Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes Meeting of the Psychopharmacologic Drugs Advisory Committee
December 1, 2015

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed the efficacy and safety data for new drug application (NDA) 21164, gepirone hydrochloride extended-release tablets, submitted by Fabre-Kramer Pharmaceuticals, Inc., for the proposed indication of major depressive disorder.

These summary minutes for the December 1, 2015 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on Janaury 4, 2016.

I certify that I attended the December 1, 2015 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Kalyani Bhatt, BS, MS
Designated Federal Officer
Psychopharmacologic Drugs Advisory Committee (PDAC)

/s/
Ralph B. D'Agostino, Sr., PhD
Acting Committee Chairperson, PDAC

Summary Minutes of the meeting of the Psychopharmacologic Drugs Advisory Committee
December 1, 2015

The following is the final report of the Psychopharmacologic Drugs Advisory Committe held on December 1, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Psychiatry Products and posted on the Food and Drug Administration (FDA) website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm461701.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee (PDAC) of the FDA, Center for Drug Evaluation and Research, met on December 1, 2015, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided briefing materials from FDA and Fabre-Kramer, Pharmaceuticals. The meeting was called to order by Ralph D'Agostino, PhD (Acting Chairperson); the conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS, and (Designated Federal Officer). There were approximately 115 people in attendance. There were seven Open Public Hearing speakers.

Issue: Agenda: The committee discussed the efficacy and safety data for new drug application (NDA) 21164, gepirone hydrochloride extended-release tablets, submitted by Fabre-Kramer Pharmaceuticals, Inc., for the proposed indication of major depressive disorder.

Attendance:
Psychopharmacologic Drugs Advisory Committee Members Present (Voting): David Pickar, MD; Murray Stein, MD

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): David A. Brent, MD (Chairperson); Thomas A. Grieger, MD

Temporary Members (Voting): Ralph B. D'Agostino, Sr., PhD (Acting Chairperson); Victor De Gruttola, ScD (via phone); Dean Follmann, PhD; Nitin Gogtay, MD; Judith D. Goldberg, ScD; Jennifer Higgins, PhD (Acting Consumer Representative); Dawn F. Ionescu, MD; J. John Mann, MD; Rajesh Narendran, MD; Natalie Compagni Portis, PsyD (Patient Representative); Matthew V. Rudorfer, MD

Acting Industry Representative to the Committee (Non- Voting):
Robert Russell Conley, MD

FDA Participants (Non-Voting): John Jenkins, MD; Robert Temple MD; Mitchell Mathis, MD; Lisa LaVange, PhD; Peiling Yang, PhD

Designated Federal Officer (Non-Voting): Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Diana Zuckerman, PhD (President, National Center for Health Research); Sarah Sorscher, JD, MPH (Researcher, Public Citizen's Health Research); Beth Salcedo, MD, (Medical Director, The Ross Center for Anxiety and Related Disorders, LLC); Dr. James A. Simon, MD (Simon of Healthcare for Women); Steven B. Israel, MD (Private Practice of Adult and Adolescent Psychiatry); Dr. Kenneth Weiss, MD (Clinical Professor of Psychiatry Perelman School of Medicine) (statement read by Beth Salcedo); Jay D. Amsterdam, MD (Director, Depression Research Unit and Professor of Psychiatry, University of Pennsylvania)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Ralph B. D'Agostino, PhD** (Acting Chairperson), PDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, PDAC
FDA Opening Remarks	**John Jenkins, MD** Director Office of New Drugs (OND), CDER, FDA
	Mitchell Mathis, MD Director Division of Psychiatry Products (DPP) Office of Drug Evaluation-I (ODE-I) OND, CDER, FDA
INDUSTRY PRESENTATIONS	**Fabre-Kramer Pharmaceuticals, Inc**
Introduction	**Daniel Burch, MD** Vice President Global Therapeutic Area Head for Neuroscience Pharmaceutical Product Development, LLC
Rationale for Gepirone Development	**Michael Thase, MD** Professor of Psychiatry Perelman School of Medicine University of Pennsylvania
Totality of Evidence for Effectiveness	**Gary Koch, PhD** Professor of Biostatics and Director of Biometric Consulting Laboratory Gillings School of Global Public Health University of North Carolina at Chapel Hill
Gepirone Clinical Experience	**Stephen Stahl, MD, PhD** Professor of Psychiatry University of California San Diego Founder and Director of Neuroscience Education Institute

Conclusions	**Daniel Burch, MD**
Clarifying Questions to Industry	

FDA PRESENTATIONS

Efficacy	**Peiling Yang, PhD** Biostatistics Team Leader Division of Biometrics I Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Safety	**Mitchell Mathis, MD**
Substantial Evidence of Effectiveness – Office of Drug Evaluation-I Perspective	**Robert Temple, MD** Deputy Director for Clinical Science CDER, FDA Deputy Director (Acting) Office of Drug Evaluation-I (ODE-I) OND, CDER, FDA
Office of Biostatistics Perspective	**Lisa LaVange, PhD** Director OB, OTS, CDER, FDA
Clarifying Questions to FDA	
Open Public Hearing	
Clarifying Questions to the Sponsor or FDA	
Summary/Charge to the Committee	**John Jenkins, MD**
Questions to the Committee/Committee Discussion	
Questions to the Committee/Committee Discussion (cont.)	

ADJOURNMENT

Questions to the Committee:

The Food Drug and Cosmetic Act requires a sponsor to provide substantial evidence of effectiveness to support approval of a new drug. The Act defines the level of evidence necessary as generally requiring two positive adequate and well-controlled trials.

1. **DISCUSSION:** Please discuss the following questions related to substantial evidence:

    a. In the situation where two positive adequate and well-controlled trials have been completed, how much and what type of "negative evidence" from other negative or failed trials would it take to undermine a finding of substantial evidence of effectiveness?

    Committee Discussion: *The committee agreed that it is important to have trials as similar to one another in design, patient characteristics and primary outcomes in order to be able to assess them against each other. The committee further commented that it should be robustness across the trials and they should avoid post hoc issues. Please see the transcript for details of the committee's discussion.*

    b. What approaches for synthesizing evidence across positive and negative/failed trials in a development program are useful for decision-making?

    Committee Discussion: *The committee discussed several options for synthesizing evidence including: using meta-analysis with all patients considered and using the binomial method with p-value kept at 0.05. These should be used to look at the totality of results against all studies and evaluate the consistency across the studies. It was also discussed to pool possibly data from negative trials to use as a third trial if methodology permits. Please see the transcript for details of the committee's discussion.*

2. **DISCUSSION:** Please discuss your views on ways to evaluate clinical trials for assay sensitivity.

Please consider the following questions in your discussion:

    a. Is the primary endpoint for efficacy prospectively defined in the protocol the only meaningful way to evaluate assay sensitivity?

    Committee Discussion: *The committee agreed that it is important to keep the primary endpoint and have a drug meet this endpoint. The committee also agreed that other ad hoc endpoints can be meaningful, but these must be clearly labeled as ad hoc and exploratory. It was also commented that is important to consider carefully how much weight these non-primary endpoint are given. There was also discussion on the importance of the selection of the active comparator for the evaluation of assay sensitivity. It was also discussed that the comparison of the active control to the placebo is not a true assay as in the laboratory activity but still is useful and important to pre-*

specify the assay sensitivity before beginning. Please see the transcript for details of the committee's discussion.

b. Can *post hoc* analyses of other efficacy endpoints or use of other analysis methods contribute to the determination of assay sensitivity?

Committee Discussion: *The committee agreed that post hoc analyses and other efficacy endpoints can be helpful, but must be considered exploratory and secondary. Further, the committee commented that there must be careful consideration of bias and inappropriate Type I Error rates. It was also reiterated that post hoc analyses may be more helpful as exploratory research. Please see the transcript for details of the committee's discussion.*

3. **VOTE:** Has the sponsor provided substantial evidence of effectiveness for gepirone extended-release (ER) in the treatment of major depressive disorder (MDD)?

Yes: 4 ***No: 9*** ***Abstain: 0***

Committee Discussion: *The majority of the committee agreed that the sponsor did not provide evidence that was substantial enough and that the negative evidence undermined the positive findings despite the two positive studies. In contrast, those who voted, "Yes", agreed that the two positive studies and other evidence such as the sensitivity meta-analysis presented by the sponsor provided enough evidence of effectivness for gepirone ER in the treatment of MDD. Please see the transcript for details of the committee's discussion.*

4. **VOTE:** Has the sponsor adequately characterized the safety profile of gepirone ER in the treatment of MDD?

Yes: 11 ***No: 2*** ***Abstain: 0***

Committee Discussion: *The majority of the committee agreed that the sponsor adequately characterized the safety profile of gepirone ER and that the drug is adequately safe. But most members indicated that "substantial evidence of effectiveness" in treating major depressive disorder (MDD) was lacking. Those who voted, "No", disagreed because there was no evidence regarding suicide potential and that evidence was supported by short-term trials for a long-term drug. Please see the transcript for details of the committee's discussion.*

5. **VOTE:** Do the available data support a favorable benefit risk profile of gepirone ER to support approval?

Yes: 4 ***No: 9*** ***Abstain: 0***

Committee Discussion: *The majority of the committee's consensus was that available data did not support a favorable benefit risk profile of gepirone ER to support an approval. The majority of the committee agreed that the benefits outweighed the risk of the medication to be a new option for patients but needed further studies. Those who voted, "Yes", agreed that the drug could offer another option for patients due to its impressive safety profile and efficacy being shown in the short-term studies. Please see the transcript for details of the committee's discussion.*

6. **DISCUSSION:** What, if any, additional studies are needed pre- or post-approval to address outstanding issues, e.g., an additional effectiveness study, an additional randomized withdrawal maintenance trial?

Committee Discussion: *The majority of the committee agreed that more studies are needed and that assay sensitivity built-in to studies may not be necessary. Some types of additional studies discussed included: post-marketing surveillance, monitoring blood levels and biomarkers, whether to use a placebo or active control, longer duration of studies, age analysis, comparing different dosages and severities, and using an external rater system. It was also mentioned to use 2016 standards and analysis. Please see the transcript for details of the committee's discussion.*

The meeting was adjourned at approximately 4:20 p.m.