CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 25, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Non-Approval Action for
Gepirone ER for Major Depressive Disorder (MDD)

TO: File NDA 21-164
[**Note:** This overview should be filed with the 5-1-07 response to our 6-23-04 non-approvable letter.]

1.0 BACKGROUND

Gepirone ER is an extended release formulation of gepirone, an azapirone that is structurally and pharmacologically similar to buspirone, a drug marketed as Buspar for GAD. Like buspirone, gepirone acts primarily at 5HT1A receptors, as a full and partial agonist. Gepirone is not approved for any indications, and this NDA provides data in support of a claim for MDD, in a dose range of 20 to 80 mg/day. No other drugs with this particular pharmacological profile are approved for MDD.

IND 33,626 for gepirone ER was originally submitted 8-28-89. There is also an IND 23,952 for gepirone immediate release (IR) that was originally submitted 4-2-84. The shift in focus from the IR to the ER formulation was based on poor tolerance of the IR formulation, i.e., dizziness, nausea, and insomnia. It should be noted that these INDs were originally held by BMS, but they discontinued all trials in 1992. In 1993, rights to gepirone ER were transferred to Fabre-Kramer, and then Organon reached agreement with Fabre-Kramer to further develop and market gepirone ER in 1998. More recently, Fabre-Kramer has again taken over the NDA. These transfers of ownership resulted in several disruptions in the flow of the development program.

This NDA was originally submitted 9-30-99. Although there were a total of 16 placebo-controlled trials submitted (10 with IR and 6 with ER), there were notable problems with many of these, and in fact, the sponsor focused on only 4 of these as worthy of particular attention: 1 ST ER study (53); 2 ST IR studies (003 & 001B); and 1 randomized withdrawal study (002). We had previously agreed with the sponsor on the principle of bridging to a positive IR database with a single positive ER study. However, it had now become apparent that the study offered as a positive ER study, i.e., study 53, was in fact a 2-center study in which the protocol specified analysis called for a pooling of the data for the 2 centers. However, this analysis was not

positive overall, yet the sponsor had looked at each center independently, and submitted positive results for 1 center as a positive trial. Consequently we issued a RTF letter on 11-30-99.

The NDA was resubmitted 5-18-01. We had previously reached agreement with the sponsor that one additional positive short-term trial with the ER formulation would be sufficient, providing there was independent evidence for the IR formulation. We agreed with the sponsor that ER study 134001 could be considered a positive study. Upon review of the NDA, however, we had concluded that none of the 3 candidate IR studies could be considered positive. Thus, we issued a nonapprovable letter on 3-15-02. We subsequently modified our view on IR study 03A7A-003, and did consider that a positive study. However, given the accumulating negative data, we indicated that we would want at least 2 positive ER studies for support of this NDA.

The NDA was resubmitted for the second time on 12-23-03, but did not include the results from a second positive short-term ER study. Rather, the sponsor included the results of a randomized withdrawal study that they considered positive (28709). However, we did not agree with the sponsor's exclusion of patients and events from their analysis, and we had become increasingly concerned about the mounting number of negative trials. Thus, we issued a second nonapprovable letter on 6-23-04. We advised the sponsor that they would need both a second positive short-term ER study and a positive longer-term randomized withdrawal study.

This 5-1-07 third resubmission of this NDA did include the results of a second short-term ER study that the sponsor considered positive (FKGBE007), but did not include the results of another randomized withdrawal study. Rather, the sponsor presented the results of yet another analysis of study 28709 which they now again considered a positive study. This resubmission also included the results of various analyses of sexual dysfunction data which they felt provided evidence that gepirone ER is not associated with sexual dysfunction.

2.0 CHEMISTRY

The only definitive issue is a stability concern, and we will be asking for an update on this in our action letter. In addition, however, the only drug substance manufacturing site has been recently inspected and we have not yet received a recommendation from OC.

3.0 PHARMACOLOGY

The only new pharmacology/toxicology data submitted were results of a chromosomal aberration study. In the 3-15-02 nonapprovable letter, we had noted that their in vitro chromosomal aberration test was not adequate, however, we had not required them to repeat it. Nevertheless, the sponsor did repeat it, and submitted the results in this resubmission. Unfortunately, the second study was also inadequate, and the pharm/tox group has decided that an acceptable resolution is to remain silent in labeling regarding the issue of these two studies.

4.0 BIOPHARMACEUTICS

The resubmission included results of 2 food effect studies and a request for a biowaiver for a BE study for the proposed 40 and 60 mg tablet strengths. OCP considers the food effect studies acceptable, agrees with the requested biowaiver, and recommends a phase 4 commitment for a rifabutin interaction study. They also have comments for labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

As noted, the third resubmission of this NDA did include the results of a second short-term ER study that the sponsor considered positive (FKGBE007), but did not include the results of another randomized withdrawal study. Rather, the sponsor presented the results of yet another analysis of study 28709 which they now again considered a positive study. They have also done various meta-analyses of the 12 gepirone ER studies they consider adequate from the standpoint of dose. The details of these various analyses are provided in the clinical and statistical reviews of this resubmission, and I refer to these reviews by Drs. Kong, Hearst, and Khin for these details. I will provide an overview of what I consider to be the critical efficacy issues in this memo.

In my view, the major deficiency in this application continues to be a failure to provide substantial evidence for the effectiveness of gepirone ER in the short-term or longer-term treatment of major depressive disorder (MDD). Although I agree that the sponsor has provided evidence of short-term antidepressant effectiveness for gepirone ER from 2 adequate and well-controlled trials, i.e. from studies FKGBE007 and 134001, this evidence is derived from a total pool of 12 studies for which the remaining 10 studies do not provide evidence of the effectiveness of gepirone. I acknowledge that 4 of these remaining 10 studies were terminated early for business reasons, and, therefore, might not be expected to provide such evidence because they did not reach their planned sample sizes. However, there are other findings among these trials that amplify my concern about the potential value of gepirone ER as a treatment for MDD.

We have re-evaluated all 12 trials with a focus on the HAMD-17 total score as a common measure of efficacy. Although this was not the protocol specified primary endpoint for 3 of the 12 trials, we felt it was a reasonable common measure because it is so widely used as a primary endpoint in depression trials. In fact, the sponsor selected this as a common endpoint for their meta-analyses. Using this measure, we found the following:

In 3 of these 12 trials, an active comparator antidepressant was statistically superior to gepirone ER, as follows:

Trial	Active Comparator	Active Comparator vs Gepirone ER
ORG 134004	Fluoxetine	-1.71 (p=0.027)
ORG 134017	Fluoxetine	-1.54 (p=0.042)
ORG 134006	Paroxetine	-1.85 (p=0.012)

In 2 of these 12 trials (CN105-053 and ORG 134006), an active comparator was superior to placebo and gepirone ER was not, as follows:

		P-Values	P-Values
Trial	Active Comparator	Act Comp vs Pbo	Gepirone ER vs Pbo
CN105-053	Imipramine	-3.19 (p=0.038)	-2.00 (p=0.190)
ORG 134006	Paroxetine	-1.63 (p=0.026)	0.22 (p=0.760)

I agree that meta-analysis is a reasonable approach to try to better understand the totality of the short-term efficacy evidence for gepirone ER, however, I don't agree with the sponsor's approach to looking at "supportive" subsets of the data, and I don't think the appropriate meta-analyses help their case. The major reason for conducting a meta-analysis in this situation is to determine if, among the remaining 10 trials that were not considered positive for gepirone ER, a meta-analysis would provide any support for gepirone ER. Using the sponsor's meta-analytic model for these 10 trials, we found an effect size of -0.09 (p= 0.62). The one reasonable alternative approach that the sponsor utilized, i.e., including all 12 trials, resulted in an effect size of -0.48 (p= 0.09). Thus, neither approach provides additional confidence that gepirone ER is an effective antidepressant therapy.

The negative outcome for the longer-term maintenance efficacy trial (study 28709) is also a concern for this drug. First, we disagree with the sponsor's approach to trying to repair this study by establishing rules for identifying so-called protocol violators, either because they did not technically meet criteria for randomization or were non-compliant in some manner during the trial. The protocol for this study stated that "All protocol violations will be determined by medical, clinical and biometrics personnel prior to breaking the blind…." Thus, we do not find this post hoc attempt to rescue this study by eliminating 40 patients several years after the blind was broken credible or valid. Second, the fact that this trial is negative is significant in that antidepressant trials of this design rarely fail to show a drug effect. Thus, this finding also brings into question the clinical value of this drug in the treatment of MDD.

As noted in our 6-23-04 not-approvable letter for this application, it is difficult to know how to advise the sponsor regarding any future work to salvage this program with such a preponderance of negative findings. Given that they have never, despite our repeated advice to conduct proper dose finding studies, addressed the issue of dose/concentration response, it is possible that better dose finding might help to better understand the multiple failures with this drug. I do not feel that simply conducting additional flexible dose studies is going to address my concern that this is a drug that, while it may have some marginal antidepressant efficacy, is likely inferior to other available antidepressants. I consider MDD a serious illness and it is hard to imagine what the

justification would be for approving an antidepressant drug that is demonstrably less effective than other available agents. Delaying effective treatment with the use of gepirone ER is not something I would be willing to support. The sponsor has provided some findings that suggest there might be a lesser risk of sexual dysfunction with gepirone ER than is seen with many other antidepressant agents (see 5.2, Safety Data). I am not yet convinced, however, that the data they have accumulated regarding sexual dysfunction consistently support this premise. Although additional analyses of the available sexual dysfunction data may help to convince us of the merit of this argument, I do not feel this would be a worthwhile effort, given the striking weakness of the efficacy data for gepirone ER at the present time. I would be willing to discuss the efficacy data with the sponsor, but I am not optimistic that there is a reasonable path forward for any further development of this drug as an antidepressant.

5.2 Safety Data

5.2.1 Overview

This resubmission of the NDA includes both an overview of safety data plus more detailed findings for new studies. There have been roughly 5000 patients exposed to gepirone in this development program up to this point (about 3000 for the ER formulation and about 2000 for IR). Safety concerns have not been a primary issue in previous nonapproval actions, and are not now. The most common and drug-related adverse events appear to be dizziness, nausea, and vomiting.

5.2.2 Safety Issues of Particular Interest

Two safety issues of particular interest have been sexual dysfunction and suicidality, and I will comment briefly on these issues.

<u>Lack of Sexual Dysfunction</u>

The sponsor has tried to make a case that gepirone ER is superior to other antidepressants regarding sexual dysfunction and no different than placebo in this regard. They conducted several different analyses because different information on sexual function was collected in different trials (DISF/DISF-SR; CSFQ; DSM-IV diagnoses reflecting sexual dysfunction, and adverse events suggesting sexual dysfunction). They evaluated both change from baseline and AUC data for these measures. We had met with the sponsor on 10-12-05 to discuss an approach to establishing this claim, and had stated they would have to show both a signal for sexual dysfunction for other antidepressants and a noninferiority of gepirone ER to placebo (using formal hypothesis testing), at doses relevant for efficacy. Dr. Kong has summarized these findings in detail in his review, and has concluded that there is not consistent evidence of an advantage for gepirone ER. It is true that the signal is not consistent for the trials involving DISF/DISF-SR and DSM-IV diagnoses. However, I think the analyses involving adverse events and those for the 2 trials involving the CSFQ measure are quite strong. We have endorsed the CSFQ as a valid measure, and gepirone ER meets our noninferiority standard in both of these trials. It is not as clear that the active control in those studies was shown to be worse than placebo, however, that may not be a reasonable standard to set. In any case, this apparent

advantage regarding sexual dysfunction would not be relevant if the drug has not been shown to have a benefit regarding depression.

Suicidal Ideation/Suicide Attempt

The sponsor conducted analyses for possibly suicide-related adverse events that were classified using the Columbia classification system. Two different pools were used: all phase 2-3 studies (presumably including open label extensions) and limited to the controlled phases of the trials. The first pooling yielded statistically significant results both for suicidality overall (p=0.022) and for suicidal behavior (p=0.048). These signals lost significance when limited to the controlled phases of these trials (p=0.08 for suicidality overall and p=0.12 for suicidal behavior), probably because the inclusion of open extension data biases the analyses against drug. Nevertheless, the data even for the controlled only phases numerically trend in the direction of a suicidality signal for gepirone ER. If this drug were to be approved for MDD, it would have the same strong warning language regarding suicidality as other antidepressants.

5.2.3 Conclusions Regarding Safety of Gepirone ER

There are no safety findings that would preclude the approvability of gepirone ER, however, I agree with the review team that the weak efficacy findings for gepirone ER represent an obstacle to the approval of this drug. The possible advantage of gepirone ER over other antidepressants on sexual dysfunction, even if demonstrated to be consistent, would not be sufficient to overcome the efficacy problem.

5.3 Clinical Sections of Labeling

Since the clinical/statistical review team is in agreement with recommending a nonapproval action for this NDA, we have not included a draft of labeling with the package.

6.0 WORLD LITERATURE

The sponsor provided a brief literature review in this resubmission. Dr. Hearst did not discover any new safety issues of concern for this drug in this material.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, neither gepirone IR nor gepirone ER is marketed anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC. We did discuss our findings for this application at an internal regulatory briefing on 10-19-07, and there was unanimous agreement that this application does not provide sufficient support for effectiveness in MDD to justify approval.

9.0 DSI INSPECTIONS

It is my understanding that an inspection has been conducted for 2 sites in the most recent positive study, FKGBE-007, and data from these sites were judged to be acceptable.

10.0 LABELING AND NONAPPROVAL LETTER

10.1 Labeling

As noted, we have not proposed labeling for this application.

10.2 Foreign Labeling

Gepirone ER is not marketed anywhere at this time.

10.3 Nonapproval Letter

The nonapproval letter explains the basis for the action.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the current sponsor for this NDA has not submitted sufficient data to support the conclusion that gepirone ER is sufficiently effective in the treatment of MDD to justify an approval action. Thus, I recommend that we issue the attached nonapproval letter.

cc:
Orig NDA 21-164 (Gepirone ER)
HFD-130/TLaughren/MMathis/NKhin/EHearst/RGrewal/WBender
ODE-I/RTemple

DOC: Laughren_Gepirone MDD_NA3. Memo.doc

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/s/

Thomas Laughren
10/25/2007 12:27:40 PM
MEDICAL OFFICER

MEMORANDUM

DATE: June 14, 2004

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-164

SUBJECT: Recommendation for action on NDA 21-164, for the use of Gepirone Hydrochloride Extended Release (ER) Tablets in Patients with Major Depressive Disorder (MDD)

NDA 21-164, for the use of Gepirone Hydrochloride Extended Release (ER) Tablets in Patients with Major Depressive Disorder (MDD), was submitted by Organon, Inc., on 9/30/99. The Agency issued a Not Approvable letter on 3/15/02; the critical deficiency at that time was noted to be the lack of substantial effectiveness for the ER tablet. In the original application, a total of 18 controlled trials (utilizing either the IR or ER tablets) had been submitted. Out of this array of studies, only one study, Study 134001, a short term study of the ER formulation, was considered a positive study. The sponsor had proposed that three other controlled trials of the IR formulation were positive, but we disagreed (see, for example, my previous memo of 3/8/02 and Dr. Thomas Laughren's memo of 3/5/02). It should be noted that although we agreed that many of the other 14 controlled trials were not adequate trials (some were done at inappropriately low doses, others were discontinued by the previous sponsor), there were three trials of the ER formulation that were not positive for any obvious design or conduct reasons. In addition to this critical deficiency, we noted a lack of adequate long-term safety data at doses of 40 mg/day (the dose thought to be potentially effective). In the letter, we informed the sponsor that they would need to submit another positive study with the ER formulation. Finally, a number of other, non-critical deficiencies were identified.

The sponsor responded to the Not Approvable letter in a submission dated 12/23/03. This submission contained a report of a long-term, randomized withdrawal study. This submission needs some explanation.

After the Not Approvable letter was issued, the division met with the sponsor to discuss the further development of the drug. In one meeting (7/3/02), we determined that an additional one of the original studies submitted by the sponsor (Study 03A7A-003), a short term study of the IR formulation, and one we had originally concluded was not acceptable, was, in fact, acceptable as a positive study (for the IR formulation). In our original thinking, this study was considered unacceptable because it appeared that the sponsor did not enroll patients with MDD, although this study was clearly a positive study by protocol, a

fact we acknowledged in our letter. Specifically, the mean baseline HAM-D 17 scores were about 10 points lower than those of patients typically enrolled in MDD studies (and in the other MDD studies included in this application). These patients were characterized as having "atypical depression", and our letter expressed concern that patients with other diagnoses, in particular GAD, might have been enrolled. However, in our meeting with the sponsor (and based in part on their pre-meeting submission), they convinced us that at least 65-88% of patients in this study met diagnostic criteria for MDD, that the low baseline HAMD scores were related to a few items not relevant for atypical depression, but that they had MADRS scores in the more typical range, that they did not meet criteria for GAD, and that analysis of the subset with a bona fide diagnosis of MDD also was positive for gepirone. Therefore, we had concluded that the application contained one positive study with the ER formulation and one positive study with the IR formulation, but still required that the sponsor submit another clearly positive study with the ER formulation. Indeed, the sponsor noted that a short term trial with the ER formulation (Study 134004, a study that compared gepirone, fluoxetine, and placebo) was nearing completion.

However, the sponsor informed the division in a 4/17/03 submission that this study was a failed study. They asserted, however, that their randomized withdrawal study of the ER formulation, (Study 28709) was a positive study, and they argued that the panoply of positive results (one short term study each with the ER and IR formulations and the long term ER study) should be a sufficient basis for the demonstration of substantial evidence of effectiveness of the ER formulation. We informed the sponsor that we would review such an application (with obviously no assurance that this package would be acceptable).

The sponsor's resubmission has been reviewed by Dr. Earl Hearst, medical reviewer (review dated 5/20/04), Dr. Roswitha Kelly, statistician (review dated 5/6/04), Dr. Sherita McLamore, chemist (review dated 6/14/04), Dr. Sally Yasuda, Office of Clinical Pharmacology and Biopharmaceutics (review dated 5/25/04), Dr. Linda Fossom, pharmacologist (memo dated 4/7/04), Dr. Ni Khin, Division of Scientific Investigations (memo dated 5/21/04), Dr. Tia Harper-Velazquez, Division of Medication Errors and Technical Support (DMETS; review dated 4/30/04), and Dr. Tom Laughren, Psychiatry Drugs Team Leader (memo dated 5/20/04). The clinical review team recommends that the application not be approved. I will very briefly describe the results of Study 28709 and offer the division's recommendation for action on the application.

Study 28709 was a multi-center, multi-national study in which patients with MDD who met responder criteria at 8-12 weeks after treatment initiation (at doses between 40-80 mg/day) in an open-label phase were randomized to continue active treatment or placebo for 40-44 weeks. The primary outcome measure was the proportion of patients who met relapse criteria, analyzed by CMH with adjustment for centers. A relapse was considered to have occurred if the patient had a HAMD-17 of at least 16, or was discontinued because the investigator

determined that the treatment was not effective. Time to relapse was a secondary outcome.

According to the sponsor, the rate of relapse on gepirone was 29/126 (23%) compared to a rate of relapse on placebo of 43/124 (35%). By the sponsor's analysis, the p-value for the primary outcome was p=0.024.

However, as all of the reviewers have noted, two problems complicate this outcome as reported by the sponsor.

Prior to unblinding the data, the sponsor classified 5 additional gepirone patients as having met relapse criteria due to lack of effect, although they had not been so identified in the CFR (a company memo indicated that these patients would be classified as failures). When the data were unblinded, the sponsor noted that these patients had not met the HAMD criterion of at least 16, but at that point it was impossible to verify with the investigators the status of these patients, given that all parties had been unblinded.

When these five patients are included in the analysis, the p-value for the primary outcome becomes p=0.1.

Further, as the team notes, the sponsor excluded an additional 32 patients from the analysis because either 1) they were in centers that enrolled patients in only one treatment arm, or 2) there were no relapses in these centers. When these patients are included in appropriate analyses, the p-value for the between-treatment contrast is p=0.08 - 0.1. When the 5 additional patients described above are included in these latter analyses, the p-value becomes p=.31 - .33.

Analyses of Time to Relapse, a secondary outcome in this study, but the more traditional outcome considered primary in most other studies of this type, yielded p-values of p=0.09 (including the 32 patients at small centers) to p=0.28 (when the additional 5 patients are included).

As the team also points out, Study 134004, the short term trial comparing gepirone, fluoxetine, and placebo, not only failed to distinguish the active drugs from placebo, but, in fact, in this study, gepirone was numerically worse than placebo, fluoxetine was numerically superior to placebo, and the p-value for the fluoxetine-gepirone contrast was p=0.068; the chart below describes the relevant comparison:

Drug	Change from Baseline (Mean HAMD-25)
Gepirone (N=125)	-9.9
Fluoxetine (N=136)	-11.8
Placebo (N=136)	-10.6

Other issues

As Drs. Laughren and Hearst note, the sponsor has provided sufficient long-term safety data at doses of at least 40 mg/day. Further, they have provided adequate responses to the other specific safety issues raised in the Not Approvable letter (which were not reasons for the NA action), although several of the reviewers have additional questions for the sponsor (specifically there remain CMC and OCPB questions, and DMETS finds the sponsor's new proposed names, Variza and Alrize, unacceptable).

COMMENTS

Subsequent to the Not Approvable letter, the sponsor has submitted the results of two additional controlled trials examining the effectiveness of gepirone as a treatment for patients with MDD; Study 134004, a short term trial comparing gepirone, fluoxetine, and placebo, and Study 28709, a randomized withdrawal study. Study 134004 failed, as described by the sponsor, to distinguish gepirone (and fluoxetine) from placebo, but Study 28709, according to the sponsor, is a positive study. In addition, we have agreed with the sponsor that Study 03A7A-003, a short term study of the IR formulation, is acceptable as a positive study. Therefore, the sponsor argues that they have submitted data from three controlled studies (one with the IR, two [one short term and one randomized withdrawal] with the ER) that establish the effectiveness of gepirone ER as a treatment for patients with MDD.

Unfortunately, we cannot agree with the sponsor that Study 28709 is a positive study. As described above, the sponsor had identified 5 patients (all on gepirone) that they considered as having met relapse criteria, while the study was still blinded, but then, ***after the data were unblinded***, decided that these patients should not be included in the analysis, because they could not confirm the patients' status with the investigators. The team concludes, and I completely agree, that these patients appear to have met the criteria for relapse (recall that these criteria include physician decision that the patient had failed treatment, independent of any particular HAMD score), and that they should be included in the analyses; as we have seen, when these patients are included, the results are no longer significant.

Beyond this, the sponsor has also excluded data from 32 patients because they were at centers that enrolled patients only on one treatment, or there were no events at those centers. The team has concluded, and I again agree, that these patients should be included in the analyses, and Dr. Kelly has included these patients in analyses that are fairly typically performed under these circumstances. These analyses are not significant, and inclusion of the 5 gepirone patients discussed above in these analyses yield p-values for the

gepirone-placebo contrasts of about 0.3. For these reasons, then, I consider Study 28709 a negative study.

We are then left with two positive short term studies, one with the ER formulation, and one with the IR formulation. In our Not Approvable letter, we informed the sponsor that they would need an additional positive short term study with the ER tablet; they have not provided such a study. However, they have now presented the results of two positive studies. Is this sufficient to support a finding that there is substantial evidence of effectiveness for the ER formulation?

In answering this question, I would like to make an initial point.

Dr. Laughren has concluded that we have never approved an application for an ER product on the basis of one study with an ER, and one study with an IR, formulation, and that such an array of results should not support approval of the ER. I noted in my memo of 3/7/02 that we have approved applications on the basis of similar reasoning in other contexts, but agreed that we have never approved an application for one formulation based on two trials, one of which was with a different formulation (as is the situation here). I did, however, allow for the possibility that two studies of this sort might support approval of the ER (see my 3/7/02 my reasoning). I still believe that this would be a possibility, all other things being equal.

However, I do not believe that the data before us support approval, even though there are two positive trials.

We now have a total of 5 short term trials with the ER formulation that are capable of demonstrating effectiveness, only one of which is positive. Further, in the most recent such trial, fluoxetine is almost statistically significantly superior to gepirone. Additionally, the new randomized withdrawal study, when appropriately analyzed, does not yield a statistically significant difference in favor of gepirone (indeed, the most appropriate analyses yield p-values of about 0.3 for the gepirone-placebo differences).

I believe that this panoply of results raises serious doubts about the effectiveness of gepirone, and especially about the effectiveness of gepirone ER. Although there are two “positive” studies, the existence of many well designed and conducted studies that fail to find an effect is troubling, and I agree with Dr. Laughren that it is difficult to imagine what else the sponsor could do to convince us that the drug is effective. However, I suppose that an additional clearly positive short term study as well as a clearly positive long term maintenance, randomized withdrawal study would provide the sufficient additional data necessary to support the approval of gepirone ER.

For these reasons, then, we recommend that the attached Not Approvable letter be sent to the sponsor.

APPEARS THIS WAY ON ORIGINAL

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/s/

Russell Katz
6/15/04 09:36:23 AM
MEDICAL OFFICER

MEMORANDUM

DATE: March 7, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-164

SUBJECT: Recommendation for Action on NDA 21-164, for the use of Gepirone hydrochloride Extended-Release Tablets in Patients with Major Depressive Disorder (MDD)

NDA 21-164, for the use of Gepirone hydrochloride Extended-Release Tablets in Patients with Major Depressive Disorder (MDD), was submitted by Organon, Inc., on 5/18/01. It had previously been submitted on 9/30/99, but the division refused to file the application for review; the reason for this action was detailed in a letter to the sponsor on 11/30/99. Specifically, prior to that submission, we had informed the sponsor that marketing of the ER formulation could be supported by a single "positive" controlled trial with this formulation if there were at least 2 "positive" controlled trials with the immediate release formulation, which the sponsor had asserted there were. In addition, in discussions prior to the submission, the sponsor asserted that they did have a "positive" trial with the ER formulation.

However, upon receipt of the application, the review team noted that the single "positive" trial was, in fact, one of two centers of a planned 2 center, multi-center trial, that, when analyzed as per protocol, failed to yield a statistically significant between-group difference, by the sponsor's admission. Because the division believed that this nominally significant post hoc finding at this single center did not constitute a bona fide "positive" trial, the application was not filed for review. The sponsor subsequently performed new trials with the ER formulation, and the application was re-submitted on 5/18/01, and filed for review.

The application has been reviewed by Dr. Earl Hearst, medical reviewer (review dated 2/19/02), Drs. Roswitha Kelly and Kooros Mahjoob, statisticians (review dated 3/4/02), Dr. Tarek Hammad, safety reviewer (review dated 2/26/02), Dr. Judy Racoosin, safety team leader (memo dated 2/28/02), Dr. Linda Fossom, pharmacologist, Dr. Sherita McLamore, chemist (reviews dated 1/31/02 and 2/26/02, Dr. Gerald Fetterly, Office of Clinical Pharmacology and Biopharmaceutics (review dated 2/19/02), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 3/5/02).

While Dr. Hearst recommends that the application be considered Approvable, Drs. Kelly and Mahjoob have concluded that the application contains only one adequate and well-controlled trial that yielded a reliable statistically significant

between treatment difference, and Dr. Laughren recommends that the application be considered Not Approvable.

Dr. Laughren's memo provides a comprehensive, detailed, yet concise summary of the relevant data in the application.

Briefly, the sponsor presents the results of 18 controlled trials, 10 performed with the IR formulation, 8 with the ER formulation (the large number of studies is related to the fact that this drug was originally developed by Bristol Myers Squibb, who started many trials and then decided to abandon the project). Of these studies, the sponsor proposes that four are adequate and well-controlled trials that, taken together, provide substantial evidence of effectiveness for Gepirone as a treatment for MDD.

Study 001 was an 8 week trial in which patients were randomized to Gepirone ER 20-80 mg/ day or placebo. The primary outcome was change from baseline on HAMD-17. This study yielded a between-treatment p-value of 0.018 for the LOCF analysis.

Study 003 was an 8 week trial performed at a single US site in which patients were randomized to receive Gepirone IR 10-120 mg/day, given BID, or placebo. Patients in this trial were diagnosed with MDD with atypical features. Critically, the mean HAMD on entrance into the trial was about 13 (compared to >20 in the other trials in this application, as well in other studies in other anti-depressant development programs). The primary outcomes in this trial were change from baseline in HAMD-17 total score, and percent of responders, defined as patients with a score of 1 (very much improved) or 2 (much improved). The p-values for the drug-placebo contrasts were 0.009 and 0.009.

Study 001B was an 8 week study performed in 3 US sites in which patients were randomized to Gepirone IR 5-60 mg/day given BID, Gepirone 10-120 mg/day given BID, or placebo. The primary outcomes were as in Study 003. The p-values for the drug-placebo contrasts were significant for both dose-range groups on both outcomes. However, there was a very significant treatment-by-center interaction. The following display describes the results by center for the HAMD-17, LOCF analysis:

	Carmen (N=89)	Haggerty (N=89)	Cole (N=28)
Gepirone 5-60	-10.5	-11.3	-8.2
Gepirone 10-120	-10.1	-10.2	-13.6
Placebo	-8.5	-9.5	-1.1

Analyses for the HAMD-17 excluding data from the Cole site yielded p-values of 0.3 (Gep 5-60 vs placebo) and 0.8 (Gep 10-120 vs placebo).

Study 002 was a randomized withdrawal trial in which patients were treated with open-label Gepirone IR for 6 weeks. Responders were re-randomized to continue on their previous dose of Gepirone IR (10-90 mg/day given BID) or placebo for an additional 6 weeks. The protocol did not specifically identify primary outcomes, but did state that change from baseline in HAMD-17 and percent of responders on CGI were "important" endpoints. The p-values for the drug-placebo contrasts were 0.08 and 0.24, respectively. However, the sponsor presented the results of analyses of time to reaching 6 different exit criteria, all of which were apparently constructed after the data had been examined. The results of the drug-placebo contrasts for 4 of these outcomes were nominally significant (including one of the six that the sponsor considered most important).

As noted, the sponsor submitted the results of 14 short term (6-8 weeks) additional controlled trials. None of these studies yielded statistically significant between-treatment differences on their primary outcomes, save for one (2486), with a 70% dropout rate. Seven of these studies included an active control (4 with the IR formulation, 3 with the ER formulation; all studies utilized appropriate doses of the active control); in 5 of these studies, the active control group was not distinguished from placebo. In two studies (022 and 028), the active control was significantly superior to placebo; the mean Gepirone dose in the first was about 15 mg/day, and in the second about 13 mg/day.

As Dr. Laughren notes, many of these 14 studies employed relatively low doses. As he points out, any trial that limited the maximum daily Gepirone dose to 40 mg was "negative", and in most of these studies, the mean daily dose (they were all flexible dose range trials) was below 20 mg. In addition, a number of the studies were stopped by the sponsor before they reached their originally planned total sample size.

However, as Drs. Laughren, Kelly, and Mahjoob note, there were a number of studies that appeared to be well-designed and which utilized doses of Gepirone which were comparable to those used in the studies which the sponsor asserts demonstrate effectiveness. While it is not unexpected that a certain number of trials of effective anti-depressants will not distinguish drug from placebo, there are at least 4 such trials in this application.

I completely agree with Dr. Laughren's reasoning for concluding that the sponsor has not submitted substantial evidence of effectiveness for Gepirone ER as a treatment for MDD.

Specifically, Study 001 is a well-controlled trial that is one source of evidence that could contribute to a finding of substantial evidence of effectiveness.

However, the other studies, while ostensibly yielding significant between-treatment differences, do not, in my view, support the conclusion that gepirone is effective as a treatment for patients with MDD.

Study 003 enrolled patients that were clearly not comparable to the other patients enrolled in studies in this program (or in other anti-depressant development programs). While the sponsor asserts that these patients were appropriately diagnosed as having MDD, the extraordinarily low mean baseline HAMD scores would suggest otherwise. It is clear, given this data, that these patients were not typical MDD patients, and therefore I cannot consider this study as evidence that the treatment is effective as a treatment for MDD. I also agree with Dr. Laughren that the reasons cited by Drs. Kelly and Mahjoob for questioning the results of the trial (single center with a small sample size and about a 40% dropout rate), in and of themselves, are not sufficient for discounting the results of this trial.

Study 001B yielded "positive" results that were entirely due to the outcome at one of the 3 sites. This site was by far the smallest site (enrolling 1/3 the number of patients at each of the other 2 sites), 7/9 placebo patients discontinued, and, most critically, the placebo response seen at this site was extraordinarily and uniquely small; it was essentially non-existent. This highly anomalous placebo response makes the result at this site unreliable in my view. In such a case, I would argue that a reliable conclusion can be reached only on the basis of re-analysis of the 2 remaining centers; this analysis does not yield statistically significant between-treatment contrasts.

Finally, Study 002 was designed and conducted as a typical randomized withdrawal study of the sort ordinarily performed to demonstrate long-term effectiveness (although the treatment periods were fairly short). I believe that such a trial could reliably support a short-term effectiveness claim as well. However, in this case, the primary outcomes in the protocol (as best we can tell) were not of the sort normally employed in this type of trial. That is, the sponsor did not designate time to relapse as a primary measure of effectiveness; rather, the protocol suggests that the primary the outcomes were more typical of short-term studies, namely change from baseline in HAMD and proportion of CGI responders. Such a choice for this design is not inappropriate, but the results were not significant. The sponsor did, retrospectively, create 6 different failure criteria, all constructed and chosen after the original study had been unblinded and analyzed. Even in this case, only 4 reached nominal significance, and, as noted by Dr. Laughren any or all of these would likely have been considered appropriate had they been prospectively designated, so there is no valid reason to ignore the 2 negative contrasts. The fatal flaw in this trial, though, is the creation and analysis of "primary" outcomes after the trial data have been unblinded and the contrasts on the protocol specified primary outcomes were not significant.

Although I do not believe that the sponsor has provided substantial evidence of effectiveness at any dose, it is likely that if they ultimately do provide such evidence, the effective dose will probably be greater than 40 mg/day. As the review team has noted, the sponsor has not submitted sufficient long-term safety

data at this dose to adequately characterize the long-term safety. At the moment, there appear to be no adverse events seen at what might turn out to be appropriate doses to preclude ultimate approval, although the presentation of the safety data has been marred by a number of problems, including an inadequate presentation of the adverse event data separately for the ER and IR formulations. There are other issues that require clarification, and the sponsor should be requested to address these (see Dr. Laughren's and Dr. Racoosin's memos on this point). The one additional point I would add is that there were a number of patients whose final laboratory values were abnormal; I believe we should ask the sponsor to obtain follow-up for these patients.

There are additional points that need to be made in our action letter, including a number of CMC issues, the finding that the proposed tradename (Ariza) has been found to be unacceptable (similarity to Arava; we informed the sponsor of this in a letter dated 1/14/02), additional biopharmaceutics requirements, including the fact that the 40, 60, and 80 mg tablets have not been shown to be equivalent to the 20 mg tablet, and an additional pharmacology requirement (a phase 4 commitment to perform an additional in vitro chromosomal aberration test).

The clinical program presented in this application is remarkable in a number of aspects. The sponsor has provided results of 18 controlled trials, only one of which can be considered, in my view, unambiguously "positive" by the usual standards. While a number of these studies randomized patients to 2 dose groups, these groups were not fixed doses but flexible ranges, and often the ranges for the 2 dose groups overlapped with each other. This resulted in a very large development program with no useful dose response data; this serious deficiency in the development program might very well have been responsible for the lack of "positive" studies.

For the reasons cited above, then, I believe that the sponsor has not provided substantial evidence of effectiveness of gepirone ER in the treatment of patients with MDD. I recommend that the Agency issue a Not Approvable letter with an explicit requirement for at least one, fixed dose controlled trial of, ideally, the ER formulation. Dr. Laughren also recommends that we issue a Not Approvable letter, but that we also issue labeling. This would be quite unusual, and I would recommend that we not issue labeling with the letter, primarily because, if the drug is ultimately approved, the final label might be considerably different from what we wish to propose at this time (although I acknowledge that certain sections are unlikely to change significantly).

I wish to address one final point.

As Dr. Laughren has described, we had originally informed the sponsor that a single "positive" trial with the ER formulation, in the context of at least 2 such trials with the IR formulation, would support the approval of the ER tablet. He

notes in his memo that even if one of the 3 submitted IR studies were “positive”, in his view this would be inadequate to support approval of the ER tablet, because there would be no replicated finding for either of the dosage forms.

I believe I would entertain the possibility that a single “positive” study with each formulation could be considered sufficient to support the approval of both formulations. Such an outcome could be argued to provide independent replication of the finding that the moiety is effective. Indeed, there are precedents in this division for similar, though not identical, actions.

For example, we have granted claims for monotherapy and adjunctive therapy for drugs to treat patients with Parkinson’s Disease on the basis of a single study in each of these settings. I would be willing to consider an argument that a single study with each gepirone formulation would support approval of both as being analogous to the former situation. However, because I believe that the sponsor needs to provide at least one additional trial to support approval of gepirone ER, it would be least controversial for that study to be performed with the ER tablet.

Russell Katz, M.D.

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/s/

Russell Katz
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