CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-164

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

Dear Dr. Kramer:

Please refer to your new drug application dated September 30, 1999 received October 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gepirone Hydrochloride Extended Release 20mg, 40mg, 60mg, and 80mg tablets.

We acknowledge receipt of your submissions dated May 1, 2007, July 13, 2007, & October 8, 2007.

The May 1, 2007 submission constituted a complete response to our June 23, 2004 action letter.

We have completed our review of your resubmission and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Non-Approval Deficiencies:
There are two major deficiencies in the application. First you have failed to provide substantial evidence for the effectiveness of gepirone ER in the short-term or longer-term treatment of major depressive disorder (MDD). In addition, if the data could be considered as representing such evidence we also believe the effect size that would have been demonstrated is unacceptably small compared to alternative therapy for a serious illness. Although we agree that you have provided two well – controlled trials that show a significant effect, i.e. studies FKGBE007 and 134001, this evidence is derived from a total pool of 12 studies. The remaining 10 studies do not show evidence of an antidepressant effect. Indeed, they do not even show favorable trends in almost all cases. We 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, but in one of these an active control was effective and none of the studies show reasonably strong favorable trends. Moreover, there are other findings among these trials that amplify our 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, you selected this as a common endpoint for your 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:

Trial	Active Comparator	P-Values Act Comp vs Pbo	P-Values 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)

Thus, among a total of 5 trials with active comparators, 3 clearly possessed assay sensitivity, yet failed to show an effect of gepirone. We have not seen such results with any effective drug.

We regularly use meta-analysis as an approach for evaluating demographic subsets within trials (the integrated summary of effectiveness) and for considering, at least at the exploratory level, other hypotheses that a single trial might not be powered to demonstrate, but we have not accepted pooled data as a substitute for a showing of effectiveness in individual trials. Nonetheless, we did examine the 10 failed studies to determine whether they might collectively suggest clinical effectiveness. This meta-analysis would of course need to exclude studies FKGBE007 and 134001 because the major reason for conducting it would be to determine if, among the remaining 10 non-supportive trials, there was any suggestion of an affect of gepirone ER. Using your meta-analytic model for these 10 trials we found an effect size of essentially zero, -0.09 (p= 0.62). Even your proposed approach of including all 12 trials, gives an effect size of -0.48 (p= 0.09), showing that the remaining trials weaken the effect of your two favorable studies. A finding of two positive trials among 12 could occur by chance (about 3.5%) and does not represent substantial evidence of effectiveness.

The negative outcome for the longer-term maintenance efficacy trial (study 28709) is also a concern for this drug. First, we disagree with your 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. Your 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 almost never fail to show a drug effect. Thus, this finding further casts doubt on the evidence that gepirone is effective.

As noted in our June 23, 2004, not approvable letter for this application, it is difficult to know how to advise you regarding any future work with gepirone ER. Even if another positive study were to provide further support of an effect, the overall results and 3 studies showing inferiority to an active control indicate that gepirone, if it has any effect at all, is far less effective than standard therapy. We consider MDD a serious illness and it is hard to see a basis for approving an antidepressant drug that was demonstrably and substantially less effective than other available agents, essentially leaving

patients untreated until they substitute effective therapy. The only possible basis for approval we can see at present would be is a determination that an inadequate dose was used in studies to date with studies at an appropriate dose showing an effect similar to other antidepressants. We note that you have provided some evidence of a lesser risk of sexual dysfunction with gepirone ER than is seen with many other antidepressant agents but this cannot support approval. First, the data you have accumulated regarding sexual dysfunction do not consistently support this premise. Second, we do not feel such a finding would overcome the disadvantage of the observed decreased effectiveness. We would be willing to discuss the efficacy data with you, but we are not optimistic that there is a reasonable path forward for any further development of this drug as an antidepressant.

Although not a reason for this not approvable action, you will need to also address the Chemistry Manufacturing and Controls deficiencies below:

1. Revise your acceptance criterion for Individual unspecified impurity to NMT (b) (4)% in accordance with ICH Q3B guideline. Any individual impurities at levels higher than identification threshold of (b) (4)% should be specified by name, relative retention time or some other suitable identifier.

2. The provided stability data for the original biconvex tablets and the Organon modified flat tablets is not sufficient to support your request for 36 month expiration date for the drug product. Please provide long-term and accelerated stability data for the commercial to-be-marketed drug product in each of the proposed packaging configurations.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact LCDR Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
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

11/2/2007 02:23:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-164

Organon, Inc.
Attention: Edna Gilvary, Ph.D.
Regulatory Scientist II
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Dr. Gilvary:

Please refer to your new drug application (NDA) dated September 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gepirone hydrochloride Extended-Release 20 mg, 40 mg, 60 mg, and 80 mg Tablets.

We acknowledge receipt of your submissions dated December 23, 2003, February 9, February 27, March 19, April 5, and May 19, 2004.

The December 23, 2003 submission constituted a complete response to our March 15, 2002 action letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Nonapproval Deficiencies

You have still not, in our view, provided substantial evidence of the effectiveness of gepirone ER in the short-term or longer-term treatment of major depressive disorder (MDD). We acknowledge our earlier discussion with you on July 3, 2002, at which time we agreed that you had produced evidence of short-term efficacy for gepirone ER in study 134001 and for gepirone IR in study 03A7A-003. At that meeting, you indicated that the results from another short-term ER study (134004) would soon be available, as well as results from a longer-term randomized withdrawal study (28709). We indicated that, if study 134004 were robustly positive, you would have sufficient efficacy data for filing the application. We subsequently learned, however, in an April 17, 2003 package outlining your proposed response to our March 15, 2002 nonapprovable letter, that study 134004 failed to distinguish gepirone from placebo. Although at first glance, the failure of fluoxetine to show superiority to placebo suggests that study 134004 lacked assay sensitivity, fluoxetine was in fact nearly significantly superior to gepirone, a very unusual outcome in comparisons of two active antidepressants and a more troubling result. You indicated, however, that your randomized withdrawal study (28709) was positive, and argued

that this combination of two positive short-term studies, one for each of the two formulations, together with one positive gepirone ER long-term study, should be sufficient to file the application. In a July 14, 2003 teleconference, we agreed only that we would probably be willing to file such an application, without reaching any agreement that this combination of studies would represent sufficient support of the effectiveness of gepirone. We noted that part of the difficulty was a preponderance of negative studies for gepirone in the application, making the overall program very weak indeed.

Now that we have had an opportunity to review the data for study 28709, we do not agree that it is a positive study. It was a fairly typical randomized withdrawal study in adult depression (MDD), with an 8-12 week open label phase, followed by a double-blind phase in which patients responding to open treatment with gepirone (HAMD-17 total score $\leq$ 8, at week 8 or week 12) were randomized to either continuation of gepirone (at the same dose that was associated with a "response") or to placebo, with a 40-44 week period of observation for relapse (defined as a HAMD-17 $\geq$ 16, or discontinuation due to lack of efficacy as determined by the investigator). The primary outcome was the proportion of patients who had relapsed at the end of the observation period, and the primary analysis was the Cochran-Mantel-Haenszel test (CMH), with adjustment for centers. Time to relapse was a secondary endpoint. Survival curves were estimated using Kaplan-Meier methodology and the log-rank test was used to compare survival distributions. Both analyses were based on a modified intent-to-treat sample, i.e., all patients randomized who received at least 1 dose of assigned treatment and who had at least 1 post baseline efficacy evaluation.

According to your analysis, the results on the primary endpoint, rate of relapse at study end, favored gepirone:

Gepirone:	29/126 (23%)	
Placebo:	43/124 (35%)	p=0.024

However, there were two important problems with your analysis:

1. 5 patients on gepirone appeared to have had relapses, but were not included in your analysis:

   Prior to unblinding the data, you identified 5 gepirone patients who appeared to have met relapse criteria, since they were discontinued due to worsening of depression, but had not been so designated on the CRF (as noted, discontinuation due to lack of efficacy was one of two criteria for relapse). In fact, you have produced an internal memo, prepared prior to unblinding, indicating that these patients would be redefined as having relapsed, and they were so redefined. Subsequent to unblinding and analysis, you discovered that these patients' scores had not met the $\geq$ 16 criterion, but it was too late to query investigators, since they had also been unblinded. Nevertheless, you then decided to exclude the patients as relapsers, on the grounds that the redefinition had not been done by formal amendment and it had not been possible to query investigators. As it turns out, this redefinition is critical to the outcome, since, if these 5 patients are included as relapsers, the results are as follows:

Gepirone:	34/126 (27%)	
Placebo:	43/124 (35%)	p=0.101

We consider it inappropriate, after looking at the results of the analysis, to decide not to include these patients as relapsers, when they had already been quite reasonably reclassified as relapsers by you prior to unblinding the data. It seems obvious, on face, that these 5 patients who were discontinued for worsening depression should be counted as relapsers, given that their discontinuations were for "worsening of depression," whether or not there was an opportunity to query the investigators to try to verify this result. Thus, we believe the appropriate analysis is the one that includes these 5 patients as having relapsed.

2. Failure to include all ITT patients in the analysis

We also note that you excluded 32 patients from the analysis (CMH) because they came from centers that had patients in only 1 treatment arm, or had no relapses. A more appropriate analysis, grouping these centers, gives a nonsignificant result: p=0.10, with grouping of small centers; p=0.08, with grouping by country. These results are negative, even with your exclusion of the 5 relapsed patients we feel should be included. When these 5 patients are included in these analyses with appropriate grouping of centers, the results are far from significant (p=0.33 and p=0.31, respectively, for groupings by small center and by country).

The results on the secondary endpoint, time to relapse, also did not favor gepirone, with a p-value of 0.089. When the additional 5 patients are included, the p-value is 0.28. Generally for this type of study, we consider the time to relapse analysis as the more appropriate analysis, and the one that we always recommend. The CMH analysis of proportion relapsed does not properly address censored patients, in that it implicitly treats them as successes.

The finding of only two positive short-term trials for gepirone, one for IR (03A7A-003) and one for ER (134001), out of a total of 19 short-term placebo controlled trials is a significant concern. While we have accepted your explanation for the failure of many of these trials, we noted in our March 15, 2002 letter that 3 of the short-term ER studies appeared adequate, on face, and would have been expected to succeed. Thus, the finding of only one of four adequately designed short-term ER studies having a positive outcome was not reassuring. This concern was the basis for our indicating that an additional "robustly positive" ER study would be needed. The result of the most recent ER study (134004) adds to our concern. Although this study is on face a failure for both fluoxetine and gepirone, it actually favors fluoxetine over gepirone. The results for gepirone are actually numerically worse than placebo, while the results for fluoxetine are numerically superior to placebo, and the p-value for the fluoxetine/gepirone contrast on the primary outcome (HAMD-25) is strongly trending toward statistical significance (p=0.068). Thus, of 5 short-term seemingly well- designed ER studies, only one of the five was positive. Given this very marginal set of results for the gepirone short-term efficacy data, a robustly positive result for the randomized withdrawal study became even more pressing. As noted, we do not consider 28709 to be a positive study.

In summary, you have not provided substantial evidence that gepirone ER is effective in the treatment of MDD. While it is true that you have provided evidence of an effect from 2 short-

term studies, these used 2 different formulations (1 for IR and 1 for ER). We do not find these data sufficient to support the effectiveness of gepirone ER. The negative outcome on study 28709, which used a randomized withdrawal design that regularly is successful in showing the effectiveness of effective agents, further weakens what evidence there was to support an antidepressant claim for gepirone ER. Furthermore, as the negative data continue to accumulate, it becomes difficult to advise you on what further work you might do to address such a preponderance of negativity. At this point, we would want at least a "robustly positive" short-term trial with gepirone ER and a positive randomized withdrawal study. The short-term trial should look at different fixed doses of gepirone ER, and the randomized withdrawal study would need to involve a period of "response" for a minimum of 6 months before randomization.

Additionally, we have the following comments and requests that will need to be addressed in your resubmission.

Proposed Tradename

Our Division of Medication Errors and Technical Support (DMETS) has completed their review of your proposed tradenames of "Variza" and "Alrize". The Variza tradename was found unacceptable because there are existing drug names that sound like or look like Variza to a degree that potential confusion between drug names could occur under the usual clinical practice settings. The Alrize tradename was found unacceptable because the name is misleading.

Please submit another proposed tradename for review by the Agency.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified several areas of possible improvement that might minimize potential user error.

A. Blister Label (14 Count Patient Starter Kit)

   1. Please include product strength.

   2. If the starter kit is available in different strengths, ensure that the strengths are clearly differentiated by using contrasting color, boxing, or some other means.

   3. Add a net quantity statement.

   4. Please include the statement "Each tablet contains xx mg……..etc".

B. Container Label (Professional Sample – 7 count)

   See comments A-2 and A-4.

C. Container Label (20 mg, 40 mg, 60 mg, and 80 mg - 30 count and 500 count)

   1. Increase the prominence of the established name, relative to the dosage form.

2. Relocate the product strength so that it appears below the established name, and away from the net quantity.

3. Please ensure that the multiple strengths are clear differentiated by using contrasting color, boxing, or some other means.

4. Decrease the prominence of the net quantity statement for the 500 count label.

5. Please add a Child Resistant Closure (CRC) statement to the 30 count bottle.

D. Carton Labeling (20 mg, 40 mg, 60 mg, and 80 mg - 30 count and 500 count)

See comments C-1, C-3, and C-4.

Chemistry, Manufacturing, and Controls

1. Provide a stability protocol and updated stability data for the commercial drug product.

2. The Office of Compliance has informed us that the Organon Inc. Sub Akzona Inc. (West Orange, NJ; CFN #2211109) site will be closing in June 2004. As a result, this site will need to be withdrawn from the NDA. Please verify that Organon N.V. (OSS, NL; CFN #9610342) and Pliva USA Inc. (East Hanover, NJ; CFN #2243128) will continue to serve as the drug product release testing facilities.

Clinical Pharmacology and Biopharmaceutics

Your resubmission provided studies or explanations that addressed the recommendations of the Office of Clinical Pharmacology and Biopharmaceutics in our March 15, 2002 action letter. Although your responses were generally acceptable, there are several recently identified issues regarding the pharmacokinetics of gepirone as well as recent changes in the drug product that are of some concern. They are as follows:

1. You have now changed the tablet shape with a change in commercial tooling from the original biconvex tablet to the modified flat tablets. Dissolution has only been evaluated for the 20 mg and 80 mg strength tablets. Therefore, the 20 and 80 mg strength tablets (with the modified flat tablet shape) are acceptable, but the 40 and 60 mg strength tablets (with the modified flat tablet shape) are not acceptable.

   Please submit results of dissolution comparisons (of the original vs. modified shape) in multiple media with f2 comparisons to request a biowaiver for the 40 and 60 mg strength tablets.

2. Your proposed dissolution specifications are acceptable on an interim basis. The dissolution specifications are as follows:

   15-25% at 1 h
   40-85% at 5 h
   65-86% at 12 h
   > 86% at 20 h

   These specifications are acceptable provided that you adhere to your stated commitment to re-evaluate the specification at 12 hours after the manufacture of 20 batches of each strength.

3. We ask that you agree to conduct the following studies as a Phase 4 commitment:

   a) Measurement of the effect of intermediate inducers such as rifabutin.
   b) You previously agreed to conduct an *in vivo* study evaluating the effects of different meal compositions on gepirone ER pharmacokinetics as a Phase 4 commitment, and you have stated that the study has been initiated.
   c) We note your commitment to re-evaluate the dissolution specification at 12 hours after the manufacture of 20 batches of each strength.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
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

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-164

Organon, Inc.
Attention: Edna Gilvary, Ph.D.
Regulatory Scientist II
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Dr. Gilvary:

Please refer to your new drug application (NDA) dated September 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gepirone hydrochloride Extended-Release 20 mg, 40 mg, 60 mg, and 80 mg Tablets.

Reference is also made to an Agency letter dated November 30, 1999, refusing to file this application, and to your resubmission of the above referenced NDA dated May 18, 2001.

We acknowledge receipt of your submissions dated August 31, September 18, October 11, November 13, 21, December 10, 28, 2001, January 9, 15, 23, 24, 31, and February 15, 2002.

We have completed our review and find the information presented is inadequate. The critical deficiency that is the basis of this nonapproval action is the lack of adequate efficacy data to support a claim in major depressive disorder as well as the inadequate amount of long-term safety data. In addition, we have included in the letter other issues that, while not the basis for this action, would need to be addressed, in some cases prior to any final approval action, and in others, postapproval. Because of the lack of substantial evidence of effectiveness and the inadequate amount of long-term safety data, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

NONAPPROVAL DEFICIENCIES

1. Inadequate Efficacy Data

You have not provided substantial evidence of effectiveness for the claim of short-term efficacy for gepirone ER in major depressive disorder (MDD). We acknowledge our earlier discussions with you, at which time we had agreed that a single positive short-term trial with the ER formulation, in the face of independent evidence for the efficacy of the IR formulation in MDD, would be sufficient to support a claim for the efficacy of the ER formulation in MDD. We have concluded, however, that you have not provided such evidence for the IR formulation.

We are in agreement with you regarding the short-term gepirone ER study (134001) and consider this a positive study in support of gepirone ER in MDD. However, we do not feel that any of the 3 gepirone IR studies proposed by you as support for the MDD claim can, in fact, be considered positive studies in support of this claim.

-Study 03A7A-003: While we do not dispute the fact that this study has a positive outcome on the protocol specified coprimary outcomes, we have a serious concern about the characterization of the population studied. While a majority of patients reportedly met RDC criteria for MDD (about 2/3), their baseline HAMD-17 scores belie this assertion. The mean baseline scores of 13-14 are roughly 10 points below the usual scores on this measure in MDD, and this finding raises a serious question of the diagnoses of these patients. While "atypical depression," as defined in this protocol, is in fact described as an accepted "specifier" for MDD in DSM-IV, there is still, in our view, much controversy about what population is actually captured when, as was the case here, "atypical features" are the primary criteria for selection of patients. Clearly, patients with a mood disorder other than MDD could have been recruited, and we think the relatively low HAMD-17 scores are reflective of the diversity of patients in this sample. In fact, many of these patients likely overlapped with patients having GAD, and if this were the case in this study, the outcome would not be surprising, given the fact that a very closely related drug, buspirone, has been shown to be effective in GAD. We therefore do not consider it a study that can support a claim of effectiveness in MDD. You may, of course, choose to challenge this objection. If you do, you will need to describe very clearly how you have determined that at least some of the patients did meet criteria for MDD. We may then ask for an additional analysis of the subgroup of patients who could have been reasonably considered to meet the criteria for MDD.

-Study 03A7C-001-B: While this study appears to have an overall positive outcome on the protocol specified coprimary outcomes, we explored the significant treatment by center interaction, and discovered that the overall positive results are coming from one center, i.e., the smallest center (Cole), while the other centers show little effect.

Efficacy Results by Center on HAMD-17 Total Score for 03A7C-001-B (LOCF)

Carmen (n=89)

	Baseline HAMD-17
Gepirone IR (5-60)	**-10.5**
Gepirone IR (10-120)	**-10.1**
Placebo	**-8.5**

Cole (n=28)

	Baseline HAMD-17
Gepirone IR (5-60)	**-8.2**
Gepirone IR (10-120)	**-13.6**
Placebo	**-1.1**

Haggerty (n=89)

	Baseline HAMD-17
Gepirone IR (5-60)	**-11.3**
Gepirone IR (10-120)	**-10.2**
Placebo	**-9.5**

In fact, an analysis conducted without the Cole center does not yield positive results on the HAMD-17 change from baseline (p=0.28 for the 5-60 mg group and p=0.84 for the 10-120 mg group). A critical consideration in our judgement is the finding of essentially no placebo effect in the Cole center. This is an extremely unusual finding in depression trials, and brings into question any results seen in this center.

-Study 03A7A-002: This study had the usual randomized withdrawal design ordinarily employed to document long-term effectiveness of antidepressants, although it was quite atypical for this design in that both the run-in period and the randomized withdrawal period were quite short. Despite this, it might have provided some indication of antidepressant activity, had there been an effect on the primary outcomes specified in the protocol. In fact, the protocol was not clear on the primary outcome but specified change from baseline in the HAMD-17 as an "important" endpoint. The study report also refers to 6 different definitions of relapse as key endpoints, but these endpoints were apparently defined long after the conduct and analysis of this trial. There were no statistically significant differences favoring gepirone IR over placebo on change from baseline in HAMD-17, or on CGI-I responder status, another outcome that would have been relevant to the claim, and that appears from the protocol also to have been considered an "important" outcome measure. The results on time to relapse favored gepirone 20-90 over placebo for 4 of the 6 definitions of relapse. Although none of the 6 definitions would have been rejected as unreasonable primary endpoints, their post-facto identification, together with failure to show an effect on the primary endpoints, leaves Study 03A7-002 unable to provide primary support for the claim of efficacy of gepirone IR in MDD.

An additional concern for all three gepirone IR studies was that interim analyses were planned in the protocols for these trials, but we have no information about whether or not such analyses were actually carried out. This is an additional source of potential bias for these trials that greatly complicates their interpretation, although we wish to be clear that, even in the absence of any interim analyses, the deficiencies described above make these latter three studies unacceptable.

In addition to the specific problems identified in the "positive" studies presented, there is a general concern about the many negative trials in the overall development program for both the IR and ER formulations. The 4 studies that you have proposed as positive in support of the efficacy claim arise from a total of 18 short-term placebo-controlled trials in depression. We agree with the explanations proposed to explain the negative findings for many of these studies, in particular, the dose likely being too low, and an active control arm that also failed to beat placebo. Nevertheless, 3 of the 14 remaining studies are negative without good explanation. These studies are as follows: 134002, CN105-078, and CN105-083, all for gepirone ER. All 3 studies were sufficiently adequate by design, including gepirone ER dose, duration, population studied, assessment methods, and study conduct otherwise, to be considered relevant to the efficacy of gepirone, and yet all 3 failed to show a benefit for gepirone ER. While we agree that these studies are not readily interpretable, we still think they need to be considered as negative trials for gepirone ER, and therefore, should be considered in the overall benefit assessment for this drug. Thus, in summary, of 4 studies that appear, on face, to be relevant for consideration of the efficacy of gepirone ER, only one yielded a positive result. Although the result seen here (i.e., 1 of 4 relevant studies being positive) is not a result that would lead us to conclude that gepirone ER is ineffective as an antidepressant, we believe one additional positive study for the ER formulation is needed to demonstrate that this formulation has antidepressant efficacy.

The additional study should be a dose-response study. There is at present little data pertinent to the question of dose response. Given the uniformly negative results in studies with a maximum dose of ≤ 40, it is tempting to conclude that doses lower than 40 mg are not likely to be effective. However, it would be highly preferable to have the finding of lack of effect below 40 mg/day come from the same study in which doses above 40 mg/day were shown to be effective, i.e., a dose response study, as well as to explore the effective dose range. If you choose to continue to develop this drug for MDD, you should design a study that looks at different fixed doses of gepirone ER in MDD. In addition, we recommend that you collect, through sparse sampling, plasma level data for gepirone and its two major metabolites, 1-pyrimidinyl-(2-piperazine) (1-PP) and 3'OH-gepirone. These data could help in understanding the relationship between exposure and clinical response.

2. Inadequate Safety Data

Long-Term Safety Data

As conveyed to you in a conference call dated October 11, 2001, your long-term exposure data is inadequate to assess the safety of gepirone. The ICH guidelines indicate that there should be 300-600 individuals exposed to an effective dose for 6 months and 100 individuals exposed to an effective dose for 1 year. While we have concluded that you have not provided substantial evidence of effectiveness for any dose, it is likely that, if the drug is effective, the effective dose is likely to be at least 40 mg/day. Your application contains data showing that there were only 124 subjects exposed to a modal dose ≥40 mg for approximately 6 months and only 35 subjects exposed to a modal dose ≥40 mg for approximately 1 year. At a minimum, you will need to augment this safety database to meet the ICH guidelines for long-term safety data exposure at clinically effective doses as described above.

OTHER REQUESTS AND COMMENTS

1. Safety Update

As part of any resubmission of this application, it will be necessary for you to provide an update on your safety database since your last safety update submission of September 18, 2001. We have already provided you detailed advice on what needs to be included in this safety update in a January 14, 2002 fax transmission. In addition to following that general advice, the safety update should address the following specific issues:

Dizziness

We feel that dizziness is a sufficiently common and important adverse event to justify additional analyses to better understand and characterize this event. At a minimum, we request that you characterize the course of dizziness over time; for example, how long does it last, does the severity change with subsequent episodes, do patients develop tolerance to this symptom. In addition, please provide a discussion of the relationship, or lack thereof, between gepirone-associated dizziness, syncope, objectively measured orthostatic changes, and accidental injury.

Adverse Events Associated with Discontinuation of Treatment

The NDA noted that 761 subjects had "adverse event" identified on the "End of Study" CRF page as the reason for discontinuing from a study; however, 18% (N=138) did not specify the adverse event resulting in discontinuation. Please attempt to re-evaluate those adverse events. One approach would be to go to the AE page in the CRF and identify the outcome for each specific AE. This process affords an additional opportunity to determine which AE led to discontinuation for those patients that didn't have it specified on the "End of Study" page in the CRF.

Adverse Event Tables in Proposed Labeling

In any resubmission of labeling, we ask that you recalculate table II for adverse events associated with discontinuation by lowering the threshold for inclusion of common events leading to discontinuation down to 1%.

For each of the tables in the Adverse Events section of the proposed labeling (II, III, and IV), we ask that you recalculate the placebo AE incidences based on the inclusion of only those patients treated with placebo in the gepirone ER controlled depression trials.

ECG Changes

For controlled trials of gepirone ER in depression, please provide a comparison of the frequency of outliers for QTc duration with a change from baseline of $\geq$30 msec and of $\geq$ 60 msec in each treatment group (gepirone IR, gepirone ER and placebo).

In addition, please clarify which trials were included in the ECG analysis you refer to in your proposed labeling.

Vital Sign Changes

We ask that you conduct additional analyses of the vital signs data. In particular, please provide the risk ratios for the incidence of orthostatic changes in the controlled trials of gepirone ER in depression.

In any resubmission of this NDA, please propose a section for vital signs in labeling.

Weight Changes

The data in the cited appendix in support of your proposed labeling statement regarding weight changes address only the changes in the BMS development program. Please recalculate changes in weight based on the gepirone ER data from short-term controlled depression trials.

Effect on Sexual Function

The data pertaining to sexual function that support your proposed labeling statement regarding sexual function appear to come from AEs reported in the placebo controlled depression trials. Please indicate what self-report instrument was used and provide the data from this analysis. Until you show that the approach used was sensitive to the detection of

sexual dysfunction, we do not believe you can include labeling language suggesting that gepirone is free of this adverse effect. We would be willing to discuss with you the design of studies that could definitively answer this question.

Suicidal ideation/ Suicide Attempt

We ask that you recalculate the rate of suicidal ideation and suicide attempt using person-time exposure in the denominator.

Allergic reaction/ Hypersensitivity syndrome

In order to more thoroughly identify patients whose symptoms may have represented an allergic reaction or hypersensitivity syndrome, we ask that you develop a case definition for allergic reaction/hypersensitivity syndrome, taking into account the multiple symptoms that may be part of such a syndrome. Using this case definition, you should identify patients whose AE profile fits that of an allergic reaction/ hypersensitivity syndrome. This investigation should also include an assessment of eosinophilia in the controlled clinical trials, including mean change from baseline and outlier analyses.

Follow-up for patient with evidence of hepatic dysfunction

We note that there was a patient, 0415 in ongoing study 28709, who had elevated hepatic enzymes. After three months on blinded treatment, the subject's AST, ALT, and alkaline phosphatase values increased to 52, 93, and 151, respectively, from normal values pretreatment. Seven days after stopping study drug, the values were 148, 393, and 485. There was no information about bilirubin values, diagnostic work-up, or outcome of this event. Should this patient turn out to have been on gepirone ER treatment, follow-up on this event will be needed.

Adverse Event Dose Response Analysis

You should provide a dose response analysis using all reported treatment-emergent AEs. In the NDA submission, you used only "treatment-related" AEs as judged by the investigator.

2. Regulatory Status Update

Before resubmitting this application, please provide any new information on the regulatory status of gepirone worldwide, i.e., information available subsequent to the regulatory status update provided in your May 18, 2001 resubmission.

3. Worldwide Literature Update

Before resubmitting this application, please provide an updated worldwide literature search. We note that you have in the NDA submission provided 286 literature references, including links to the full papers for 21 of these. This alone is inadequate. We request that you conduct a comprehensive review of all of the available literature pertinent to gepirone, including papers published since your original literature review, and provide commentary on the relevance, if any, of these published papers to the safety of gepirone.

4. Proposed Tradename

Please refer to our Agency letter dated January 14, 2002, informing you that your proposed tradename of Ariza was unacceptable. Please submit another proposed tradename for review by the Agency.

PRECLINICAL TOXICOLOGY

The *in vitro* chromosomal aberration assay was inadequate because although gepirone was negative for 5-hour treatment, with and without metabolic activation, this negative finding (without activation) should have been followed up with a study using continuous treatment with gepirone (without activation) for ~ 24 hours (1.5 cell doubling times) in accordance with current guidelines. Since the weight of evidence suggests that gepirone is neither genotoxic nor carcinogenic, we are not requiring that this study be repeated; however, it will have to be repeated if it is to be included in product labeling.

CMC

1. At several places in the manufacturing process section you use the term "or equivalent" to describe the equipment to be used. Please clarify.

2. Your specification for (b) (4) is NMT (b) (4)%. Please update your specification from NMT (b) (4)% to NMT (b) (4)% for these impurities.

3. The specification for (b) (4) is NMT (b) (4)%; however, the actual amount of these substances found in the drug product has not exceeded (b) (4)%. Please tighten this specification to be more reflective of the data.

4. The specifications for the drug product do not include a specification for the (b) (4) content. As the drug product is (b) (4), for all future batches of the drug product, please provide a specification for and monitor the (b) (4) content in the drug product on release and stability until a significant body of data is obtained to warrant excluding this test from the specifications.

5. DMF 2880 (Sud-Chemie Performance Packaging) is deficient for the (b) (4). The DMF Holder is being notified of this by separate letter which includes a list of the deficiencies.

6. You indicate on page 167 of volume 1.10 in the table pertaining to the package insert that the requirements for the dimension and shipment marking are "conforms to specification" however it is not clear what these specifications are. Please clarify.

7. You indicate on page 168 of volume 1.10 in the table pertaining to the folding cartons that the requirements for the color, dimension and shipment marking are "conforms to specification" however it is not clear what these specifications are. Please clarify.

8. In your marketed stability protocol on page 179 of volume 1.13 you indicate that one batch of each strength will be stored annually and tested at intervals of 0, 6, 12, 24 and 36 months and then yearly thereafter if expiration dating extension is desired. This reduced testing is

not acceptable. Please commit to testing at intervals of 0, 3, 6, 9, and 12 months then yearly thereafter.

9. The proposed cartons and blister backing labels for the drug product has Ariza™ (Gepirone HCl) Extended-Release Tablets listed as the name of the drug product. As noted above, this name is not accepted by the Office of Post–Marketing Drug Risk Assessment (OPDRA). Please commit to submitting revised container carton labels information when a new name is agreed upon.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

1. In the pivotal bioequivalence study comparing different strengths of gepirone ER, the 40 and 80 mg strengths were not shown to be bioequivalent to the 20 mg tablets, which was the tablet strength used in the clinical trials. No adequate data were provided comparing the 60 mg strength to the 20 mg strength of gepirone ER. Based on the available data, the 40, 60 and 80 mg strengths of gepirone ER are not approvable.

2. In the food effect study, the data showed that food has a significant effect on gepirone bioavailability (increase in Cmax approximately of 62%). Prior to resubmitting this application, you should conduct an *in vivo* study evaluating the effects of different meal compositions on gepirone ER pharmacokinetics.

3. A strong pharmacokinetic interaction was observed between gepirone and ketoconazole (5-fold increase in gepirone concentrations). The effect of other CYP3A4 inhibitors that can be potentially coadministered with gepirone ER has not been evaluated. Prior to resubmitting this application, you should conduct an *in vivo* drug interaction study to evaluate the effects of gepirone coadministration with an intermediate inhibitor of CYP3A4, such as verapamil.

4. Prior to resubmitting this application, you should conduct an *in vitro* assessment of (a) potential drug-drug interactions between gepirone and potent CYP3A4 inducers and (b) the drug's ability to induce CYP3A4 enzymes.

5. Prior to resubmitting this application, we recommend that you conduct an *in vivo* drug-drug interaction study with a potent CYP2D6 inhibitor to assess its effects on the pharmacokinetics of gepirone and its metabolites.

6. We request that you agree to change the dissolution specifications at 12 h and 20 h to 65-85% and >85%, respectively.

7. We request that you clarify whether or not plasma gepirone (and any metabolites) concentrations were measured in any of the pivotal efficacy trials following administration of the IR and/or ER formulations of gepirone.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
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
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