As described in my previous review, the effectiveness of cariprazine has been well-demonstrated. Dr. Mathis's previous review shows detailed results and time course of effects of all 3 successful schizophrenia studies (RG4-MD-04; RG4-MD-16, and RG4-MD-05), which show significant effects at doses of 1.5, 3, 4.5, 6, 3-6, and 6-9 mg/day, with a consistently greater effect of higher doses in each study. (See Table on pg 1 of my previous review, included as Appendix I). Although these were not designed as comparative trials, effect sizes were similar at 6 mg to aripiprazole 10 mg but smaller than risperidone 4 mg (at 4.5 mg of cariprazine, however). The higher doses tended to give a more rapid response, again suggesting possible utility of a loading dose.

Although safety concerns led us in our CR letter to call for a new study to define optimal dosing that might reduce adverse effects, further safety assessments [redacted] (b) (4) have led us to conclude that the dose range of 1.5-6 mg provides acceptable effectiveness and safety and should be approved. We are, however, asking for a Post-marketing Requirement (PMR) that will examine, in the usual randomized withdrawal design maintenance study, the dose needed to sustain long-term effectiveness, comparing 1.5, 3, and 6 mg.

III. Safety

As noted, at 6 mg, blood pressure elevation concerns are minimal as are CPK concerns. There may be some infrequent effect on transaminase, and this is noted on labeling. Dr. Senior's review is reassuring and with a total exposure of several thousand patients there are no Hy's Law cases.

Preclinical studies raised several other concerns:

- Cataracts and retinal degeneration in dogs and rats will be noted in labeling under adverse reactions (section 6.1) and Non-clinical Toxicology (section 13.2).
- Phospholipidosis was seen in adrenal glands in several species and led to adrenal cortex hypertrophy in rats and mice. This is noted in section 13.2 of labeling.

Akathisia rates at 6 mg (12.5%) are still slightly greater than risperidone (8.6%) or aripiprazole (7.2%) and extrapyramidal effects are lower than risperidone but greater than aripiprazole. The rate of persisting akathisia and extrapyramidal effects was similar for all 3 drugs. On balance, we therefore consider the adverse effects of cariprazine, which are monitorable, acceptable. As they are dose related, however, it still remains important to assess the dose needed in long-term use.

IV. Conclusion

Cariprazine should be approved at doses of 1.5-6 mg/day. Labeling will note the pre-clinical concerns described above (cataracts, adrenal hypertrophy, pulmonary fibrosis) as well as dose-related toxicities. The application was not referred to an FDA advisory committee because effectiveness was clear in schizophrenia and bipolar disease using standard study designs and scales and side effects were those characteristic of the atypical antipsychotic class.

The applicant will be required to conduct 2 Post-marketing Clinical Trials (PMRs, post-marketing requirements), to better assess dose.

Specifically, placebo-controlled, dose-response (probably 1.5, 3, and 6 mg) maintenance studies in schizophrenia and bipolar disease to assess long-term adverse effects and the dose that best balances benefit and risks must be conducted. The studies will also assess adrenal function.

Appendix I is 9 duplicate pages from the Complete Response OD Memo dated November 19, 2013 that can be found in the Medical(s) Review section of this Approved NDA.

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/s/

ROBERT TEMPLE
09/16/2015