CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Center Director Decisional Memo

NDA : 21164
Drug: Gepirone
Sponsor: Fabre-Kramer

This memorandum represents the Center's decision on an appeal from Dr. Temple regarding the 2-26-16 decision by Dr. Jenkins that the above NDA contains substantial evidence of effectiveness of gepirone for the indication of treating major depressive disorder (MDD).

I have read Dr. Jenkins' memo, Dr. Temple's appeal of April 1, 2016, other relevant documents from Dr. Jenkins and Dr. Temple, a transcript of the December 1, 2015 Psychopharmacologic Drugs Advisory Committee meeting on this subject, and multiple memos from Dr. Lisa LaVange, CDER's head of biostatistics, as well as numerous review memoranda from the Division of Psychiatry Products (both from the current and previous review cycles).

I conclude that substantial evidence of effectiveness has been provided and concur with Dr. Jenkins' disposition of the dispute between the sponsor and FDA. My analysis is discussed below.

In his appeal, Dr. Temple raises four issues:

1. That the clinical trials submitted with the gepirone NDA do not meet the statutory standard for substantial evidence.
2. That some of the active controlled trials in the development program should be considered "negative trials" instead of "failed" trials and thus should count strongly against the effectiveness of gepirone.
3. How to evaluate the contribution of a positive IR study, mentioned by Dr. Jenkins in his decisional memo.
4. The consequences of approving a potentially ineffective antidepressant.

I will address each of these issues, but I consider the first one the most important, because the other three are related to the decision about the first issue.

Issue 1. Do the data in the gepirone NDA meet the statutory standard for substantial evidence?

The standard of two adequate and well-controlled trials (each meeting a conventional level of statistical significance with a pre-specified analysis) has been well established as the ordinary requirement for substantial evidence under the Food, Drug and Cosmetic Act. However, while outlining circumstances under which one trial might suffice, or how trials in related areas might represent evidence similar to a second trial, the Agency has never formally addressed situations where, in addition to two adequate and well-controlled trials,

there are one or more adequate and well-controlled trials that do not show a statistically significant effect of the drug. Dr. Temple is concerned that, as a result of the statistical nature of the effectiveness test, a sponsor could repeatedly conduct trials until getting two positive results by chance alone, thus leading to an approval of an ineffective drug if the two studies were viewed in isolation. Because trials of approved antidepressant drugs fail to show effectiveness about half the time, the issue of how to synthesize information across both successful and unsuccessful trials is an important one in this field.

The informal method that has been used to evaluate this situation for antidepressants might be described as "trial counting": the trial results are put into categories of "successful", "failed" (see Issue #2), and "negative" and the successful and negative columns are compared. As Dr. Jenkins noted, this procedure results in the loss of a tremendous amount of information, and could lead to two studies with nearly indistinguishable results being put in two different categories due to the dichotomous nature of the statistical test used. I do not agree with this method of synthesizing trial results, and conclude, when this situation arises, that more formal meta-analytic approaches should be used. Nevertheless, I provide my analysis of the "counting trials" approach, in the following, since this procedure forms part of the basis for Dr. Temple's position.

There were 13 efficacy trials conducted for the ER formulation of this drug by multiple sponsors during several decades. Of the 13, there are two agreed-upon adequate and well-controlled trials that demonstrate effectiveness of the drug. Four trials were stopped prematurely due to business reasons (mentioned both by the sponsor at the Advisory Committee meeting and by Dr. Thomas Laughren of FDA in his review memorandum during a prior review cycle). Three two-arm trials were negative. Two studies were in atypical depression and were "failed" studies by the FDA criteria, based on the performance of the active control on the pre-specified primary endpoint. Similarly a study with MADRs as the primary endpoint is a "failed" study based on its pre-specified analysis. There is also a longer-term randomized withdrawal study that did not achieve statistical significance on its primary endpoint.

Although I do not agree with the "failed" and "negative" schema (see Issue #2), I have the following conclusions about ODE 1's analysis of this development program:

a. I do not find it appropriate to include trials stopped prematurely for "non-trial" reasons when doing a "trial count" of positive and negative studies, because such trials should not be given equal weight to completed trials. Therefore four of the 11 trials should not be entered into this calculation, including CN 105053, one of the

disputed trials (i.e., a dispute over whether or not it "failed".) Data from such trials could be included in a meta-analysis.

b. I do not find it appropriate to re-analyze trials based on results other than the primary endpoint and analysis method to determine whether or not they "failed". Therefore I conclude that the trials ORG 134004, 134006, and 134017 should be considered "failed" trials by this convention.
c. These conclusions result in a count of two positive short-term trials, three negative (two-arm) short-term trials, and one negative randomized withdrawal trial.
d. Dr. Temple, in his appeal, describes the chance of two spuriously positive studies, given the current standard, as 0.0625%, a very small likelihood. This calculation, however, assumes that there are only two trials and both are positive. Dr. Mathis, in his presentation to the Advisory Committee, showed an antidepressant development program, resulting in approval, that had four positive, four negative and one "failed" trial. This particular development program (and others that were described Dr. Mathis's table) clearly had more chances at false positive results, so it is obvious that no clear threshold has been established. (Parenthetically, it is unclear to me why attempting studies that ultimately "fail" should exempt those attempts from this sort of probabilistic reasoning.)

e. Therefore, the Center has not articulated how many negative trials, in a trial count approach, would constitute "too many" when compared to the number of positive trials in the setting of MDD. Apparently, a 1:1 ratio of successful-to-negative is acceptable, or 4:5 if you count trials attempted. The three "negative" gepirone short-term trials lacked an active control and thus the opportunity to be exempted from a trial count due to "failure".
f. In a prior review cycle, the Division performed additional post-hoc analyses on the "failed" studies in atypical depression. In two of these studies, the active control was not statistically different from placebo on the primary endpoint and the gepirone result was numerically less favorable than the placebo result. In post hoc analyses comparing active control to gepirone on a different endpoint (HAMD-17), the active control was nominally significantly better than gepirone in both trials. Dr. Temple feels this finding is very atypical in antidepressant trials and highly likely to indicate that gepirone is ineffective. There are serious statistical problems with assigning a "p value" to such comparisons. Leaving that aside, I looked at the trial results, both for the primary endpoint and the HAMD-17. Clearly gepirone was not different from placebo in these trials, but the two active controls also did not perform particularly well compared to placebo. I did not find these results disturbing for a trial setting in which approved

drugs routinely fail to differentiate from placebo, and with inclusion criteria (atypical depression) that differ from the usual trials.

g. In summary, using the "trial count" method, I do not find the results of the gepirone ER development program strikingly different from the programs of other approved drugs for MDD, when taking the history of this development program into account (for example, early termination of multiple trials, exploration of different populations).

I believe the best method of summarizing across trials is to use one of the many meta-analytic techniques available. Meta-analysis is complicated in this case by the use of different endpoints and analysis approaches in various trials. Dr. LaVange's review of May 5, 2015 goes into this issue in some depth. None of the analyses (and many have been done) using the proposed indicated population lead to a conclusion that the two positive studies of this drug are "false positive" results due to multiple attempts. I do not consider meta-analyses that include only the "failed" trials to be informative. The meta-analyses point to a treatment effect that may be more modest than some of available antidepressants, although this was not seen in the two "positive" trials.

Additionally, as pointed out by Dr. Jenkins, gepirone was numerically better than placebo in many of the

"negative" or "failed" trials of gepirone, including the randomized withdrawal study and two of the three "negative" trials. Also, the two "positive" studies were robust and had concordance across many secondary endpoints, arguing against a random statistical finding.

Taking into account all the evidence that has been generated comparing gepirone to placebo, I conclude that substantial evidence of effectiveness has been provided and that the trials submitted in the NDA meet the statutory standard. I read the transcript of the December 1, 2015 advisory committee meeting on this subject, and reviewed the slide presentations. Although the advisory committee advised that an additional trial should be conducted pre-market, I found nothing in these materials, including the discussions of the AC members, that changes my conclusions. Clearly, this is a matter of regulatory judgment, as there are no established standards in this area.

2. "Categorization of "failed trials" and "negative trials"

While use of an active control can be very useful in many settings, I do not agree with the practice of using an approved antidepressant as an active control to determine "assay sensitivity" in trials of MDD. Therefore, although I have addressed Dr. Temple's conclusions, using this method, in the discussion of issue #1, it did not enter into my independent

assessment of substantial evidence. This practice seems to be a way to "exculpate" trials from being used as evidence against effectiveness in "trial count" methods of synthesizing evidence across development programs. I discuss my conclusions about this practice in the following.

According to all parties, it is very common for short-term (12 week) efficacy trials of approved (or subsequently approved) antidepressants to fail to show a positive effect of the drug at a conventional level of statistical significance. This happens at least as frequently as half the time. It is also agreed that the incremental effect of current antidepressants over placebo in these trials is much less than the overall improvement seen in placebo groups in the trials. There also seems to be extensive evidence that this overall drug effect size is "small" i.e., a small percentage of the rating scale used (the "HDRS") and possibly just on the border of a "clinically significant" effect. These matters are all related, of course, and the first observation (that trials of effective drugs often do not show a statistically significant effect) is likely, at least in part, to be caused by the other facts (that the overall effect size is small and that patients randomized to placebo improve during the trial). These findings are reminiscent of those seen in certain other symptomatic diseases (e.g., NSAIDs in osteoarthritis, irritable bowel syndrome) where substantial improvement is observed in placebo arm patients during the trial.

To deal with this problem, the FDA has asked for an approved antidepressant to be included as a third randomized arm in addition to placebo and test drug. In the case that the test drug is not statistically significantly better than placebo, a comparison of the approved drug to placebo is evaluated. If the approved antidepressant was not superior to placebo, then the trial is declared "failed" and is not counted against the test drug. If the approved drug is statistically better than placebo, the trial is declared "negative" with respect to the test drug, and the trial is counted against it. In cases where the test drug "wins" and the approved drug does not, the "win" for the test drug is counted.

While I am sure these designations are a useful heuristic when evaluating development programs, I find the practice of deeming these results "failures" and disregarding them to be non-rigorous. The data presented by Dr. Mathis at the recent advisory committee meeting on 46 3-arm short-term trials, with both active arms being (currently) approved antidepressant drugs, showed that in almost two-thirds (63%) of the trials, one or both active arms did not meet the statistical test for difference from placebo. I believe this performance must be considered a property of the drugs and the test system used (i.e., the entry criteria, duration of the trial, the endpoints used, and so forth). For a class of drugs widely held to be useful in practice, one explanation would be that this test system is not

very good at assessing the actual effects of antidepressant drugs. Another might be that these drugs actually have a negligible effect in the short term. Indeed, these hypotheses have been widely debated in the psychiatric and lay literature, with some parties claiming that antidepressants "don't work", other arguing that they are effective only in severe depression, and others discerning a small, proportional effect across the disease severity spectrum. Of note, however, none of the parties disregard the existence of a large proportion of "negative" trials in discussing the treatment effects of antidepressants.

The concept of "assay sensitivity" must rest on the assumption that the positive control will (usually) be effective and therefore its failure to be so must result from some anomaly in the placebo group or problem in trial design or execution. There is no empirical evidence, to my knowledge, that supports the fact that unusual behavior of the placebo group is what leads to a finding that an approved antidepressant is not statistically better than placebo. In fact, current evidence suggests this will happen about 50% of the time in an otherwise acceptable trial, so nothing about this result is unusual. The response of placebo groups in depression trials has become larger, over decades, according to NIMH (possibly due to enrollment of less-depressed patients); however, this represents a change in the actual comparison group, not an anomaly. The concept of "assay sensitivity" is rather tenuous when

the positive control has less than a 50% chance of performing as such, based on extensive prior experience and I do not think this failure is particularly informative about the placebo group's appropriateness.

Another reason for an approved active control to not be effective could be that the trial overall enrolled subjects unlikely to be responsive. Depression is a clinical diagnosis without useful diagnostic biomarkers and therefore highly likely to be heterogeneous at the level of pathogenesis and response to various drug classes. It is certainly possible that some depression trials could enroll subjects not typical for other depression trials, who are less likely to respond. However, because such subjects fit into the current definition of MDD, their results are just as legitimate as those of any other MDD group, and should not be discounted. It is also possible that likely non-responders could be, by chance, randomized a higher rate into the active control group. Nevertheless, any imbalance in the active control arm with respect to these factors is not likely to be informative about imbalances that occurred in the test drug arm versus placebo.

In the data presented by Dr. Mathis to the Advisory Committee on "failed trials" versus "negative trials" versus successful trials, there was more concordance (about 70%) on results in the two active arms (each of which was a currently approved antidepressant), i.e., win-win and lose-lose, versus discordant results (about

30%), than would be expected by chance alone. This makes me think that the use of the active control does pick up some trial factors (perhaps the behavior of investigators, overall characteristics of enrolled patients, or problems with statistical power) that led to successful or non-successful results. However, I do not believe this fact should lead to ignoring the results of the test drug versus placebo.

In summary, the failure rate of antidepressant drugs in short-term trials appears to be inherent to properties of the drugs and the test system used. I do not believe that discarding trials where the active control failed is a useful maneuver. I recognize that FDA has current guidance advocating this practice, and I believe it should be re-evaluated. I don't oppose active controls; rather, I do not agree with using them to disregard information.

For these reasons, and those articulated in Issue #1, I am not further addressing the distinction between "failed" and "negative" trials in the gepirone development program.

3. Performance of gepirone IR in trials.

Dr. Jenkins mentions a positive trial of gepirone IR in his decisional memo. This trial (03A7A-003) was considered a positive study by FDA, as discussed by Dr. Laughren in his October 25, 2007 review memo. In fact,

FDA initially (prior to 2001) told the sponsor that a single positive trial of the ER formulation would be sufficient because of the existence of the positive IR trial. To Dr. Temple's point, the Division at that time as aware of the fact that there were also a number of negative IR trials. However, because of an additional negative ER trial (053, the randomized withdrawal trial that had been terminated early), the Division (in 2002) recommended that a second positive ER trial be submitted. I believe Dr. Jenkins's point is that FDA considered that there was evidence of effectiveness from the IR program, which is the case according to Dr. Laughren's memo.

5. Consequences of approving a ineffective antidepressant drug

Dr. Temple points out that major depression is a serious disease and that approval of an ineffective therapy could have serious consequences. I agree that major depression is serious and that better interventions are needed. Short-term (12 week) placebo controlled trials are considered ethical and are required by FDA to obtain an initiation of therapy indication, based on the finding that 12 weeks of placebo does not lead to increased harm (suicide) in this population. This is not at all surprising given the small magnitude of the treatment effect observed.

I do not conclude that gepirone is ineffective, although I agree that it may be less effective than some other antidepressants. A major limiting factor for the use of antidepressants is tolerability. Many patients discontinue treatment because of side effects. Additionally, while it is probably not possible to test this rigorously due to the small treatment effect, many in the psychiatric community believe that individual patients do not respond the same to various antidepressant drugs, thus the common practice of therapeutic trials and switching patients until a response is seen using a drug the patient can tolerate. Both because of inter-individual variability in tolerance and effectiveness of various drugs, I believe that availability of antidepressant drugs from different classes is useful. Therefore, gepirone would be a useful addition to the antidepressant armamentarium, even if it is slightly less effective than some other antidepressants.

I agree that the sponsor should conduct a longer-term randomized withdrawal study of adequate size as a postmarketing commitment. The sponsor will also need to meet other obligations as laid out in Dr. Jenkins's memo.

After circulating a draft of this memo to Dr. Temple, I received additional comments from him about the IR study's inadequacies, and his continued assessment that gepirone has not met the substantial evidence standard.

He and I discussed these issues on 8/11/16. Since the existence of the IR study was not factored into my conclusions, its deficiencies did not alter my position, and I conclude that substantial evidence has been demonstrated.

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/s/

JANET WOODCOCK
08/11/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21164

MEETING MINUTES

Fabre-Kramer Pharmaceuticals, Inc.
Attention: Stephen J. Kramer, MD
Chief Executive Officer
5847 San Felipe
Suite 2000
Houston, TX 77057

Dear Dr. Kramer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gepirone hydrochloride extended-release tablets, 20 mg, 40 mg, 60 mg and 80 mg.

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2017. The purpose of the meeting was to discuss the status of several NDA related subjects with the Division of Psychiatry Products and reach agreement on necessary steps and contents of NDA amendment(s) required to be considered a Complete Response and accepted by the Division for review. Additionally, you requested confirmation that:

- the totality of the clinical trial data submitted to the NDA establishes substantial evidence that gepirone HCl ER is effective for the treatment of MDD, and
- the safe use of gepirone HCl ER in adults has been established.

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 Hiren Patel, Senior Regulatory Project Manager at (301) 796-2087.

Sincerely,
{See appended electronic signature page}

Mitchell V. Mathis, M.D.
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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Other

Meeting Date and Time: January 30, 2017 from 2:30pm to 4:00pm (EST)
Meeting Location: CDER WO Bldg. 22, Room 1313

Application Number: NDA 21164
Product Name: gepirone hydrochloride
Indication: Treatment of Major Depressive Disorder
Sponsor/Applicant Name: Fabre-Kramer Pharmaceuticals, Inc.

Meeting Chair: Dr. Tiffany Farchione

FDA ATTENDEES

Robert Temple, MD	Deputy Director (acting), Office of Drug Evaluation I (ODE I); Deputy Director for Clinical Science, CDER
Ellis Unger, MD	Director, ODE I
Tiffany Farchione, MD	Deputy Director, DPP
Paul David, RPh	Chief Regulatory Project Management Staff, DPP
Hiren Patel, PharmD	Senior Regulatory Project Manager, Team Leader, DPP
Javier Muniz, MD	Clinical Team Leader, DPP
David Millis, MD	Clinical Reviewer, DPP
Ikram Elayan, PhD	Nonclinical Supervisor, DPP
Violetta Klimek, PhD	Nonclinical Reviewer, DPP
Hao Zhu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Praveen Balimane, PhD	Clinical Pharmacology Reviewer, OCP
Wendy Wilson, PhD	Branch Chief, Office of Pharmaceutical Quality (OPQ)
David Claffey, PhD	CMC Lead, OPQ
Ta-Chen Wu, PhD	Biopharmaceutics Team Leader, OPQ
Mei Ou, PhD	Biopharmaceutics Reviewer, OPQ
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I
Jinglin Zhong, PhD	Biometrics Reviewer, Division of Biometrics I
Hari Sachs, MD	Team Leader, Division of Pediatric and Maternal Health (DPMH)
Yeruk Mulugeta, MD	Medical Officer, DPMH
Jacquline Yancy, PhD	Regulatory Project Manager, DPMH
Dhananjay D. Marathe, PhD	QT Interdisciplinary Review Team Lead

Lolita White, PharmD	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Loretta Holmes, PharmD	Reviewer, DMEPA

SPONSOR ATTENDEES

Stephen J. Kramer, MD	Chief Executive Officer
Edward H. Koehler, Jr., MBA	Executive Vice President
(b) (4)	CMC Consultant
(b) (4)	TQT Consultant
Anita H. Clayton, MD	Medical Advisor/Clinician
(b) (4)	Statistical Consultant
Steven M. Weisman, PhD	Clinical and Regulatory Consultant
(b) (4)	Regulatory Consultant

1.0 BACKGROUND

Gepirone hydrochloride extended release tablets (gepirone HCl ER) is a new molecular entity for the treatment of major depressive disorder (MDD). It is a member of the azapirone class and an analog of buspirone. Gepirone HCl ER is to be supplied as 20 mg, 40 mg, 60 mg, and 80 mg tablets. The recommended initial treatment is 20 mg daily, to be increased to 40 mg daily (b) (4) The maximum recommended dose is 80 mg daily.

The gepirone development program generated 12 short-term treatment trials and one maintenance trial. The FDA and the Sponsor have differed in their assessment of the results of the trials and in the relative weight that each of the trials should contribute to the overall evaluation of the efficacy of gepirone.

Gepirone was originally developed by Mead Johnson and Bristol-Myers Company for the treatment of both anxiety and depression. In 1992, a business decision by Bristol-Myers Squibb led to termination of the gepirone development program. In 1993, Fabre-Kramer acquired the rights to gepirone. In May 1998, Organon, Inc. executed an agreement with Fabre-Kramer, granting Organon rights to continued development and marketing of gepirone.
Organon submitted the original NDA for gepirone on October 1, 1999. The FDA issued a Refuse To File letter dated November 30, 1999. Organon resubmitted the NDA on May 18, 2001. The FDA issued a Not Approvable letter dated March 15, 2002, citing inadequate evidence of effectiveness. Organon resubmitted the NDA on December 23, 2003 and included additional data from the long-term maintenance trial. The FDA noted problems in the interpretation of the study data related to reclassification of relapsed subjects after unblinding and definition of the intent-to-treat population. The FDA issued a second Not Approvable letter to Organon, dated June 23, 2004.

In June 2005, all rights to develop and market gepirone were reacquired by Fabre-Kramer. On May 3, 2007, Fabre-Kramer resubmitted the NDA with 12 short-term trials and one maintenance trial as support for the efficacy of gepirone ER in the treatment of major depressive disorder. On October 19, 2007, the Division of Psychiatry Products (DPP) held a regulatory briefing with the

leadership of the Center for Drug Evaluation and Research (CDER) to discuss the resubmission. The CDER leadership agreed with DPP that the data submitted did not support the efficacy of gepirone ER. The FDA issued a third Not Approvable letter on November 2, 2007. This letter included discussion of several Chemistry Manufacturing and Controls (CMC) deficiencies that would also have to be addressed before gepirone ER could be considered for approval. Fabre-Kramer requested a face-to-face guidance meeting, which was held on January 14, 2008. The FDA restated that the data submitted did not provide sufficient evidence of efficacy for gepirone ER.

On May 2, 2011, the Sponsor submitted a request for reconsideration of the 2007 not approvable action. At a Type C meeting held on November 29, 2011, the FDA responded that the analysis of four short-term trials and the single maintenance trial remained controversial. The FDA suggested that the Sponsor provide additional justifications to support their argument for approval. The Sponsor submitted an NDA amendment in support of Informal Appeal on December 10, 2012. This submission included arguments for interpretation of results for each of the 12 short-term studies and the single maintenance study. On April 18, 2014, the FDA issued a General Advice Letter, stating that the short-term trials and the maintenance trial were considered negative. In weighing the two positive short-term trials against seven short-term trials and one maintenance trial that were considered negative, the FDA concluded that the Sponsor had not provided substantial evidence of the efficacy of gepirone ER.

On June 16, 2014, the Sponsor submitted a Formal Dispute Resolution Request appealing the November 2, 2007, Not Approvable letter and the April 18, 2014, General Advice letter. FDA met with the Sponsor on February 23, 2015. At this meeting, FDA suggested that an advisory committee meeting may be helpful in evaluating the evidence of efficacy for gepirone ER given the disagreement on the analysis of the short-term studies. In an Interim Response to the Appeal letter dated June 1, 2015, Dr. John Jenkins, Director of the Office of New Drugs (OND), expressed a need for additional input from an expert advisory committee before a decision could be rendered on the appeal. A Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting was held on December 1, 2015. The PDAC voted on three questions:

- 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)
- Has the sponsor adequately characterized the safety profile of gepirone ER in the treatment of MDD? (Yes 11, No 2)
- Do the available data support a favorable benefit risk profile of gepirone ER to support approval? (Yes 4, No 9)

On March 16, 2016, OND issued an Appeal Granted letter. However, the Deputy Director (Acting) of the Office of Drug Evaluation-I (ODE-I) appealed OND's decision to the CDER Director. On August 11, 2016, OND issued a General Advice letter stating that the CDER Director had completed her review of the appeal by ODE-I and would uphold OND's decision to grant the Sponsor's appeal.

The Appeal Granted letter from March 16, 2016 included a recommendation for a QT study to complete the NDA application. The Sponsor opines that a QT study should not be required given

the extent of safety information collected over the course of the gepirone clinical development program.

The Sponsor plans to submit data (b) (4) The Sponsor also is submitting (b) (4) Neither of these issues were addressed by the PDAC or in the dispute resolution process.

No additional adult subjects have received gepirone ER since the May 3, 2007 NDA Resubmission; therefore, there are no new clinical data.

The Sponsor has requested a pre-NDA meeting to review the status of several NDA-related issues, including previously unresolved CMC deficiencies, and to reach agreement on the steps that DPP will require to consider the NDA application complete and acceptable for review.

2. DISCUSSION

2.1. Chemistry, Manufacturing, and Controls (CMC)

Question 1: The following (see also Section 10.1.2.3) requested modification to the CMC section information addresses the first of the two points raised by the FDA in FDA's November 2007 Complete Response letter (dated November 2, 2007): Individual impurities at levels higher than the identification threshold of (b) (4)% will be identified by relative retention time.

Does the Division agree?

FDA Response to Question 1: *We recommend that individual impurities at levels higher than their identification threshold be identified by chemical name or other identifier (e.g.,* (b) (4)*, etc.). Identification by relative retention time (RRT) may be problematic in a lifecycle management perspective as the RRT values may change with updates to the analytical method. Note that impurities at levels above the identification threshold need to be structurally characterized. When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful efforts to identify it should be included in the application (refer to the ICH Q3B(R2) guideline).*

Discussion: *No further discussion.*

Question 2: The following (see also Section 10.1.2.4) requested modification to the CMC section information addresses the second of the two points raised in FDA's November 2007 Complete Response letter (dated November 2, 2007): Long-term and accelerated stability data will be provided for the commercial to-be-marketed drug product in each of the proposed packaging configurations (Reference: Oct 8 2007 communication to the FDA by Fabre-Kramer, Attachment 1: Post-Approval Stability Commitment and Protocol).

Does the Division agree?

FDA Response to Question 2: *We generally agree with your proposal to submit the requested drug product stability data. However, we do not agree with your proposal to submit stability data on one batch each of the highest, lowest and an intermediate strength – mainly due to the risk presented by the change in drug product manufacturing site. Further, the drug product manufacturing failures after NDA submission required* (b) (4) *that present additional risk to future product quality; data provided to support these changes were previously found to be "not sufficient." We note also that the proposed dosage form is an extended release product that is considered a higher risk product and no stability data have been provided on the final commercial tablet (shape, embossing, etc.) in the proposed commercial packaging. We also note that you previously indicated detection of possible stability issues during* (b) (4)*. The Complete Response submission should address these risks, as well as any other identified product risks with the potential to impact patient safety or product efficacy, quality, or performance, along with the mitigation strategies.*

Given the risks listed above, and given that the drug product strengths are not compositionally proportional, our expectation is that the NDA will include at least 12 months of long-term stability data and 6 months of accelerated stability data for three batches of drug product for each proposed strength. However, if adequate bridging – including, but not limited to comparison of formulation, commercial image, process conditions and equipment, and batch release results – is established between the (b) (4) *product and the* (b) (4) *product, we may consider a justified reduced stability testing design (refer to ICH Q1D). For a reduced stability testing design, we recommend, at a minimum, testing of at least three batches for the highest and lowest strengths and at least one batch each of the intermediate strengths. As tablet color is a critical quality attribute used to differentiate tablet strength, we recommend photostability testing for at least one batch of each tablet strength to evaluate potential fading of tablet color over the shelf life.*

Please note that because the NDA is not currently approved, a prior approval supplement, as noted in Section 10.1.2.2.5 of the meeting package, for CMC information is not appropriate. The SUPAC-MR document provides guidance specifically for post-approval changes; however, the general approach may be used to support the manufacturing site change proposed for the Complete Response submission if: 1) the aforementioned bridging is established; and 2) stability information from the (b) (4) *product batches is included in the submission and deemed sufficient and supportive. Please note that if bridging between the* (b) (4) *and* (b) (4) *products cannot be established or if the* (b) (4) *stability information is found to be not supportive, additional stability data for the* (b) (4) *product may be required to support approval. The drug product expiry assigned will be based on the quantity and quality of data provided in the Complete Response submission.*

Additional Comments:

- *Ensure that the current drug product specification and updated tests are included in the resubmission. Outline any differences from information provided in prior submissions.*

Justify any differences to the tests recommended in the ICH Q6A guideline (e.g., chloride content, microbial limits, polymorph, water content, etc.)

- *Note that we expect the drug product's name and strength will be expressed in terms of free base rather than the hydrochloride salt as per FDA Guidance: Naming of Drug Products Containing Salt Drug Substances.*

Discussion: *The Sponsor indicated that they generally concurred with the Agency recommendations and plan to submit drug product stability data on three batches of each strength. As each batch consists of approximately* (b) (4) *tablets, they asked if data on one full scale and two one-tenth scale batches of each strength would be acceptable. The Agency indicated that this would be an acceptable approach.*

The Sponsor asked whether six months rather than 12 months drug product stability data at time of submission would be acceptable. The Agency indicated that this may be an acceptable approach, but that this would likely limit the length of the drug product expiry period. The Agency encouraged the Sponsor to provide as much supportive drug product stability data as possible with detailed justification. The Sponsor indicated that they have 24 months stability data on the batches manufactured in 2006-2007 and that these batches were very similar to the proposed commercial product. The Agency indicated that these batches may not have been packaged in the commercial packaging configuration. The Sponsor stated that they would provide full details in the resubmission.

The Sponsor asked whether the real-time appearance data from the stability studies would fulfill the request for photostability studies. The Agency indicated that this was an acceptable approach but that data from accelerated studies such as those described in ICH Q1B are also recommended.

Post meeting note: Although the stability data from the final commercial product will carry the most weight in determining the expiry period, we will consider data from supportive batches if they are fully justified, including providing a detailed tabular listing of all CMC differences to the final commercial product, including packaging. As the previous submissions were paper-based, they may not be readily available to the reviewers; therefore, we encourage you to include all supportive stability data tables, even if they were previously submitted.

Question 3: With regard to current CMC requirements for an NDA, the 20, 40, 60 and 80 mg gepirone HCl ER tablets can be approved, pending demonstration of satisfactory test results for batches prepared at the new product manufacturing site, (b) (4) (see Section 10.1.2.2.1 and reference e-mails between Martin Lobel and Hiren Patel, dated June 20 - July 3, 2012 in Appendix 1).

Does the Division agree?

FDA Response to Question 3: *In addition to the test results, we request that you provide all relevant CMC information on the proposed new commercial manufacturing site, manufacturing process and controls to allow its complete evaluation. We also request a tabular list of all CMC changes since initial submission of the NDA and since the previous action.*

Discussion: *No further discussion.*

Question 4: Bioequivalence analysis data were sufficiently in agreement to justify concluding that there are no meaningful differences between the products manufactured by (b) (4) and Bristol-Myers Squibb. Additionally, the in vitro dissolution data and in vivo percent absorbed data are sufficiently in agreement to justify concluding that there is a direct correlation between the in vitro dissolution and the in vivo bioavailability of gepirone HCl ER tablets. (Reference: Report on Protocol FK-GBE-001: "Bioequivalence of Bristol-Myers Squibb Gepirone 20 mg ER Tablets and Fabre-Kramer Pharmaceuticals, Inc. Gepirone 20 mg MR Tablets ((b) (4)) in NDA 21-164, dated May 1, 2001)").

Given that FDA has previously accepted the in vitro/ in vivo correlation established in Study FK-GBE-001, does the Division agree the bioequivalence study requirement of the SUPAC-MR Guidance for a Level 3 manufacturing site change can be waived?

FDA Response to Question 4: *We disagree with your request to waive the BE study requirement for the Level 3 manufacturing site and process change. Study FK-GBE-001 provided the bridging for only the lowest 20 mg strength of gepirone ER tablets manufactured by (b) (4) to the Bristol-Myers Squibb (BMS) site, but not to the new (b) (4) site. The in vitro/in vivo correlation (IVIVC) (b) (4) Per FDA guidance recommendation, a minimum of two or more formulations with different release rates for each of the proposed strength should be developed for a valid IVIVC model to support a biowaiver for the manufacturing site change.*

You will need to demonstrate PK bridging between the to-be-marketed product and the product used in the past successful efficacy studies. Given that the old product might not be available at this time for an in vivo BE study, you can proceed with establishing BE of the to-be-marketed product to the historical PK results for the old product. In addition, given that the different strengths of the product are not compositionally proportional, you should establish BE for both the lowest planned strength (20 mg) and the highest planned strength (80 mg). You should also consider conducting a strength proportionality study across the 20 mg to 80 mg range for the to-be-marketed product, if such information does not exist for the old product.

You should provide the comparative dissolution results for the 20 mg strength manufactured by (b) (4) and by (b) (4) sites (i.e., the only available bridging between these two sites) and generate the complete comparative dissolution data for all strengths of your proposed drug products manufactured by the new site in the future NDA submission. The acceptability of the proposed dissolution acceptance criteria for your proposed ER drug products will be determined during the NDA review. With regard to the dissolution information (including the dissolution method

development and the proposed acceptance criteria) that should be provided in your NDA for review, please refer to the general advice comments that we provide under Additional Biopharmaceutics Comments.

Discussion: *No further discussion.*

Question 5: Because some of the API Release specifications are no longer consistent with current ICH Guidelines, the CMO has proposed revising the gepirone HCl release specifications (summarized in Section 10.1.1.3, Table 3).

None of these changes are expected to affect API Quality. All changes would become effective for the next batches of gepirone HCl, except for the proposed change in the (b) (4) will also be accepted, to be implemented following process revalidation.

Does the Division agree these changes are acceptable?

FDA Response to Question 5: *Your approach appears to be reasonable. Ensure that in the NDA, adequate information is provided to justify the elimination of the heavy metals test per ICH Q3D risk assessment.*
We also note that you will be referencing DMF (b) (4) for drug substance information. Work with the DMF holder to ensure that the DMF is current, and provide an update to the DMF summarizing all the changes made over the years in tabular format.

Discussion: *Time did not allow further discussion at the meeting; however, the Sponsor included the following request for clarification in a 30 JAN 2017 email:*

> *Please clarify that the expectation to "provide an update to the DMF summarizing all the changes made over the years in tabular format" is to be done by the DMF holder in the DMF (b) (4) update, not included in Fabre-Kramer's future NDA Amendment. It is unlikely the DMF holder would provide this information to Fabre-Kramer for inclusion in their NDA Amendment.*

Postmeeting FDA Response: *Our intention was for this update to be included in the DMF, not the NDA.*

2.2. Clinical

Question 6: Based on the APPEAL GRANTED letter, dated March 16, 2016, and the GENERAL ADVICE letter, dated August 11, 2016, both issued by Dr. John Jenkins, Director of the Office of New Drugs, the Sponsor requests confirmation that the totality of the clinical trial data submitted to the NDA establishes substantial evidence that gepirone HCl ER is effective for the treatment of MDD, and there is no need to submit additional evidence to satisfy the regulatory standard for efficacy for an antidepressant. Further, the Sponsor requests confirmation

that, since there have been no safety issues raised since 2004, that gepirone HCl ER has been determined to be safe for the treatment of adults with MDD.

Would the Division confirm?

FDA Response to Question 6: *The Appeal Granted letter indicates that the Director of the Office of New Drugs has concluded that Fabre-Kramer has provided data to support a finding of substantial evidence of effectiveness for gepirone in the short-term treatment of MDD. The Division of Psychiatry Products will abide by this conclusion and will not require the submission of additional evidence to support the efficacy of gepirone. Regarding issues of safety, please see our response to Question 7.*

> ***Discussion:*** *We clarified that we have no new safety concerns to present at this time, but that the upcoming NDA review will include a safety review of the available data. Question 7 is referenced here because the need for a QTc study is a safety issue that has been discussed in previous communications and that still requires resolution.*

Question 7: Per the APPEAL GRANTED letter, dated March 16, 2016, a Thorough QT study was suggested for completeness of the NDA under current regulatory standards. The Sponsor believes the issues addressed in such a study have been adequately explored in the clinical program and that sufficient information exists in the collected clinical data to eliminate any material concern of QT prolongation with gepirone HCl ER treatment. Therefore, a Thorough QT study is not needed. Additionally, FDA verified this position to the Sponsor on two occasions prior to the submission of the 2007 NDA. The background and data supporting the Sponsor's position is included in Section 10.2.1.

Does the Division agree?

FDA Response to Question 7: *Because of problems with data quality, assessment schedule, and lack of appropriate controls, the QTc data collected in the course of the gepirone clinical program are insufficient. Based on the anticipated benefit-risk profile of the drug, we will require a thorough QT study to exclude small mean QTc effects (10 ms) in accordance with the ICH E14 guideline.*

The data presented in the current submission have the following deficiencies:

- (b) (4)
-
-

- (b) (4)
-

For these reasons, we will require a thorough QTc study in order for the NDA application to be considered complete.

> ***Discussion:*** *The Sponsor asserted their belief that the existing QT assessment may be sufficient to file the NDA and requested that the TQT study could be done as a post-marketing study. The Agency stated that there were several deficiencies in the existing QT assessment including* (b) (4) *Further, the Agency stated that, given the drug has considerable drug-drug interaction potential, the lack of assessment at sufficiently higher exposures is a concern. The TQT study must be conducted prior to approval.*

Question 8: As there have been no additional adult subjects who have received gepirone HCl ER since the 2007 NDA Amendment, there is no new clinical safety data and no need for a Safety Update to the NDA.

Does the Division agree?

FDA Response to Question 8: *We agree that a Safety Update to the NDA will not be required, given that there has been no additional exposure of adult subjects to gepirone since the 2007 NDA Amendment. It will be important to conduct a rational safety analysis based on standard MedDRA queries – combinations of adverse event preferred terms that are essentially the same or pathophysiologically related. We'll be glad to discuss this further at the meeting.*

> ***Discussion:*** *The Division noted that Standard MedDRA Queries (SMQs) may reveal previously unrecognized adverse event patterns. This type of analysis will be part of the NDA safety review.*

Question 9: The Sponsor plans to submit, as part of the NDA Amendment, data and analyses of the sexual functioning characteristics of gepirone HCl ER consistent with FDA recommendations presented in the August 2015 J. Clin. Psychiatry article by Khin et al. (b) (4) (b) (4) (see also Q14). Background information and a table summarizing the gepirone HCl ER Phase III clinical trials that assessed sexual function in depressed patients, including the parameters and scales utilized in each, is provided in Section 10.2.2. We request

that the Division review these data (b) (4) as part of its review of the NDA Amendment.

Does the Division agree to review this data (b) (4)?

FDA Response to Question 9: *Yes, we will review this data* (b) (4) *as part of our review of the NDA Amendment.*

We reviewed the sexual dysfunction data included in your May, 2007, and December, 2012, submissions while preparing for the Advisory Committee meeting held on December 1, 2015, but (b) (4) *, these data were not discussed at the meeting* (b) (4)

In general, we note there would be two requirements for a study to demonstrate the lack of an adverse effect on sexual function. It would be critical: 1) to show that the drug, as administered in the study, is active, i.e., effective for the treatment of depression. This would require a clear demonstration of efficacy in the study. 2) to establish that the study has assay sensitivity. This would require the use of a positive control drug (an antidepressant that is thought to cause sexual dysfunction), where, in the same study, the known positive drug causes sexual dysfunction and gepirone does not.

In terms of the data submitted to date, we note the large amount of missing data and missing item scores. In two of the short-term studies there was only one post-baseline assessment. The design of the three extension studies does not appear to be appropriate for assessing incidence of adverse reactions (such as sexual dysfunction) because the population in these studies is enriched for individuals who have tolerated the drug. If you plan to re-submit the data and post-hoc analysis results, below are a few suggestions.

(1) Provide complete SAS programs that generated derived variables from raw variables and that produced analysis results along with detailed documentations that can be executed with minimum re-programming by the FDA.
(2) Provide a rationale for use of the DISF and DISF-SR scales, including any available information on validity, reliability, and ability to detect change.
(3) Missing data related to dropout may be associated with the unobserved sexual function measurements. You will need to justify the robustness of the analysis results.

(b) (4)

(b) (4)

Question 10: The Sponsor presents herein a re-assessment of previously submitted data (b) (4) for efficacy of gepirone HCl ER in long-term treatment of major depression and intends to include this in the NDA Amendment (b) (4) The background, analysis and data supporting the Sponsor's position are included in Section 10.2.3.

Does the Division agree?

FDA Response to Question 10: *We will review your re-assessment of the data on long-term efficacy of gepirone as part of our review of the NDA Amendment. We previously reviewed this study while preparing for the Advisory Committee meeting. If you plan to re-submit the data and post-hoc analysis results, please provide complete SAS programs along with detailed documentation. Note that post-hoc analyses pose significant problems that will need to be addressed.*

Discussion: *The Sponsor presented a rationale for reassessing gepirone's performance in the long-term maintenance study as positive. The discussion was based on several factors, including a reassessment of decisions made regarding exclusion of some patients from the original analysis, and a reconsideration of the criteria used to classify patients as being in remission. We reiterated our general concerns about post hoc analyses. We will not decline to review the post hoc analysis of the maintenance study; however, we will require a very convincing justification for us to accept the results of the post hoc analysis.*

2.3. Regulatory

Question 11: Fabre-Kramer intends to update the NDA with one or more eCTD-NDA Amendments, as determined by the Division's responses to the CMC and Clinical questions and further discussion (as needed).

Does the Division agree with this submission mechanism?

FDA Response to Question 11: *Yes. However, protocols should be submitted to the IND for review including for the Thorough QT study; therefore, you will be required to reactivate the IND.*

Discussion: *No further discussion.*

Question 12: The Sponsor submitted complete documentation for the proposed tradename TRAVIVO™ in 2006 to IND 033626 (see Appendix 4: Cover Letter and FORM FDA 1571 for Serial No. 173, dated November 13, 2006) and has not received any response.

Please provide instruction on how to proceed to receive approval of the proposed tradename.

FDA Response to Question 12: *Given the amount of time that has elapsed since your previous request for review of the proposed proprietary name, Travivo, we request that you resubmit the name for review. If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following the FDA Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names.*

> ***Discussion:*** *The Sponsor stated there was a name submitted for review in 2006; however, they did not receive notification on the conditional acceptability of the proposed name. The Agency acknowledged that a proprietary name review of Travivo was completed in 2007 and the name was found acceptable at that time. However, in 2007 there was no required notification process on the conditional acceptability of the proposed name if the application was not approved. The Sponsor asked if the 2007 conditional acceptability of the name could be included in the meeting minutes for the name Travivo. The Agency agreed; however, we requested that the Sponsor resubmit a request for proprietary name review for the name Travivo when the NDA is resubmitted. The Sponsor was referred to the Guidance which contains the information needed in regards to resubmitting a proposed proprietary name.*

Question 13: The Sponsor does not believe there will be any Phase 4 requirements after Division review of the Complete Response (NDA Amendment) and approval of NDA 21-164.

Does the Division agree?

FDA Response to Question 13: *This will be determined in the course of our review of the NDA Amendment.*

> ***Discussion:*** *No further discussion.*

Question 14: The Sponsor will include proposed labeling in PLR format in the NDA Amendment, (b) (4)

Is this acceptable to the Division?

FDA Response to Question 14*: We will review the material included in the application to support the proposed labeling.* (b) (4)

> ***Discussion:*** *No further discussion.*

Question 15: A summary of the history and status of the Pediatric Written Request (PWR) and listing of the completed pediatric studies is presented in Section 10.3.1. As is presented and discussed, FDA and the Sponsor had reached agreement regarding extending the time to submit the pediatric study results to the IND, but final documentation of this agreement was not completed prior to the issuance of another PWR. The Sponsor believes that the pediatric studies completed and submitted to associated IND 033626 are sufficient to comply with the extension agreement and the existing Pediatric Written Request and that the only requirement is to submit these pediatric study reports to the NDA post-approval.

Does the Division agree?

FDA Response to Question 15: *No, we do not agree that you should submit the pediatric study reports to the NDA post approval.*

We note that the Written Request issued in 2007 has expired and no Written Request is in effect at this time. Furthermore, there are no existing patents or exclusivities for which we could issue a new Written Request. The data obtained from studies conducted under the written requests must be submitted with the NDA Amendment for review by the Division.

> ***Discussion:*** *The Division deferred discussion of this item so that we could seek additional guidance within the Agency.*
>
> ***Postmeeting DPMH Response:*** *The Division will not issue a new Written Request for these completed pediatric studies as they are not in alignment with what the Division would require for this indication. Therefore, the completed studies would not offer a potential for a public health benefit in pediatric patients. The Sponsor should submit their completed studies with their NDA resubmission.*

Question 16: Are there any other issues that need to be addressed and included in a Complete Response (NDA Amendment) in order for the Division to be able to complete the review of this application?

FDA Response to Question 16:

Clinical Pharmacology:

- *Although you have conducted comprehensive metabolism-based drug interaction studies, transporters can also have important effects on PK and drug exposure. According to our most recent drug interaction guidance, we recommend that you conduct in vitro transporter studies to determine if gepirone is a substrate, inhibitor, or inducer of major transporters. In addition, assess the inhibition potential for transporters by any major circulating metabolite(s).*
- *Conduct a food-effect study using the highest strength of the final to-be-marketed formulation of the product.*
- *Conduct in vitro alcohol dose-dumping study.*
- *Conduct an in vivo study or PBPK analysis to assess the effect of moderate CYP inhibitors and moderate CYP inducers on the PK of gepirone.*

- *Because the prevalence of depression in patients with severe hepatic impairment is high, plan to conduct a PK study in subjects with severe hepatic impairment to enable identifying the right dose and labelling instructions for such patients.*

Biopharmaceutics:
We have the following general advice regarding the dissolution information that should be provided in your NDA submission:

I. Dissolution Method: *Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution development report should include the following information:*

a. Solubility data for the drug substance over the physiologic pH range;
b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable and sampling time points of 10, 15, 20, 30, 45 60, 90 and 120 min;
c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);
d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables);
e. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.);
f. A list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution;

II. Dissolution Acceptance Criterion: *For the selection of the dissolution acceptance criterion (a) of your product, the following points should be considered:*

a. The dissolution profile data (i.e., 15, 20, 30, 45, and 60 min) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) should be used for setting the dissolution acceptance criterion (a) of your product.
b. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution occurs.

c. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).
d. The selection of the specification time point should be where Q= (b) (4) % dissolution occurs.
e. A detailed discussion of the justification of the proposed dissolution acceptance criterion should be included in the appropriate section of the CTD.

III. Data Presentation: *In the dissolution method development report, present detailed experimental data as follows:*

a. Include individual vessel data as much as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
b. In addition to the mean dissolution data presented in graphical and tabular formats in the dissolution development report, submit all individual vessel dissolution data for the clinical and registration/stability batches in ".xpt" format.
c. Batch release and stability dissolution data should be presented graphically; the plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review process based on the totality of the provided dissolution data.

IV. Alcohol-Induced Dose Dumping: *The consumption of alcoholic beverages may affect the release of a drug substance from an MR formulation. The formulation may lose its MR characteristics, leading to more rapid drug release and altered systemic exposure. This more rapid drug release may have deleterious effects on the drug's safety and/or efficacy.*

In vitro assessments of the drug release from the drug product using media with various alcohol concentrations should be conducted on the lowest and highest strengths of the MR drug product. The following points should be considered during the evaluation of the in vitro alcohol-induced dose dumping of MR drug products:

a. Dissolution testing should be conducted using the optimal apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
b. The following alcohol concentrations are recommended for the in vitro dissolution studies: 0 %, 5 %, 10 %, 20 %, and 40 %.
c. The general considerations for the media selection are as follows:

i. ***If the optimal dissolution medium is 0.1N HCl****: dissolution profiles in 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.*
ii. ***If the optimal dissolution medium is NOT 0.1N HCl****: dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.*
iii. ***If the optimal dissolution medium has not been identified****: dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (i.e. pH 1.2, 4.5, and 6.8) are recommended.*
iv. ***If the dissolution of the MR product is pH-independent****: dissolution data in 0.1N HCl with the above range of alcohol concentrations are sufficient.*
v. ***For a delayed-release (enteric coated) product,*** *dissolution data in 0.1N HCl with the above range of alcohol concentrations are sufficient.*

d. The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
e. The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
f. The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol-induced dose dumping study should be provided to FDA for review and comment.

Discussion: *No further discussion.*

Post-meeting Comment

Controlled Substance Staff
Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft Guidance for Industry: Assessment of Abuse Potential of Drugs.

You should follow the recommendations in the above guidance document and compile and submit the appropriate studies that would comprise your abuse potential assessment.

3.0 OTHER

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the

Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request 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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
03/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21164

APPEAL GRANTED

Fabre-Kramer Pharmaceutical
Attention: Stephen J. Kramer, CEO
5847 San Felipe
Suite 2000
Houston, TX 77057

Dear Dr. Kramer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gepirone hydrochloride extended release tablets (gepirone ER or gepirone).

I also refer to the following:

- Your June 13, 2014, request for formal dispute resolution (FDRR) appealing the November 2, 2007, Not Approvable (NA) letter and the April 18, 2014, General Advice letter in which the Office of Drug Evaluation I (ODE I) concluded that Fabre-Kramer had not demonstrated substantial evidence of gepirone ER's effectiveness in the treatment of major depressive disorder (MDD).
- The June 30, 2014, Dispute Not Accepted letter stating that the June 13, 2014, request for formal dispute resolution was not accepted because it contained new information/re-analysis of previously submitted information, that was not previously reviewed by the original deciding authority. The Dispute Not Accepted letter stated that Fabre-Kramer could appeal the November 2, 2007, NA letter and the re-analysis submitted after the NA action would not be considered as part of the appeal. The Dispute Not Accepted letter also offered Fabre-Kramer an advisory committee (AC) meeting to discuss the clinical issues and the re-analysis submitted after the NA action.
- Your November 12, 2014, letter to Elizabeth Dickinson, J.D., Chief Counsel, FDA, in which you requested that the Office of New Drugs (OND) accept Fabre-Kramer's formal dispute resolution request submitted on June 13, 2014, regarding the November 2, 2007, NA letter and the April 18, 2014, General Advice letter from ODE I.
- The January 27, 2015, Acknowledgement and Meeting Granted letter stating that your request for formal dispute resolution, dated June 13, 2014, was accepted, and that the FDA receipt date for the request for formal dispute resolution was January 27, 2015.
- The meeting between FDA and Fabre Kramer held on February 23, 2015.
- Your March 6, 2015, letter providing follow-up information on issues that were raised at the February 23, 2015, meeting between the FDA and Fabre-Kramer.
- The March 18, 2015, Interim Response letter stating that I required discussion with internal FDA experts, prior to reaching a final decision on the appeal. I requested that Lisa LaVange, Ph.D., Director, Office of Biostatistics (OB), Center for Drug Evaluation

and Research (CDER), and her staff re-review the available data from the twelve short-term trials and the one long-term maintenance trial.

- Your March 26, 2015, letter, received on March 31, 2015, in which you raised several points regarding the consultation to Dr. LaVange and her staff, and provided a comment to the minutes from the February 23, 2015, meeting between the FDA and Fabre-Kramer.
- The April 7, 2015, General Advice letter in response to your March 26, 2015, letter.
- The June 1, 2015, Interim Response letter stating that I required additional input from an expert advisory committee (AC) prior to reaching a final decision on the appeal.
- Your July 7, 2015, letter, received on July 8, 2015, in which you raised several issues in response to the Interim Response letter dated June 1, 2015.
- The July 24, 2015, email in response to your July 7, 2015, letter.
- The December 1, 2015, Psychopharmacological Drug Advisory Committee (PDAC) meeting.
- The December 10, 2015, Interim Response letter providing Fabre-Kramer and FDA staff an opportunity to provide brief response/comments pursuant to the AC proceedings and discussions for my consideration.
- Your December 31, 2015, correspondence in response to the December 10, 2015, Interim Response letter.
- The January 10, 2016, Interim Response letter providing CDER staff an opportunity to provide a response to your December 31, 2015, correspondence.
- The March 2, 2016, teleconference between myself and Fabre-Kramer in which I communicated my decision on your appeal and stated that I would provide a final written response to the appeal no later than March 16, 2016.

I have carefully reviewed the materials you submitted in support of your appeal, as well as reviews, meeting minutes, and decision memoranda prepared by FDA, the NA letter and other pertinent material (e.g. material and transcripts from the December 1, 2015, PDAC meeting). I have also consulted with staff in the Division of Psychiatry Products, ODE I, Office of Biostatistics, Robert Temple, M.D., Acting Deputy Director, ODE I, and Lisa LaVange, Ph.D., Director, Office of Biostatistics.

I have completed my review of your request for formal dispute resolution and grant your appeal. I describe below the basis for my decision and the path forward.

Your dispute with Division of Psychiatry Products (DPP) and ODEI over the approvability of gepirone for treatment of major depressive disorder (MDD) raises complex scientific and regulatory issues. At its core this dispute relates to FDA's interpretation and application of the statutory standard for demonstration of "substantial evidence of effectiveness." Substantial evidence of effectiveness is defined in section 505(d) of the Food Drug and Cosmetic Act (FDCA) as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed

labeling thereof."[1] FDA's longstanding interpretation of the statutory language, as documented in our 1998 "Effectiveness Guidance," has been "that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."[2]

The FDCA and the Effectiveness Guidance are silent on how FDA should approach a case like that presented by the gepirone NDA; i.e., where both the sponsor and DPP/ODEI agree that two positive adequate and well-controlled trials exist supporting the efficacy of gepirone in the short-term treatment of patients with MDD but a significant number of other trials, variously categorized by the sponsor or the review team as "failed" or "negative," raise doubts about whether substantial evidence of effectiveness has been provided. Stated another way, DPP/ODEI have raised concerns that the two positive trials could have occurred by chance (i.e., may be false positives).

Studies FK-GBE-007 and ORG134001 were strongly positive on the pre-specified primary endpoint of HAMD-17 (p=0.018 and 0.013, respectively) and many secondary endpoints. The drug effect was observed early and persisted to week 8 in both trials. The effect size of the drug-placebo difference was of a similar magnitude to that generally seen for approved drugs in MDD. These adequate and well-controlled trials provide the evidence that is normally expected to support a demonstration of substantial evidence of effectiveness.

In contrast, Studies FK-BDE-008 and ORG134002, which were conducted using identical protocols to Studies 007 and 001, respectively, did not reach statistical significance. Both trials numerically favored gepirone over placebo on the primary endpoint and in the case of Study 008 there was a trend (p=0.2). There were 8 other non-positive short-term treatment trials that variably numerically favored gepirone over placebo, numerically favored placebo over gepirone, or were neutral. Four of these trials were stopped early by a prior sponsor for business reasons and therefore did not achieve their pre-planned sample size and statistical power.

Study ORG28709, a maintenance trial of gepirone in MDD, was not positive, but did show a numerical advantage of gepirone over placebo. A positive maintenance trial is not required by DPP to support approval for short-term treatment of MDD, and Fabre-Kramer is not seeking a maintenance indication for gepirone at this time.[3] While a positive maintenance trial would have provided additional support for the efficacy of gepirone in treatment of MDD, a negative maintenance trial does not prove that gepirone does not work for this indication.

Prior to development of the ER formulation of gepirone, a number of short-term treatment trials were conducted with an immediate-release (IR) formulation of gepirone. Fabre-Kramer and DPP/ODEI agree that one of these trials was positive in patients with MDD. Many of the IR

[1] 21 USC 355(d)
[2] See http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8
[3] DPP approved another drug, milnacipran, in July 2013 for short-term treatment of MDD even through the NDA included a negative maintenance trial.

trials used a lower total daily dose than was used in the two positive ER trials, and the IR formulation was poorly tolerated by many patients.

As noted above, the main issue in dispute between Fabre-Kramer and DPP/ODEI has been related to whether the non-positive short-term treatment (10) and maintenance (1) trials of the ER formulation create sufficient doubt about the true effect of gepirone to support a conclusion that substantial evidence of effectiveness has not been demonstrated. I have been unable to identify FDA policy statements or guidance for how to consider such a case, though FDA has approved other drugs where there were both positive and non-positive trials.

DPP/ODEI approached this situation by categorizing the ER trials as positive, negative, or failed. Positive trials were those where gepirone beat placebo, negative trials were those where gepirone failed to beat placebo and the trial was considered to have assay sensitivity, or assay sensitivity could not be determined due to the design of the trial (i.e., no active control), or failed if both gepirone and the active control failed to beat placebo. Based on this categorization DPP/ODEI calculated the probability of observing 2 false positive trials in the development program. There has been much debate between Fabre-Kramer and DPP/ODEI on which trials should be included in this "counting" analysis. DPP/ODEI also conducted a meta-analysis of the non-positive short-term treatment trials to see if they provided "supportive evidence" of the efficacy of gepirone. DPP/ODEI concluded based on the counting analysis that the probability that the two positive trials were false positives was unacceptable and that the meta-analysis of the non-positive trials provided no evidence to support the efficacy of gepirone.

I do not consider assay sensitivity of a trial to be a dichotomous variable; i.e., it is not simply yes or no, but rather a continuum. Assigning a yes or no metric to assay sensitivity fails to fully utilize all available information from a trial and can lead to misleading conclusions; for example when a p value falls slightly above or below a threshold value. I believe the performance of the active control can help to judge the results of an individual trial, and may be useful in the drug development context to understanding trial design, conduct, and outcomes, but I do not find it a particularly useful tool for characterizing trials when synthesizing data across a program.

I also believe that "counting" trials as positive, negative, or failed in assessing the overall evidence from a development program is an inefficient method for understanding the available data on the effect of the drug. To my knowledge, FDA has not developed policy or guidance on how such analyses should be conducted and interpreted. The counting approach is a form of meta-analysis that assesses the global null hypothesis; i.e., that the treatment effect was zero in all trials. The result of the analysis can provide the probability that, for example, there would be 2 or more false positives out of "n" trials. For example, the probability of 2 false positive trials out of 2 trials conducted is 0.000625 (p=0.025 X 0.025). DPP/ODEI concluded that the probability of 2 false positives in a counting analysis of the adequate and well-controlled trials for gepirone should be close to this extremely low value. Again, FDA has not articulated policy or guidance on such analyses. In the worst case for gepirone (2 positive out of 13 trials, including the 12 short-term treatment trials and the maintenance trial) the probability of two false positives is approximately 4%. The probability of 2 false positive trials out of 8 total trials (eliminating the trials stopped early for business reasons and the maintenance trial) using the same analysis procedures gives an estimate of approximately 2%. Given the inherent limitations

of the counting trials approach, I find it problematic for this analysis to serve as the primary basis for determining whether substantial evidence has been demonstrated for the gepirone NDA. I note, however, that even this "conservative" analysis methodology suggests a low probability that the two positive adequate and well-controlled trials occurred by chance; i.e., were false positives.

I see value in assessing all the available data for gepirone in determining whether substantial evidence of effectiveness has been provided. One approach is to utilize a meta-analysis as a sensitivity analysis.[4] A sensitivity meta-analysis is different from the meta-analysis conducted by DPP/ODEI, which was designed to assess whether the other trials provided supportive evidence.[5] The meta-analyses presented by Dr. Gary Koch, an advisor to Fabre-Kramer, at the advisory committee meeting were informative in assessing the strength of evidence from the two positive trials. The analyses presented by Dr. Koch tested how the findings from the two positive trials held up when diluted by the results from the non-positive trials. Each of the sequential meta-analyses showed that the likelihood the positive findings for gepirone were due to chance was low. As expected, the drug effect size was diminished as more non-positive trials were added. An analysis that included all 12 short-term treatment trials and all patients had a nominal p value of 0.09. If only the patients with a baseline HAMD-17 of $\geq$20, which is a common entry criterion in MDD trials, were included, the nominal p value was 0.021. This meta-analysis, which makes better use of the available data than the counting trials approach, also suggests the likelihood the two positive trials were false positives is low.

Based on their analyses, DPP/ODEI expressed concern that gepirone was numerically inferior to placebo in 3 of the 12 trials, and that in 4 of the 5 active-controlled trials gepirone was numerically inferior to the active control.[6] In my view, these observations must be interpreted with caution. In the 3 trials where gepirone was numerically inferior to placebo the magnitude of the difference was small and not statistically significant by either the pre-specified primary analysis or the post hoc analyses conducted by DPP/ODEI. For the active-control trials, 2 of the 5 trials were stopped early for business reasons, which limit their interpretation. Further, 3 of the 5 active-controlled trials recruited a different patient population (i.e., atypical depression) and the active control in these trials did not demonstrate superiority to placebo on the pre-specified analyses[7]. In my view, these analyses do not support a solid conclusion that gepirone is inferior to the active controls.

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[4] Note: FDA does not accept meta-analyses as the primary basis for demonstration of substantial evidence of effectiveness. In the case of gepirone, where there are two positive adequate and well-controlled trials, meta-analysis procedures may be a useful to understand the strength of evidence provided by the two positive trials.

[5] The Effectiveness Guidance describes the role of supportive evidence in the context of determining substantial evidence of effectiveness in the case of a development program where there is only one positive adequate and well controlled trial.

[6] DPP/ODEI also concluded that the active control was superior to gepirone in three trials based on post hoc analyses that changed the pre-specified primary endpoint. In these three trials, neither gepirone nor the active control beat placebo on the pre-specified endpoint and analysis procedure. I consider these post hoc analyses to be hypothesis generating.

[7] The active control in trial CN105-053 was superior to placebo for the pre-specified primary endpoint when a corrected analysis was conducted. In this trial the point estimate for the effect of gepirone versus placebo was -2.0, an effect size not that different from the effect seen in Studies 007 and 001, and may have reached statistical significance if the trial had been completed.

Even if we were to conclude that gepirone is inferior to one or more active control, that would not necessarily preclude approval with appropriate labeling. FDA does not have a comparative effectiveness standard for approval; though we do consider such data in our decision making in some cases. There are currently 18 FDA-approved anti-depressants and we do not have a clear understanding of their comparative effectiveness. In my view, it is highly unlikely that the 18 approved drugs are truly equally effective and this means that some are likely to be less effective than others. We also expect that not every approved drug will work equally well in every patient, so all things being equal there is value in providing prescribers and patients with a wide range of effective options for use in clinical practice.[8]

After considering all the data and analyses I conclude that Fabre-Kramer has provided data to support a finding of substantial evidence of effectiveness for gepirone in the short-term treatment of MDD. This conclusion is primarily based on the two positive adequate and well-controlled trials for the proposed ER formulation, with additional evidence that gepirone is an effective anti-depressant provided by the positive trial of the IR formulation. It is not uncommon for effective anti-depressants to fail to beat placebo in adequate and well-controlled trials. An analysis presented by Dr. Mitchell Mathis, Director of DPP, at the advisory committee meeting showed that this happens on average 50% of the time for the approved anti-depressants. While it is true that the gepirone NDA has more non-positive trials than positive trials, some of the non-positive trials would be "expected" based on our historical experience, and other trials were terminated early for business reasons, which limited their interpretability. I do not agree with DPP/ODEI's conclusion that the probability the two positive trials were false positives is unacceptably high. I conclude the probability the two trials were false positives is low and these trials provide substantial evidence of effectiveness. Therefore, your appeal is granted.

As to the path forward for resubmission of the NDA, I have considered the application more broadly than just the issue (substantial evidence) you raised in your appeal. This is consistent with how I approach all appeals; i.e., I don't limit my review to the issue in dispute between the sponsor and the ODE since I sometimes uncover other aspects of the case that merit my attention. In the current case, I believe you should conduct and submit a thorough QT study of gepirone consistent with ICH E14 recommendations and in consultation with DPP and the Division of Cardiovascular and Renal Products (DCRP). This study will fill an important safety gap for gepirone and is consistent with expectations for chronically administered drugs seeking approval based on current regulatory expectations. You will also need to develop a plan for linking your to-be-marketed drug product to the clinical trial material used in Studies 007 and 001. Finally, you will need to address the other deficiencies noted in the 2007 NA letter as well as other applicable standards for drug approval in today's environment (e.g., labeling format and content, cGMP status). The list provided above is not intended to be exhaustive or all-inclusive of the issues you will need to address before a resubmitted application will be accepted by DPP for review. I strongly urge you to request a Type B pre-submission meeting with DPP to allow a more comprehensive discussion of the requirements for resubmission of the NDA.

During our teleconference on March 2, 2016, you have expressed concerns that any resubmission of your application will be decided by the same signatory authority that previously denied

[8] My decision on this appeal does not address specific labeling statements that may be appropriate to include in the prescribing information should the gepirone NDA subsequently be approved.

approval. I can assure you that any resubmission will be reviewed fairly by DPP and ODEI without prejudice based on your decision to pursue this appeal.

Finally, while I have granted your appeal my decision is under further review within CDER and is therefore effectively "stayed" from implementation. Dr. Temple has chosen to exercise his rights under CDER MaPP 4151.1 "Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain"[9] to appeal my decision to Dr. Woodcock, Director of CDER. This appeal will be managed by Virginia Behr, the CDER Ombudsman, not through the Formal Dispute Resolution Project Manager. Ms. Behr can be reached at Virginia.Behr@fda.hhs.gov or at (301) 796-3436. Dr. Woodcock has asked that she receive all materials relevant to her review by no later than April 1, 2016. This will include Dr. Temple's dispute statement, this letter, my review discussion points, the AC transcript and materials, relevant submissions from Fabre-Kramer, DPP and ODEI reviews, and other appropriate materials. The procedures under MaPP 4151.1 do not provide for input from an external party. I direct you to Ms. Behr for further information about what, if any, role Fabre-Kramer will be afforded during the Center Director's review of my decision. Ms. Behr can also advise regarding the timeline for completion of the internal review.

This constitutes the final decision at the level of the Office of New Drugs. Any questions concerning this appeal should be addressed to Khushboo Sharma at (301) 796-1270.

Sincerely,

John K. Jenkins -S

Digitally signed by John K. Jenkins -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13000 76836, cn=John K. Jenkins -S
Date: 2016.03.16 16:54:42 -04'00'

John Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research

[9] See http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm073557.pdf

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/s/

JOHN K JENKINS
03/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21164

ACKNOWLEDGE –
FORMAL DISPUTE RESOLUTION REQUEST
AND MEETING GRANTED

Fabre-Kramer Pharmaceutical
Attention: Stephen J. Kramer, CEO
5847 San Felipe
Suite 2000
Houston, TX 77057

Dear Dr. Kramer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gepirone hydrochloride extended release tablets (gepirone ER).

I refer to the following:

- The Not Approvable (NA) letter dated November 2, 2007 from the Office of Drug Evaluation I (ODE I). The NA letter contained both clinical and chemistry manufacturing and controls (CMC) deficiencies.
- The January 14, 2008 End-of-Review meeting between Fabre-Kramer and the Division of Psychiatry Products (DPP).
- Your April 27, 2011 request for reconsideration of the November 2, 2007 NA letter.
- The November 29, 2011 Type C meeting between Fabre-Kramer and DPP where the statistical report of a re-analysis provided by Fabre-Kramer's consultant, Mary F. Johnson, was discussed in support of the sponsor's request that the division and ODE I reconsider the November 2, 2007 NA decision.
- Your February 3, 2012 NDA amendment that contained additional arguments and a summary of results from the exploratory re-analysis of the effect of gepirone ER, and our May 8, 2012 information request letter (sent in response to your February 3, 2012 amendment) where we requested the original study results, data sets, study report and summary of the re-analysis.
- Email correspondences dated June 14, 2012 and June 20, 2012, between Fabre-Kramer and DPP, where Fabre-Kramer sought assurance that DPP would reconsider the clinical deficiency without requiring Fabre-Kramer to address the CMC deficiencies.
- Email correspondence dated October 2, 2012 where DPP stated that they would consider Fabre Kramer's request to review the re-analysis (intended to address the clinical deficiency) as an informal appeal, and that they would review this re-analysis without receiving a resubmission that addressed all of the deficiencies in the NDA.

- Your December 10, 2012 NDA amendment that contained the re-analysis of the efficacy data, which was a partial resubmission (not a Complete Response) to the NA action.
- The General Advice letter dated April 18, 2014 signed by ODE I stating that the data reviewed raised considerable doubts about the effectiveness of gepirone ER in the acute or sustained treatment of depression, reiterating the clinical deficiency in the November 2, 2007 NA action and the recommendations stated in that letter.
- Your June 13, 2014 request for formal dispute resolution appealing the November 2, 2007 NA letter and the April 18, 2014 General Advice letter specifically appealing that ODE I concluded that Fabre-Kramer had not demonstrated "substantial evidence" of gepirone ER's effectiveness.
- The June 30, 2014 appeal not accepted letter stating that the June 13, 2014 request for formal dispute resolution was not accepted because it contained new information/re-analysis of previously submitted information that was not previously reviewed by the original deciding authority. The appeal not accepted letter stated that Fabre-Kramer could appeal the November 2, 2007 NA letter and the re-analysis submitted after the NA action would not be considered as part of the appeal. The appeal not accepted letter also offered Fabre-Kramer an Advisory Committee (AC) meeting to discuss the clinical issues and the re-analysis submitted after the NA action.
- Your November 12, 2014 letter to Elizabeth Dickinson, J.D., Chief Counsel, FDA, where you requested that the Office of New Drugs (OND) accept Fabre-Kramer's formal dispute resolution request submitted on June 13, 2014 regarding the November 2, 2007 NA letter and the April 18, 2014 General Advice letter from ODE I.

Elizabeth Dickinson, J.D., Chief Counsel, FDA, has forwarded your letter dated November 12, 2014 to the Center for Drug Evaluation and Research (CDER) for response. This letter serves as FDA's response to your November 12, 2014 letter.

After consideration of your November 12, 2014 letter and discussion of this matter with others within CDER and the Office of Chief Counsel, we are accepting your appeal submitted on June 13, 2014. As stated above, ODE I here undertook what was characterized as an "informal review" of a partial resubmission (specifically a re-analysis of previously submitted information) that addressed just the clinical deficiency in the November 2, 2007 NA letter, as opposed to waiting for a full resubmission that addressed all deficiencies before commencing a review. In effect, you were afforded a second review of just the clinical section of your application, but including review of a re-analysis that was not in the original submission that led to the November 2, 2007 NA letter. The decision to proceed both outside of the formal dispute resolution process and without a full resubmission is not standard practice within CDER.

The re-analysis submitted in the December 10, 2012 amendment was reviewed "informally" by the original deciding authority of the November 2, 2007 NA letter. The April 18, 2014 General Advice letter was signed by the same original deciding authority of the November 2, 2007 NA letter, and the General Advice letter dated April 18, 2014 reiterated the recommendation stated in the November 2, 2007 NA letter. Hence, in this particular, and highly unusual, case, we will not consider the re-analysis as new information for the current appeal. We are treating your

appeal as an appeal of the clinical deficiencies cited in both the November 2, 2007 NA letter and the April 18, 2014 general advice letter.

Your appeal has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. In your appeal, you requested a meeting to discuss the matter. We are granting your meeting request. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A meeting.

For purposes of establishing a receipt date for your appeal, the FDA is treating the receipt date for the request for formal dispute resolution to be the date of this letter (January 27, 2015). The Type A meeting will be scheduled within 30 days of this date. I will contact you to coordinate and schedule the Type A meeting. A final response on the appeal will be provided within 30 days of either the meeting date or receipt of any additional information (e.g., advice from an advisory committee or other internal or external experts) Dr. Jenkins determines is necessary to decide the appeal.

If you have any questions regarding this letter, please call me at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Khushboo Sharma, M.B.A., R.A.C.
CDER Formal Dispute Resolution Project Manager
Center for Drug Evaluation and Research

cc:
Covington & Burling LLP
Gerald Masoudi
1201 Pennsylvania Ave, NW
Washington, DC 20004

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/s/

KHUSHBOO SHARMA
01/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21164

NOT ACCEPTED –
FORMAL DISPUTE RESOLUTION REQUEST

Fabre-Kramer Pharmaceuticals, Inc.
Attention: Stephen J. Kramer, CEO
5847 San Felipe
Suite 2000
Houston, TX 77057

Dear Dr. Kramer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gepirone hydrochloride extended release tablets (gepirone ER).

We acknowledge receipt on June 16, 2014 of your June 13, 2014 request for formal dispute resolution to the Office of New Drugs (OND) concerning the November 2, 2007 Not Approvable (NA) letter from Office of Drug Evaluation I (ODE I) wherein ODE I concluded that Fabre-Kramer had not demonstrated "substantial evidence" of gepirone ER's effectiveness.

We cannot accept your request for formal dispute resolution dated June 13, 2014 because your request contains new information. As stated in 21 CFR 10.75(d):

> *Internal agency review of a decision must be based on the information in the administrative file. If an interested person presents new information not in the file, the matter will be returned to the appropriate lower level in the agency for reevaluation based on the new information.*

This has been further clarified in guidance, Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level"
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf

The FDA has always considered and interpreted new information to be new information not reviewed by the original deciding authority and/or a new analysis/reanalysis of previously reviewed data that has not been reviewed by the original deciding authority. In terms of next steps we recommend one of the following options:

1. You can revise and resubmit your request for formal dispute resolution to the OND level. Such a request should not include any new information/reanalysis of previously reviewed data or updates that were not reviewed by the original deciding authority in making the NA decision on November 2, 2007.

2. ODE I will be amenable to holding an Advisory Committee meeting to discuss the clinical issues in your application. The new information/reanalysis of previously reviewed data post-NA decision on November 2, 2007 can be included in your background package as a basis for discussion at the Advisory Committee meeting.

   We recognize that the NA letter of November 2, 2007 included non-clinical as well as clinical deficiencies. We are open to taking the clinical issues to an Advisory Committee meeting without a formal Complete Response to all of the issues. If, on the other hand, you were able to address all of the issues noted in the NA letter and wanted to resubmit a complete response, that would be optimal.

Any questions regarding next steps with the review division should be directed to Hiren Patel, Pharm D, Regulatory Health Project Manager, at (301) 796-2087. If you have any questions regarding this letter or the formal dispute resolution process, please call me at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Khushboo Sharma
CDER Formal Dispute Resolution Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

KHUSHBOO SHARMA
06/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21164

GENERAL ADVICE

Fabre-Kramer Pharmaceuticals, Inc.
Attention: Martin Lobel, Esq.
Attorney
Law Offices of Lobel, Novins & Lamont, LLP
888 17th Street, N.W., Suite 810
Washington, D.C. 20006

Dear Mr. Lobel:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for gepirone hydrochloride extended release tablets (gepirone ER).

We also refer to the following: 1) not approvable (NA) letter dated November 2, 2007; 2) meeting minutes dated January 21, 2008; 3) meeting minutes dated December 28, 2011; and 4) December 10, 2012 amendment, containing information for an informal review of gepirone ER efficacy data along with your current arguments in support of its efficacy.

The major deficiency cited in the November 2, 2007 NA letter was a failure to provide substantial evidence of efficacy in the short-term and longer-term treatment of major depressive disorder (MDD). Although the letter noted that the available evidence suggested that gepirone appeared to be less effective than other available antidepressants, relative efficacy was not the basis for the NA decision. The NA action was based on the lack of substantial evidence of effectiveness.

A face-to-face meeting was held on January 14, 2008 to discuss your responses to the November 2, 2007 NA letter and we concluded that it was highly unlikely any additional analyses of the existing database would justify further review of the NDA. On April 27, 2011 you requested reconsideration of the 2007 non-approval decision. Another face-to-face meeting was held on November 29, 2011 to discuss the statistical report provided by your consultant, Mary F. Johnson. You submitted the report to support your request that we reconsider our non-approval decision conveyed in the November 2, 2007 NA letter.

On December 10, 2012, following meetings, communications, and exchanges of documents, you submitted an NDA amendment providing information for an informal review of the gepirone ER efficacy data along with your current arguments in support of its efficacy. The efficacy data contained in the submission were the same as those reviewed in 2007 in their entirety.

We have reviewed the referenced material dated December 10, 2012 and have the following comments:

You presented 12 short-term clinical studies (ORG134001, FKGBE007, ORG134023, CN105052, CN105078, CN105083, ORG134002, FKGBE008, ORG134004, ORG134006, CN134017 and CN105053) and 1 maintenance study (ORG28709) with gepirone ER. All of these studies have been previously reviewed with your 2007 submission. No new clinical data were submitted at this time. Of these 12 short-term studies:

- 2 studies (ORG134001 and FKGBE007), as stated in your submission, support the efficacy of gepirone ER for the treatment of MDD.
- Another study, ORG134023, is a negative gepirone ER trial, as you acknowledged in your submission.
- 3 other studies (CN105052, CN105078, and CN105083), which you considered failed studies in your submission, were probably not informative in the evaluation of the efficacy of gepirone ER for the treatment of MDD, largely because of their overall size, and were not considered further. Only Study CN105052 had an active control showing no effect, representing stronger evidence of a failed study.

The remaining 6 short-term studies (ORG134002, FKGBE008, ORG134004, ORG134006, CN134017 and CN105053) showed no statistically significant difference between gepirone ER and placebo on the primary endpoint or on HAMD-17 in the 3 studies with a primary endpoint of HAMD-25 (ORG 134004, 134006) or MADRS (CN134017). In 4 of those studies an active control did show a significant effect on HAMD-17 compared to placebo, gepirone, or both. You presented several arguments as to why, in your view, these studies should not be considered negative studies and were either supportive of gepirone ER efficacy or failed studies. Your arguments and our responses to them follow:

- High Placebo Response

You assert that the negative results of studies ORG134002, ORG134004, ORG134006, and ORG134017 are due in part to the high response in the placebo group. Such substantial responses in the placebo group are common in acute depression trials and no doubt contribute to the high failure rate with these trials. But the responses in the placebo groups with these trials are not unusually high and did not appear related to success or failure. The failure rate of gepirone, however, exceeds the rate observed for any approved drug.

In study 134002 the change from baseline in the HAMD-17 total score in the placebo group was about -9 points. Similar values were seen in study CN105053 (about -8 points in the HAMD-17). In study CN105053, however, the active control showed superiority over placebo despite the placebo group response, but gepirone ER did not. At the same time, gepirone ER showed a statistically significant effect in the positive study FKGBE007, despite a placebo group response of about -8 points in the HAMD-17.

In studies ORG134004 and ORG134006, the placebo group response (about -7 points in the HAMD-17 for both) was similar to that observed in the positive trials (ORG134001 and FKGBE007, about -7 and -8 points in the HAMD-17, respectively). However, it is worth noting that the active controls (fluoxetine and paroxetine) were consistently better numerically than placebo and were shown significantly superior to gepirone on the HAMD-17.

Study ORG134017 had a large placebo group response, with a 45% rate of HAMD-17 responders in the placebo group. Nonetheless, the HAMD-17 responder rate in the fluoxetine group was 57%, while it was only 42% in the gepirone ER group, and fluoxetine was significantly superior to gepirone for the HAMD-17 total score. The trial was thus able to distinguish fluoxetine from a less effective treatment (gepirone) despite the high placebo group responder rate.

- No Assay Sensitivity

We acknowledge that in studies ORG134004, ORG134006, and ORG134017, the active control failed to reach statistical significance over placebo on the primary endpoint (HAMD-25 for studies ORG134004 and ORG134006; MADRS for study ORG134017). However, the treatment effect favored the active controls on the HAMD-17, the primary endpoint for most of your controlled trials, by showing superiority to placebo and gepirone in ORG 134006 and to gepirone in ORG 134004 and ORG134017. The superiority to gepirone was made possible by gepirone's inferiority to placebo.

You have commented on our reliance on what you considered an unusual definition of assay sensitivity. Specifically, you argued that superiority of the active control to gepirone ER is not evidence of assay sensitivity. That is incorrect. Finding a statistically significant difference between two treatment arms shows that the study was able to detect a difference between effective and ineffective treatments, which is the essence of assay sensitivity. It is also in our experience very unusual to see statistically significant superiority of the active control to the test drug, and this is a worrisome finding.

You have also argued against relying on a non-protocol specified endpoint to justify a conclusion of assay sensitivity, and we acknowledge some concern here with multiple comparisons. We are, however, dealing with an extraordinarily low study success rate in what appear to be well-controlled studies (i.e. 7 of 9). We recognize that depression trials of effective drugs have failure/negative rates of about 50% and believe that active controls can be informative as to whether it is the drug or the study that failed. Superiority of the active control to placebo (CN 105053 and ORG 134006) and/or gepirone (ORG 134004, ORG 134006, ORG 134017) was observed in all 4 trials of adequate size with a comparator, an outcome very far from what we have seen with approved drugs. We utilized HAMD-17, a most widely used efficacy endpoint and the endpoint in 9 of your 12 controlled trials, to compare the effect of gepirone ER across studies.

- Inconsistency among Sites

You argue that, in studies ORG134004, ORG134006, and ORG134017, the gepirone ER effect was inconsistent across sites, with some sites favoring gepirone ER over the active control and others favoring the active control over gepirone ER.

In general, it is not surprising to observe inconsistent results across sites if the overall treatment effect is relatively small. Even in the positive trial FK-GBE-007, large variations in treatment effect (difference between gepirone ER and placebo) among sites were seen (p-value = 0.092 for the treatment-by-center interaction based on your own result). If we were to hold the

inconsistent findings across sites against those studies, the validity of the positive study FK-GBE-007 in support of gepirone ER efficacy would also become questionable.

Study CN105053 was conducted at two sites only. You consider this study to have failed for several reasons, including early termination at one of the sites, lower mean modal dose of gepirone ER, and higher placebo response at this early terminated site. This is of course possible but such after-the-fact explanations of study failure are rarely persuasive. Study CN10503 remains a negative study. The pooled data showed an effect of imipramine but not gepirone.

- Studies ORG134004 and ORG134006 Enrolled Atypical MDD Patient Population

You argue that the patient populations enrolled in studies ORG134004 and ORG134006, which had MDD with atypical features as an entry criterion, are significantly different from the participants in the rest of the studies and as such, HAMD-25 (not HAMD-17) is the appropriate efficacy measure.

However, we have found a similar distribution of HAMD-25 total scores, HAMD-17 total scores, the sum of the 8 items missing in the HAMD-17 total score (compared with the HAMD-25 total scores), and the sum of the 5 items from the HAMD-25 that measure atypical features in both positive studies (ORG134001 and FKGBE007), which enrolled all patients with MDD, and in studies ORG134004 and ORG134006, which enrolled patients with atypical depression. These values are also similar among treatment groups in all four studies. In our view, this shows that the patient populations in all four studies are comparable and that any of the depression rating scales commonly used in clinical trials (i.e. HAMD-17, HAMD-21, MADRS) would be able to differentiate an effective antidepressant agent from placebo.

In addition, using HAMD-17 as the primary endpoint for studies ORG134004 and ORG134006, the p-values for the gepirone ER-placebo comparison are in fact smaller than those obtained using HAMD-25. Therefore, the HAMD-17 total score seems to be at least as sensitive as the HAMD-25 total score at detecting a difference between gepirone ER and placebo in studies ORG134004 and ORG134006.

We also note that, in your own analysis, the positive trials (studies ORG134001 and FKGBE007), which had HAMD-17 as the primary endpoint, also showed positive results on the HAMD-25. In our view, this is further evidence that any of the above mentioned depression scales would be sensitive to showing a drug effect.

- Use of a Comparator with Unknown Efficacy in Atypical Depression/Inappropriate Use of the Comparator in Studies ORG134004 and ORG134006

You state that fluoxetine and paroxetine have not been thoroughly studied in patients with atypical depression and that the use of a comparator with unknown efficacy in the target population limits the value of the study to judge the efficacy of gepirone ER in that population. In fact however, in those studies, the two drugs were significantly superior to gepirone on a valid measure of depression.

- Studies ORG134002 and FKGBE008 Support the Efficacy of Gepirone ER

As you acknowledged in your submission, studies ORG134002 and FKGBE008 were adequately designed, properly conducted, and employed doses of gepirone ER in the correct therapeutic range, but these two studies did not show any difference between gepirone ER and placebo on the primary endpoints. Nonetheless, you interpreted these studies to be supportive of gepirone ER efficacy, stating that treatment effects consistently favored gepirone ER over placebo for each of the secondary efficacy variables. We acknowledge that the directional trend of the primary endpoint and the secondary variables favor gepirone ER in these studies. However, per your own analysis, gepirone ER did not reach statistical significance over placebo either on the primary endpoint or on almost every secondary variable. We continue to interpret these studies as negative gepirone ER trials.

In summary, 7 out of 9 short-term trials (ORG134002, FKGBE008, ORG134023, ORG134004, ORG134006, CN134017 and CN105053) showed no difference between gepirone ER and placebo. Four of these 7 studies included an active-control arm (ORG134004, ORG134006, CN134017 and CN105053), in which the active control performed statistically significantly better than gepirone ER or placebo on the HAMD-17 scale. Statistical significance was reached over placebo in study CN105053, over gepirone ER in studies ORG134004 and CN134017, and over both gepirone ER and placebo in study ORG134006, based on statistical models without the treatment-by-center interaction term, but where the treatment factor included all treatment arms. In our decades-long experience with antidepressant development programs, we have found few trials in which an effective antidepressant drug shows no effect while the active control does.

Another unusual finding is that, in 3 of the 7 negative trials (ORG134023, ORG134004, and CN134017), gepirone ER performed numerically worse than placebo on the primary endpoint and on many secondary variables. In our experience, this too is a very infrequent occurrence with effective antidepressant drugs.

The negative maintenance gepirone ER trial (ORG28709) is an additional piece of important evidence against the efficacy of gepirone ER for the treatment of MDD. Study ORG28709 was an adequately designed randomized withdrawal trial, with an adequate number of patients enrolled, with response and relapse criteria similar to those used in other maintenance studies with approved antidepressants, and with a sufficient number of relapse events to detect a difference between treatment arms. In our review of all maintenance trials with approved antidepressants, every single maintenance trial with these characteristics has shown positive results. In this context, the negative results of this maintenance trial with gepirone ER are difficult to ignore. You argued that not all patients randomized to the double-blind phase were "true" responders; hence, you re-analyzed data using different definitions of true responders. Although all of your re-analyses yielded significant p-values, we disagree with your results for the following reasons: (1) failure to count 5 patients that were gepirone ER relapses; (2) failure to include approximately 30 patients who came from centers that had only 1 treatment arm represented or had no relapses; (3) failure to remove all patients who should have been removed according to your various definitions of true responders. After these corrections were made, the p-values were no longer statistically significant. The negative findings with gepirone ER in a maintenance trial in patients with MDD are also worrisome from a public health point of view, since MDD is a chronic disorder which can lead to fatal outcomes.

In conclusion, although two short-term trials favor gepirone ER for the treatment of MDD, the seven negative short-term studies and one negative maintenance trial with gepirone ER raise considerable doubts about the effectiveness of gepirone in the acute or sustained treatment of depression. The 2 positive studies could represent chance findings, given the absent, negative, or minimal findings in 8 other studies.

We are amenable to meeting with you should you decide to continue the development program of gepirone for the treatment of MDD. If you have any questions, contact Hiren Patel, Pharm.D., Regulatory Project Manager, at hiren.patel@fda.hhs.gov or (301) 796-2087.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
04/18/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-164

Organon Inc.
Attention: Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

NOV 30 1999

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated September 30, and received October 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORG 33062 (Gepirone Hydrochloride) Extended Release 20 mg Tablets.

We have given your application a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

For filing of your NDA for Gepirone, the Agency is willing to accept two adequate and well-controlled short-term studies which, on face, show superior efficacy over placebo using Gepirone Immediate Release (IR) in addition to one such study using Gepirone Extended Release (ER). For a study to be considered positive, ordinarily all primary efficacy measures in the intent-to-treat (ITT) population must show statistically significant superiority over placebo in an LOCF analysis.

Preliminary evaluation of the Gepirone IR studies in your application suggests that studies 03A7C-001B and possibly 03A7A-003 may fulfill the requirement for the two positive short-term IR studies, assuming the results of these studies stand up to review. One potential problem with study 03A7A-003 is in subject selection. In addition to patients with major depression, this study includes patients with "minor depression" and "intermittent depression." Since the claim for this drug, if approved, would be for major depressive disorder, it may be necessary to reanalyze the data for this study including only the patients with major depression. Additional support for a claim in major depression may come from study 03A7A-002, i.e., the relapse prevention study.

The studies using the Gepirone ER formulation are more problematic and cannot be considered adequate to support filing of this NDA. As noted, it would be necessary to have at least one adequate and well-controlled short-term study which, on face, showed superior efficacy over placebo using Gepirone ER, in order to bridge the results from the IR studies to the ER formulation. You seem to acknowledge that, on face, neither study CN-105-078 nor CN1-105-083 showed efficacy on primary efficacy variables in the ITT population. We must, therefore, consider these negative studies. There may also be other problems with both of these studies, e.g., apparently unplanned interim analyses were done.

Study CN105-053 did not show superiority to placebo on its two primary efficacy measures in the ITT population, i.e., both study centers combined. There has been some confusion about the analysis plan for this study. It was our impression, based on your December 29, 1997 meeting package for our March 20, 1998 Pre-NDA meeting with you, that the primary plan for this study was to analyze each of the two sites independently. We had no reason to change this view, based on our meeting with you on March 20, 1998, as reflected in our minutes for that meeting. Nevertheless, our minutes did indicate that "this would be a matter for review." As we now have access to the actual protocol for that study, it is clear to us that the intent was not to analyze the centers separately. In fact, the protocol did not call for stratification by center, i.e., randomization was to treatment group regardless of center. The protocol states that "the ITT sample will include all patients who are randomized to treatment, receive at least one dose of study medication, and have at least one posttreatment evaluation." While it would not be problematic for an overall positive outcome for a multicenter trial to be coming from a subset of the centers, in this case 1 of 2, it would never be appropriate to proceed to the independent analyses of individual centers when the overall result is not positive, except as an exploratory maneuver. Thus, on face, this study also provides no support for the efficacy claim.

For the successful filing of an NDA for Gepirone ER, an additional adequate and well-controlled study showing superiority of Gepirone ER over placebo in patients with major depression will need to be conducted. If you choose to pursue the development of this drug, we recommend that you submit your plans for such an additional study to the Division for review.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

FDA will refund 75% of the total user fee submitted with the application. If you decide to file the application over protest, the filing of the application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

If you have any questions, please contact Mr. Paul David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

11/30/99

Russell Katz M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA :ORIG 21-164
NDA:DIV FILE 11-30-99
HFD-120/RKatz/TLaughren/SMolchan
HFD-120/GFitzgerald/LFossom
HFD-120/RSeevers/RLostritto
HFD-120/PDavid 11-30-99
HFD-860/VJTammara/VSekar
HFD-710/KJin/RChen
HFD-344/MThomas
HFD-094/DDMS
HFD-100/RTemple/RBehrman
DISTRICT OFFICE
Doc #GEPIRONE\NDA\GEPIRONE REFUSE TO FILE LETTER 03.DOC
rd:11/22/99pd
rev:11/24/99sm; 11/29/99tl
ft:11/30/99pd
REFUSAL TO FILE (RF)

D-4

APR 29 1998

IND 33,626

Fabre-Kramer Pharmaceuticals
Attention: Stephen J. Kramer, M.D.
5847 San Felipe, Suite 3147
Houston, Texas 77057

Dear Dr. Kramer:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gepirone Hydrochloride extended release tablets.

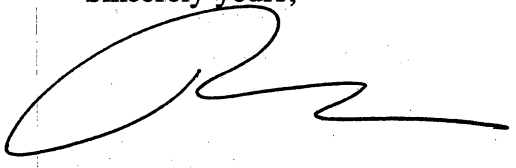
Reference is also made to a meeting between the Agency and representatives from Fabre-Kramer Pharmaceuticals dated March 20, 1998, to discuss your upcoming NDA submission.

We acknowledge receipt of your submission dated April 15, 1998, providing for your version of meeting minutes from the aforementioned meeting, and we believe that they accurately reflect the proceedings of the meeting.

Attached are the Agency's version of minutes from the March 20, 1998 meeting.

Should you have any questions concerning this application, please contact Mr. Paul David, Project Manager, at (301) 594-5530.

Sincerely yours,



Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

MEMORANDUM OF MEETING MINUTES

Meeting Date:	March 20, 1998
Time:	1:30 PM
Location:	WOCII 4th Floor Conference Room
Application:	IND 33,626 (Fabre-Kramer Pharmaceuticals; Gepirone HCl Extended Release Tablets)
Type of Meeting:	Face-to-face
Meeting Subject:	Pre-NDA Meeting
Meeting Chair:	Thomas Laughren, M.D.
Meeting Recorder:	Paul David, RPh

FDA Attendees

Thomas Laughren, MD	Clinical Group Leader
Earl Hearst, MD	Clinical Reviewer
Glenna Fitzgerald, PhD	Team Leader Pharmacology
Norman Huang, PhD	Pharmacology Reviewer
Maryla Guzewska, PhD	Team Leader CMC
David Hoberman, PhD	Reviewing Statistician
Ray Baweja, PhD	Team Leader Biopharmacutics
Sayed Al-Habet, PhD	Biopharmaceutic Reviewer
Paul David, RPh	Project Manager

External Constituent Attendees and Titles

Louis Fabre, MD, PhD	Chairman
Stephen Kramer, MD	Chief Executive Officer
(b) (4)	NDA organization Consultant
	Statistical Consultant
	Pharmacokinetics Consultant
	Clinical Studies Consultant
	CMC Consultant
	Regulatory Affairs Consultant
	Toxicology Consultant

Meeting Objectives:
The meeting was requested by the sponsor to discuss content and format of their NDA which is targeted for submission on August 1998.

Discussion:
CMC

- As of January 1998, three-months accelerated stability is no longer sufficient. The Agency requires six-months site specific accelerated stability on at least one batch at the time of NDA submission, and a commitment to place the first 3 production batches on long-term

stability. The stability data derived from the former sponsor, BMS, will be taken into consideration when the NDA is submitted.

BIOPHARMACEUTICS

- Since the NDA will only contain a single dosage strength of a 20 mg tablet, the Agency requested data addressing the linearity of multiple tablet doses. The sponsor has these data, and they will be included in the NDA.

- The Agency suggested that the data from study FK-GBE-004 (a study to examine ethnic differences in pharmacokinetics) be examined prior to conducting studies 001 and 002 (the final bioequivalence and effect of food studies). The sponsor will review the 004 data prior to initiation of studies 001 and 002. These 2 separate single dose bioequivalence bridging studies will be sufficient to establish a link to the to be marketed product and the product used in the clinical trials.

- The Agency stated that it will be necessary to present data on the relative exposure for the metabolite and parent compound.

- The Agency stated that complete dissolution data, including results for individual dosage units should be provided in the NDA.

- All tables should be submitted in electronic format such as MS Word or WordPerfect.

- It was agreed that a separate meeting, dedicated to the discussion of pharmacokinetic and biopharmaceutic issues, would be scheduled.

PHARMACOLOGY

- The Agency provided the sponsor with the format for the submission of the preclinical carcinogenicity studies.

- The Agency requested that the sponsor submit a study of the local gastrointestinal irritation potential of Gepirone in the extended release form. The details specifically concerning whether the study would need to be conducted prior to the NDA submission would be discussed at a later time between Dr. Fitzgerald and Dr. (b) (4).

CLINICAL

- The Agency will provide the sponsor with standard efficacy templates that should be filled out and submitted with the NDA submission.

- The Cohn/Ferguson study, No. CN 105-078, was abruptly discontinued at 80% enrolment. The Agency stated that the effects of this study termination would be a matter of review,

and the sponsor should provide specific documentation as to the reasons for termination of the study. The sponsor should also conduct a probability calculation given the outcome of the study to the nominal end point, i.e., use the null hypothesis to project what could have happened if the study had been completed.

- In the Feigner/Gelenberg study, No. CN 105-053, the Gelenbeg center showed a significant placebo response. The Feigner study, as it stands alone, demonstrated superiority of drug. The Agency concurs that there would be no reason to pool these studies. However, this would be a matter of review when the NDA was submitted.

- The sponsor intends to use the Quitkin study, No. 03A7A-003, which uses the immediate release formulation of Gepirone as one of the positives efficacy studies to support approval of the extended release formulation. The Agency responded that, since the immediate and extended release are not equivalent as to rate and extent of absorption, we would not normally accept the immediate release study for demonstrating efficacy in the extended release product. However, this would be a matter of review, and the sponsor should justify the use of this study to support approval in the extended release NDA

- The Agency noted that the outline of the integrated summary of safety submitted with the pre-meeting package does not contain all of the tabulations requested in the draft guidance provided to the sponsor. Specifically, the sponsor will provide the following additional information:

  1. A new outline incorporating all of the requested tables included in the draft safety review guidance.

  2. Tables of serious adverse experiences need to be submitted and sorted by treatment, patient, and preferred term. They should not be split by IR versus ER.

  3. The sponsor will submit a proposal for review by the Agency of criteria to identify outliers (i.e., patients with significant abnormalities) with respect to laboratory data, electrocardiograms, vital signs, and similar safety variables.

  4. Separate pooling by dosage form was questioned for analysis of variables like electrocardiograms. Pooling by dosage across dosage forms was suggested as an alternative. The sponsor will submit a new proposal for review and further discussion.

  5. Heart rate will be included in the analysis of ECG variables.

  6. With respect to drug-demographic interactions the presentation should include risk ratios across strata. The aim will be to identify potentially drug-related differences

(with rates 2x placebo or higher).

- The Agency stressed that the compilation of the clinical data should be an interactive process, and they encouraged the sponsor to obtain feedback as much as possible.

- The sponsor reviewed the plan for submission of case report forms (CRFs) and case report tabulations (CRTs) in electronic only format. The type of CRTs (domain profiles versus patient profiles) was discussed at some length. At present, only domain profiles exist. Providing patient profiles for certain patients would make the application easier to review by the Agency medical officer. As an alternative to patient profiles, the idea of bookmarking selected domain profiles was discussed. While this approach may be an acceptable alternative, the agency will have Dr. Randy Levin further discuss this issue with a representative from the sponsor.

Minutes Preparer:

Paul David, R.Ph.
Project Manager, DNDP

Chair Concurrence:

(or designated signatory)

4-27-98

cc:
IND 33,626
IND: DIV FILE
HFD-120/PLeber/TLaughren/EHearst
HFD-120/RSeevers/MGuzewska/PDavid
HFD-120/GFitzgerald/NHuang
HFD-700/TSahlroot/DHoberman
HFD-860/RBaweja/AHabets
DOC #IND\I33626\03-20-98.MM

cc:
IND 33,626
IND: DIV FILE
HFD-120/PLeber/TLaughren/EHearst
HFD-120/RSeevers/MGuzewska/PDavid
HFD-120/GFitzgerald/NHuang
HFD-700/DHoberman
HFD-860/RBaweja/AHabets
DOC #IND\I33626\03-20-98.LTR
ADVICE LETTER

MINUTES OF MEETING
IND 33,626
Gepirone HCl E.R. Tablets

IND #:	33,626
SPONSOR:	Fabre-Kramer Pharmaceuticals
INDICATION:	Depression
DATE/TIME:	March 14, 1994; 11:00 am - 12:00 pm
LOCATION:	Conference Room 10B-45
ATTENDEES:	

FDA

HFD-120:	P. Leber, M.D., T. Laughren, M.D., E. Hearst, M.D., G. Fitzgerald, Ph.D., S. Sparenborg, Ph.D., S. Blum, Ph.D. P. David, R.Ph.
HFD-426:	V. Hale, Pharm.D.
HFD-713:	D. Hoberman, Ph.D.

FABRE-KRAMER

Stephen Kramer:	President
Louis Fabre:	Chairman
(b) (4):	Director of Biostatistics, (b) (4)
(b) (4):	Senior Consultant, (b) (4)

BACKGROUND

Gepirone hydrochloride is a serotonin agonist. The sponsor requested a meeting with the Agency in an amendment dated December 22, 1993, to discuss their proposed Phase 3 development plans. It was noted that the rights to Gepirone I.R. and E.R. had been recently acquired by Fabre-Kramer Pharmaceuticals from Bristol-Myers Squibb. The sponsor does not intend to pursue development of the immediate-release product.

DISCUSSION

Pharmacology

All preclinical studies conducted using the immediate-release product will be accepted for the extended-release NDA. It was suggested that the sponsor refer to the Agency guidelines for the preclinical NDA requirements.

The sponsor was informed that labeling would include Pregnancy Category 'C' because of rat pup mortality in the Segment III study. However, the Agency would re-evaluate the category label based on the outcome of a cross-fostering Segment III study, if the sponsor desired to conduct one. The Agency offered to discuss this at a later time if the sponsor would like to. The pup mortality results should also be placed in the patient informed consent document. It was noted that the sponsor has not as yet submitted carcinogenicity studies. The Agency also asked for reports of abuse potential. The sponsor replied that such preclinical studies have been done and they would submit them.

Clinical

It was suggested to the sponsor that if the clinical work for the immediate release product has been completed, then they should just conduct bridging and dissolution studies using the ER product for their NDA. The sponsor replied that all of the clinical studies conducted under the IR product were flawed in one way or another.

The sponsor intends to conduct 7 placebo controlled studies in support of their NDA (6 short-term and 1 relapse prevention trial); in addition, they plan to do a dose ranging study and an open safety study. The Agency suggested that the sponsor conduct a fixed parallel dose study using widely separated dosing. Additionally, the sponsor will contact HFD-007 for suggestions on how to conduct a drug abuse study to evaluate the potential for abuse.

The sponsor intends to use fluoxetine hydrochloride as the active control drug in their placebo controlled studies. The Agency informed the sponsor that an active control is useful for assay sensitivity but could not be the basis for a comparative claim.

It was suggested that the sponsor submit the final protocols for Agency review prior to implementation.

Biopharmaceutics

Dr. Hale gave the sponsor several suggestions and requests during the meeting. All of this information would be again conveyed in a letter to the sponsor. Additionally, Dr. Hale stated that the sponsor should submit full details of their biopharmaceutic program for Agency review prior to initiation.

Miscellaneous

The sponsor stated that all of the safety information conducted and collected by Bristol Myers Squibb would be submitted with the NDA. They could not guarantee that Bristol Myers Squibb transferred all of the information to them. It was suggested that the sponsor obtain legal assistance to possibly determine if they may obtain a warrant from Bristol-Myers Squibb stating that there was full disclosure of safety data.

CONCLUSIONS

The sponsor thanked the Agency for the meeting and stated that they will be in contact with them regarding the final protocols.

Paul A. David

Paul A. David, R.Ph.
Regulatory Management Officer

cc:
ORIG IND 33,626
HFD-120/Div File PL 5-24-94
HFD-120/PLeber/TLaughren/EHearst
HFD-120/GFitzgerald/SSparenborg
HFD-120/PDavid/SBlum
RD:04/04/94pd
FT:05/23/94pd
DOC #I33626.MM
MEETING MINUTES