

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021164Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 18, 2007

FROM: Ni A. Khin, M.D.
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TO: File NDA 21-164 (This overview should be filed with the 05-01-2007 submission in response to the 06-23-2004 non-approval letter)

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

1. BACKGROUND

Gepirone HCl (previously Org 33062) is a 5HT_{1A} agonist. The IND development plan was to market this drug as an antidepressant. The IND 23,952 for the immediate release (IR) formulation was submitted on 04/2/84; and the IND 33,626 for the extended release (ER) formulation was submitted 08/28/89. Since there was poor tolerability (i.e., dizziness, nausea, insomnia) of the IR formulation, the sponsor decided to further develop their clinical programs with Gepirone ER. In 1992, the original sponsor, Bristol-Myers Squibb made their business decision to discontinue all gepirone clinical development programs and transferred the INDs to Fabre-Kramer Pharmaceuticals, Inc. There was additional ownership license transfer and agreement to Organon, Inc. in 1998; and then transferred back to Fabre-Kramer since June 2005.

The original NDA for the ER formulation was initially submitted on 09/30/99 by Organon, Inc. The application was not filed by the Agency as the submission did not include positive results from 2 adequate and well-controlled studies using gepirone ER.

The NDA was resubmitted on 05/18/01. The first NA letter was issued on 03/15/02, citing inadequate evidence of efficacy and inadequate long-term safety data. We considered one IR study [03A7A-003] and one ER study positive [134001]. We asked for one additional positive ER study. In the first NA letter in 2002, we noted our concerns about multiple negative trials in the overall development program for both the IR and ER formulations.

The second NDA resubmission was on 12/23/03 with data from a randomized withdrawal relapse prevention study [28709]. However, the division did not consider this randomized withdrawal trial a positive study, and issued a second NA letter on 06/23/04, citing a need for a robustly positive short-term trial and a positive randomized withdrawal trial. We again noted our concern about continued accumulation of negative data and asked the sponsor to address such a preponderance of negativity.

Since the time of issuance of the second NA letter in 2004, we held a couple of meetings with the sponsor, Fabre-Kramer to discuss their planned resubmission of the NDA and we gave feedback on several topics. Based on the meeting minutes of 10/12/05 and 05/31/2006 (teleconference), the discussion items included:

- the format and contents of their planned NDA resubmission in response to the CMC, OCP and Clinical issues raised in the 06/23/2004 second NA letter
- Our general agreement with their methodology proposed for the integrated efficacy summary focusing on two pivotal studies that they considered positive and their proposal for meta-analysis of pooled data
- Most of the analyses of routine safety data would focus on ER data but the safety data in regards to deaths, serious adverse events and adverse dropouts should include all gepirone exposure data (both IR and ER studies) in the integrated safety summary.
- Regarding their intended claim on potential improvement of sexual function, we pointed out that gepirone should consistently show an advantage over other antidepressants on sexual dysfunction in circumstances when all the drugs are used optimally with regard to dosing, and gepirone ER is consistently shown to be non-inferior to placebo.
- Dissolution profile data for the planned resubmission

On May 1, 2007, the sponsor Fabre-Kramer submitted in their response to the 06/23/2004 NA letter to the above referenced NDA. They included the results of two additional short-term gepirone ER studies (FK-GBE-007 & 008) in MDD. This submission also includes a meta-analysis of pooled data from 12 short-term placebo-controlled studies. Despite our clear statement in the second NA letter that we did not consider their prior relapse prevention study 28709 a positive study and had asked for another positive relapse prevention study with adequate stabilization period, in this submission, the sponsor just provided their post-hoc reanalysis results of study 28709 and intends to seek a claim for Gepirone ER in maintenance treatment of MDD. The sponsor also proposes to include a labeling statement that patients treated with Gepirone had statistically significantly better sexual functioning than placebo or SSRI-treated patients.

The proposed target dose for treatment of MDD is 60-80 mg per day. The proposed recommended starting dose is 20 mg once daily, with an increase to 40 mg once daily at Day 4 if tolerated; to 60 mg after 1 week; and then to 80 mg after additional week. The drug will be available as 20, 40, 60 and 80 mg strength extended-release tablets.

This submission has been reviewed by Earl Hearst, M.D., Medical Officer, DPP (final review pending at the time completing this memo), Fanghui Kong, Ph.D., Statistical Reviewer from the Office of Biostatistics (review dated 10/9/2007), Ron Kavanaugh, Ph.D., Clinical Pharmacologist from the Office of Clinical Pharmacology (review dated 10/01/2007), Sherita McLamore, Ph.D., Chemistry Reviewer from the ONDQA (review dated 9/24/2007), and Linda Fossom, Ph.D., Pharm/Tox Reviewer, DPP (review dated 10/10/07).

2.0 CHEMISTRY

No new CMC drug product issues in this submission that would require a review except for final market image (i.e., replacement of (b) (4) and comparative dissolution data of all four strengths). From the CMC perspective, the application was recommended approvable at this time. We are currently waiting for the Office of Compliance

inspection report of manufacturing sites. I am not aware of any other CMC deficiencies that would preclude approvability of this drug.

3.0 PHARMACOLOGY/TOXICOLOGY

The sponsor's result of the new in-vitro chromosomal aberration study was reviewed by Dr. Linda Fossom. I am not aware of any pharm/tox deficiencies that would impact approvability of this drug. This submission required for a PLR labeling review in regards to labeling language proposed in pharm/tox sections.

4.0 CLINICAL PHARMACOLOGY

In this submission, the sponsor included results from two single dose, open-label, four-way, cross-over, food effect studies (protocol 28725 and 28727). The extent of absorption of gepirone increased after administration of gepirone in the presence of food. Depending on the fat content of the food, Cmax and AUC were 1.2 – 1.7 times higher for gepirone. The OCP reviewer found the study results acceptable.

I note OCP recommends that 1) a phase IV commitment to perform a drug-drug interaction study of the effect of an intermediate CYP3A4 inducer such as rifabutin within 1 year post-approval; 2) a waiver to the requirement for a BE study for the proposed 40 mg and 60 mg tablets; and 3) the dissolution methods and specification to be set if this drug is approved. OCP also provided labeling comments.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were a total of 25 clinical studies conducted with gepirone ER. Of these 25 trials, there were 15 placebo-controlled trials: 14 short-term studies and 1 relapse prevention study (study 28709). Out of 14 placebo-controlled short-term studies, 6 studies had an active-control arm. All 14 short-term trials were 6 to 8 weeks acute MDD studies.

Our prior reviews of this NDA had already covered most of these efficacy trials. We have determined that one short-term efficacy trial (study 134001) with the ER formulation showed benefit of gepirone over placebo. In this resubmission, the sponsor states that they now have two positive studies as they claimed study FKGGBE-007 as a second positive short-term efficacy trial.

The following table (Table 1) consists of a list of short-term efficacy MDD trials conducted using gepirone ER and our determination of study results:

Table 1: List of well-controlled short-term efficacy gepirone ER studies

Study No.	Primary Endpoint	Active Control, Dose range (mean dose)	Doses Range of gepirone ER (mean dose)	Study Results for gepirone ER
FK-GBE-007	HAMD-17	None	20-80 (58.2)	Positive
FK-GBE-008	HAMD-17	None	20-80 (59.3)	Negative
134001	HAMD-17	None	20-80 (70.3)	Positive
134002	HAMD-17	None	20-80 (68.2)	Negative
134004	HAMD-25	Fluoxetine 20-40 mg (34.1)	20-80 (67.1)	Failed
134006	HAMD-25	Paroxetine 10-40 mg (28.2)	20-80 (55.3)	Negative
134017	MADRS	Fluoxetine 20-40 mg (25.9)	40-80 (58.7)	Failed
134023	HAMD-17	None	20-80 (70.1)	Negative
CN105-052*	HAMD-17/CGI	Fluoxetine 20-80 mg (23.3)	20-60 (38.7)	Failed
CN105-053*	HAMD-17/CGI	Imipramine 50-200 mg (145)	10-60 (46.4)	Negative
CN105-057	HAMD-17/CGI	None	2-4 (3.6) 5-10 (9.3) 10-20 (19.1) 20-40 (33.8)	Negative
CN105-064	HAMD-17/CGI	Imipramine 50-200 mg (96.7)	5-20 (11.6) 10-40 (22.5)	Failed
CN105-078*	HAMD-17	None	10-50 (30.4) 20-100 (52.6)	Negative
CN105-083*	HAMD-17	None	10-50 (30.4) 20-100 (57.1)	Negative

*terminated early by BMS

In this submission, the sponsor's efficacy analysis was based on results from their claim of 12 adequately designed short-term placebo-controlled gepirone ER studies. The sponsor has included results from recently conducted two placebo-controlled short-term MDD studies (FK-GBE-007 and FK-GBE-008). Of these 12 ER studies, the sponsor considered 2 to be positive (i.e., study 134001 submitted in 2001 sponsored by Organon; and a new short-term study sponsored by Fabre-Kramer, study FK-GBE-007), 5 as supportive (FK-GBE-008, 134002, CN105-083, CN105-078, 134023), and 5 failed (134004, 134006, 134017, CN105-052, CN105-053). The sponsor's classification of supportive studies was based on their post-hoc definition that gepirone ER separated from placebo in a statistically significant manner on one or more key outcome measures at one or more time points. They also conducted a meta-analysis of pooled data from these short-term studies. They included their reanalysis of randomized withdrawal study 28709.

Our review of efficacy was focused on 1) the results of one positive study (FK-GBE-007); 2) meta-analysis of pooled short-term ER data; 3) the sponsor's reanalysis of randomized withdrawal study (study 28709).

I would briefly describe the study design and positive result from additional short-term gepirone ER MDD study. I would then present a summary of results from all gepirone ER MDD studies and discuss findings from pooled data analysis in the following subsections. Our evaluation on sponsor's reanalysis of randomized withdrawal study 28709 will also be discussed.

5.1.2 Summary of Study Pertinent to Efficacy Claim of gepirone ER

5.1.2.1 Positive studies

Study FK-GBE-007

This was a 8-week, double-blind, randomized, placebo-controlled, parallel-group, multicenter, outpatient study in patients with a DSM-IV diagnosis of major depressive disorder comparing flexible doses of gepirone ER (20-80 mg/day) vs. placebo. Subjects who were assigned to gepirone ER was titrated to 20 mg on Days 1-3, 40 mg on Days 4-7. Based on subject's tolerability, gepirone ER was then administered at 40 to 60 mg on Days 8-14; and 40 to 80 mg on Days 15-56. Mean daily dose of gepirone ER was 58.2 mg.

The study was conducted in 9 U.S. study sites. A total of 248 subjects were randomized and received at least one dose of study medication (124 in the gepirone ER group and 124 in the placebo group); 238 subjects were analyzed for efficacy in the intent-to treat (ITT) population (116 in the gepirone ER group and 122 in the placebo group). 199 subjects (97 in gepirone vs. 102 in placebo) completed the study and 49 discontinued. The overall discontinuation rate was slightly higher for the gepirone ER group; 3.2% vs. 2.4%, for lack of efficacy; 4% vs. 2.4% for AE; respectively.

The mean (SD) age of all subjects was 38.1 (range 18 to 64) years. The majority of subjects were female (70%) and Caucasian (64.7%). Demographic characteristics were similar for both treatment groups in the ITT population.

The primary efficacy measure was the change from baseline to the end of study of the HAM-D-17 total score. The treatment efficacy was analyzed by the primary efficacy analysis using ANOVA with LOCF data (see table 2 below). ANCOVA analysis was also used. The difference between the ANOVA and ANCOVA was use of HAM-D-17 baseline as covariate. Similar result was obtained (p=0.018). Dr. Kong confirmed the study results. Sensitivity analysis was conducted using OC.

Table 2: Change from baseline to endpoint of HAM-D: ITT population

Treatment (N)	Baseline Mean	Change from baseline	Difference in LS mean (CI);	p-value (vs. placebo)
Gepirone ER (N=116)	24.2	-10.1	-2.4 (-4.4, -0.3)	p=0.023
Placebo (N=122)	23.9	-7.8		

Comment: Both Drs. Hearst and Kong considered this a positive study for gepirone ER, and I agree with them.

Study 134001

As previously reviewed, this study is considered to be a positive study (see table 3 below). This was a 8-week, multicenter (5 U.S. centers), double-blind, placebo-controlled, short-term MDD study with a flexible dose design using 20-80 mg of gepirone ER. Mean daily dose was 70.3 mg.

Table 3: Change from baseline to endpoint of HAM-D in ITT population (LOCF)

Treatment (N)	Change from baseline	Difference in LS mean	p-value (vs. placebo)
Gepirone ER (N=101)	-9.0	-2.5 (-4.4,-0.5)	p=0.013
Placebo (N=101)	-6.6		

5.1.2.2 Negative studies

Study FK-GBE-008

This was conducted using identical design as study FK-GBE-007. Mean daily dose of gepirone ER was 59.3 mg. Dr. Kong confirmed that this is a negative study [i.e., LS mean difference of change from baseline to endpoint of HAMD total score was -9.86 (gepirone) vs. -8.48 (placebo); -1.38 (p=0.2)].

Overall, the following 8 short-term studies are considered as negative studies as gepirone ER did not show benefit over placebo based on analysis of primary efficacy endpoints.

- FKGBE008
- 134002
- 134006
- 134023
- CN105-053
- CN105-057^T
- CN105-078
- CN105-083

As noted in table 1 before, mean daily doses of gepirone ER in all of these negative studies were above 40 mg/day except for CN105-057^T.

5.1.2.3 Failed studies

The following 3 studies had an active control group used at an adequate dose was failed to beat placebo, and therefore, the Division had determined these studies as failed studies.

- CN105-052
- CN105-064^T
- 134017

[Note^T: We have agreed to the sponsor's proposal that the studies with gepirone ER $\leq$ 40 mg/day would not be taken into account in efficacy analysis].

5.1.2.4 Active controls for assay sensitivity

It should be noted that there were 5 studies reported by the sponsor in this submission as lacking assay sensitivity: 134004, 134006, 134017, CN105-052 and CN105-053. In our 2004 NA letter, we cited that the active control fluoxetine vs. gepirone ER showed strongly trending toward statistical significance (p=0.068). For studies 134004 and 134006, when Dr. Kong used HAMD-17 which is one of the commonly used efficacy measures in MDD trials as the primary endpoint (as the sponsor also utilized HAMD-17 for meta-analysis instead of protocol specified HAMD-25), the active control (fluoxetine and paroxetine, respectively) showed significant benefit over gepirone ER. Two different active controls (imipramine and paroxetine) also showed significant treatment effect over placebo in studies CN105-053 and 134006. For study 134017, it could be regarded as a failed study because the active control fluoxetine did not beat placebo, yet, it is interesting to note that the active

control showed a significant effect over gepirone ER. The results can be seen in the following table (table 4) which is extracted from part of Dr. Kong's table 3.9 in his statistical review.

Table 4: Analysis of Change in HAMD-17 from Baseline to End of study in studies with Active-control

Study No.	Placebo	Gepirone ER	Active Control	Gepirone ER vs. Placebo	Active Control vs. Gepirone ER	Active Control vs. Placebo
CN105-052			(Fluoxetine)			
N	37	35	36			
LS Means (SE)	-10.29	-10.98	-10.95	-0.69 (2.05)	0.02 (2.06)	-0.67 (2.03)
p-values				P=0.74	P=0.99	P=0.74
CN105-053			(Imipramine)			
N	56	56	54			
LS Means (SE)	-8.16	-10.16	-11.35	-2.0 (1.51)	-1.2 (1.53)	-3.19 (1.52)
p-values				P=0.19	P=0.44	0.038
ORG 134004			(Fluoxetine)			
N	130	125	136			
LS Means (SE)	-6.79	-5.75	-7.46	1.04 (0.78)	-1.71 (0.77)	-0.68 (0.76)
p-values				P=0.18	P=0.027	P=0.38
ORG 134017			(Fluoxetine)			
N	159	160	161			
LS Means (SE)	-11.02	-10.37	-11.92	0.65 (0.76)	-1.54 (0.76)	-0.90 (0.76)
p-values				P=0.39	P=0.042	P=0.24
ORG 134006^b			(Paroxetine)			
N	148	147	144			
LS Means (SE)	-7.01	-7.26	-8.89	0.25 (0.72)	-1.88 (0.73)	-1.64 (0.73)
p-values				P=0.73	P=0.01	P=0.025

5.1.3 Comments on Other Important Clinical Issues

5.1.3.1 Subgroup analysis of study FK-GBE-007

Dr. Kong performed exploratory subgroup analyses for the pivotal study FK-GBE-007 based on age, gender (M/F) and race (Caucasian versus non-Caucasian). The treatment effect is significantly greater in female (-2.8) for gepirone ER vs. placebo (p=0.04). The significant treatment effect was seen in Caucasians (-3.9) for gepirone ER vs. placebo (p=0.002).

5.1.3.2 Dose-response relationship

As can be seen in table 1, the sponsor has not conducted any adequate studies with gepirone ER to explore dose-response relationship. Almost all of these studies were flexible dose studies. In earlier studies, there were some fixed flexible dosage groups; two of the studies (CN105-057 and 064) used inadequate ER dosing (below 40 mg/day) which failed to demonstrate efficacy and two other studies were terminated early (CN105-078 and 083).

5.1.3.3 Preponderance of negative and failed studies

This issue has been repeatedly mentioned in prior review memoranda and the NA action letters for this drug. The 7 studies which the division had determined as negative were noted to be reasonably adequate in study design, gepirone ER dose and study conduct. As stated above, the sponsor now

came back with 2 positive studies with gepirone ER; however, such preponderance of negative and failed studies with this drug remains to be the focus of our attention in determining overall efficacy of the drug. Interestingly, Dr. Kong also pointed out that placebo is numerically better than gepirone ER in 4 studies.

In this context, although data from the IR studies will not be absolutely essential in determining the effectiveness of the ER formulation, I believe it is worthy to mention that there was only 1 positive IR study (study 037A-003) out of a total of 10 well-controlled studies conducted using the IR formulation. Although study 037A-003 was determined positive, this study enrolled MDD patients (N=60) with atypical features and conducted at a single U.S. center. Three of these IR studies were considered failed studies as the active control at an adequate dose failed to beat placebo.

5.1.3.4 Meta-analysis of pooled data

The sponsor provided data for all subjects in 12 studies; in particular, the HAM-D-17 total score at the last endpoint was available for all the subjects (with LOCF for the dropouts) as they used HAM-D-17 in their meta-analysis. Three meta-analyses were conducted by the sponsor: 1) combined all 12 studies, 2) combined two positive studies (FK-GBE-007 and 134001) and five they classified as “supportive studies” (FK-GBE-008, 134002, 134023, CN105-078, CN105-083) and 3) combined only five “supportive studies.” A treatment difference (gepirone ER vs. placebo) was considered by the sponsor to be statistically significant if the corresponding p-value was below 0.05. Dr. Kong confirmed their efficacy results. He also explored the analysis by using the mixed effects model to the same combinations of the studies. Table below showed the results which were included in Table 3.10 of his statistical review.

Table 5: Combinations of Treatment Effects among various short-term Gepirone ER Efficacy Studies

Combination of Studies	Number of Subjects		Treatment Effect of Org 33062 ER			
	Placebo	Org 33062 ER	Meta-analysis		Mixed effects model	
			Efficacy (SE)	p-value	Efficacy (SE)	p-value
Five “supportive studies”	411	482	-0.68 (0.47)	0.149	-0.64 (0.48)	0.20
Five Supportive & 2 Positive studies	634	699	-1.22 (0.39)	0.002	-1.23 (0.40)	0.002
All 12 studies	1159	1213	-0.48 (0.28)	0.093	-0.57 (0.29)	0.05

In my opinion, more interesting results were observed when Dr. Kong further examined if there were any additional evidence supporting the efficacy of gepirone ER in the treatment of MDD besides the two positive studies 134001 and FK-GBE-007. I believe Dr. Kong’s approach of excluding 2 positive studies is more reasonable for the meta-analysis. Using both the sponsor’s meta-analyses approach and the mixed effects model approach, Dr. Kong looked at the results. Table 6 below showed the result which was depicted in part of Table 3.11 of Dr. Kong’s statistical review.

Table 6: Combination of Treatment Effects besides the Positive Studies among a Total of 12 Short-Term Efficacy Studies for Gepirone ER

Combination of Studies	Number of Subjects		Treatment Effect of Org 33062 ER			
	Placebo	Org 33062 ER	Meta-analysis		Mixed effects model	
			Efficacy (SE)	p-value	Efficacy (SE)	p-value
Ten non-positive studies	936	996	-0.094 (0.31)	0.62	-0.14 (0.32)	0.67

I note his concern about the multiplicity issue in that given these are post hoc analyses, the adjusted p-value could be larger than what was observed. I agree with him that none of these analyses seems to give additional support for the effectiveness of gepirone ER over placebo in the treatment of MDD unless 2 positive studies (FK-GBE-007 and 134001) data were included as any part of the analysis.

5.1.3.5 Reanalysis of randomized withdrawal study 28709

The result from this study was previously reviewed in 2003 and the Division did not consider this a positive study, and asked for another positive study with adequate stabilization period.

Briefly, this study consisted of an 8-12 week open-label phase in which subjects who was classified to be in remission with gepirone ER (titrated ER dose between 40-80 mg) treatment (remission was defined as HAMD-17 ≤ 8 at week 8 or 12) was followed in a 44 week double-blind, placebo-controlled continuation phase of observation for relapse (relapse was defined as HAMD-17 ≥ 16 or discontinuation due to LOE determined by Investigator). This study was conducted in 29 non-U.S sites (Germany, France, Finland, Estonia and Turkey). Primary efficacy was proportion of patients relapsed. The original ITT population was a total of 250 subjects; 126 in gepirone ER and 124 in placebo.

We found the sponsor's positive original CMH analysis problematic [i.e., gepirone ER 29/126 (23%) vs. placebo 43/124 (35%); $p=0.024$] because prior to unblinding, the sponsor identified 5 patients on gepirone who had relapsed based on discontinuation due to LOE as determined by investigator; but, the sponsor decided not to include these 5 patients as relapsers in their analysis. The study results changed to negative ($p=0.101$) if these 5 subjects were included. In addition, the original analysis failed to include all ITT patients (i.e., 32 patients from centers that had patients with only 1 treatment arm or had no relapses were not included). Our analysis with by grouping of small centers or grouping by country, the results were found to be negative with or without the 5 relapsed patients stated above.

In this 2007 submission, the sponsor provided their reanalysis results and still seeks for a claim of maintenance treatment. They modified the original ITT population ($N=250$) by excluding a total of 40 subjects (22 gepirone ER and 18 placebo) who were considered protocol violators based on the following conditions.

- 1) Improper randomization (subjects who did not achieve a score of HAMD-17 ≤ 8 until after Week 12 but entered into the continuation period): 13 gepirone ER-treated and 14 placebo-treated subjects
- 2) Non-compliance (serious overall non-compliance with the intake of the trial medication defined as $<75\%$ of the scheduled trial medication during the continuation phase): 5 gepirone ER-treated and 2 placebo-treated patients.
- 3) Prohibited medication (Use of disallowed concomitant medication between the last assessment of the open-label phase and the first efficacy assessment of the continuation phase): 4 gepirone ER-treated and 2 placebo-treated patients. The prohibited medications that these patients used were meprobamate, zopiclone or benzodiazepines such as clonazepam, oxazepam and lorazepam.

The per-protocol (PP) population consisted of 210 subjects were included in their reanalysis. The treatment groups were compared by means of the log-rank test for PP analysis dataset.

Based on the PP analysis, the sponsor claimed that gepirone ER relapse rate was significantly lower than placebo [i.e., 25/104 (24%) vs. 41/106 (38.7%); $p=0.023$ without adjustment for pooled center or country]. The sponsor also claimed that gepirone ER achieved statistical significance relative to placebo in terms of time to relapse ($p=0.032$).

I feel this sponsor's reanalysis was based on the above mentioned post-hoc definitions in their attempt to come up with a favourable result for gepirone ER. For example, we generally find occasional use of sleep medications in MDD trials despite these agents would be listed as part of the prohibited medications; and in most of the cases, we might not have strong objections including such patients in the efficacy analysis for longer-term studies.

Section 7.1.2 of the protocol stated that "All protocol violations will be determined by medical, clinical and biometrics personnel prior to breaking the blind and will be done at least during blind review." Both Dr. Kong and Dr. Hearst considered this study reanalysis unacceptable. As stated by Dr. Kong in his review that the sponsor's exclusion of these 40 patients was not justified and "PP" analysis results did not, therefore, provide valid evidence supporting the efficacy of gepirone ER over placebo in reducing relapse rate. I agree with him.

5.1.4 Conclusions Regarding Efficacy Data

The efficacy analyses did not show any convincing evidence regarding efficacy of gepirone ER in treatment of MDD. This could still be arguable given that the sponsor submitted efficacy results from two positive studies for gepirone ER. However, these two positives were out of a total of 12 short-term well-controlled studies. Based on our discussion with our statistical colleagues, my understanding is that it is likely that the chance of having at least 2 false positive studies out of 12 studies would be higher (i.e., false positive rate of 3.5% as compared to the rate of 0.00625% in 2 out of 2 studies). We considered results from multiple studies as negative for gepirone ER. In out of 5 active and placebo-controlled studies, the finding of active controls in 3 different studies statistically superior to gepirone ER and the active control is significantly better than placebo in 2 active controlled studies adds to our general concern that gepirone ER lacks robust efficacy in acute treatment of depression. I believe we usually find positive randomized withdrawal studies with the approved SSRI/SNRI antidepressants. In case of gepirone ER, we did not find the relapse prevention study with gepirone ER a positive study. The meta-analysis result of short-term studies was not found to be in support of efficacy of gepirone ER.

5.2 Safety Data

Safety data from gepirone were previously reviewed and had determined that there are no safety findings that would preclude the approvability of gepirone ER for MDD. I would refer to the following clinical reviews and memo for detail:

- Clinical Safety Review by Dr. Tarek Hammad dated 02/26/2002
- Safety Team Leader Memo by Dr. Judith Racoosin dated 03/01/2002
- Team Leader Memo by Dr. Thomas Laughren dated 03/05/2002
- Safety Update in Clinical Review by Dr. Earl Hearst dated 04/30/2004
- Addendum to Clinical Review by Dr. Earl Hearst dated 05/12/2004
- Team Leader Memo by Dr. Thomas Laughren dated 05/20/2004

As discussed at the 10-12-05 meeting, the sponsor has provided safety findings for deaths, SAEs, adverse dropouts, and other adverse events of special interest for both the IR and ER databases. In addition, they provide exposure information for both databases in this submission. Most of the analyses of routine safety data were focused on the ER data.

5.2.1 Safety Database

Out of a total of 8407 subjects in the phase 2/3 clinical trials (both acute and extension phases combined), 3117 (37.1%) were treated with gepirone ER; 1859 (22.1%) were treated with gepirone IR; 1216 (14.5%) received active control (i.e., fluoxetine, paroxetine or imipramine), 2483 (29.5%) subjects received placebo. In 17 placebo-controlled Phase II and III trials in MDD, 1639 patients were exposed to gepirone ER, including 189 for at least 6 months. Most patients (83.9%) received gepirone ER $\geq$ 40 mg/day.

There were 9 deaths reported during the phase 2/3 studies; among the 5 subjects in the gepirone treatment group; 4 were treated with gepirone ER. 77 out of 3117 gepirone ER treated-patients experienced serious adverse events. The percentages of subjects with any AE leading to premature withdrawal were 23.8% (57/240) in the imipramine group, 18.1% (90/4976) in the gepirone ER+IR combined group (ER: 509/3117, 16.3%; IR: 392/1859, 21.1%), 11.6% (32/276) in the paroxetine group, 9.3% (65/700) in the fluoxetine group, and 6.8% (168/2483) in the placebo group. Dizziness, nausea, headache, insomnia, and anxiety were reported as the reasons for AE dropouts in gepirone ER subjects.

It seemed Dr. Hearst's clinical review of this submission was limited to the safety data update and safety summaries of selected sections.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). As noted in previous safety reviews, the most prominent AEs were CNS effects (dizziness, headache), gastro-intestinal disorders (nausea, vomiting, abdominal pain), psychiatric disorders (somnolence) and general disorders (fatigue, malaise). Except for headache, these adverse events seemed generally drug-related.

5.2.2.2 Sexual Dysfunction Analysis

The sponsor intends to seek a claim for lack of sexual dysfunction for gepirone. We previously indicated that we might consider such a claim, however, it would depend on:

(b) (4)

Overall, since I am not convinced that there is substantial evidence that Gepirone ER is effective in treatment of MDD, this level of evidence that gepirone may not have sexual dysfunction would not influence my approvability determination of the drug.

5.2.2.3 Suicidality Analysis

The sponsor conducted the suicidality analysis based on the Columbia ratings of possible suicide-related adverse events (PSRAEs) for all 88 IR and ER studies.

Categories for PSRAEs

- 1 = completed suicide
- 2 = suicide attempt
- 3 = preparatory acts toward imminent suicidal behavior
- 4 = suicidal ideation
- 5 = self-injurious behavior, intent unknown
- 6 = not enough information, fatal
- 7 = self-injurious behavior, no suicidal intent
- 8 = other: accident; psychiatric; medical
- 9 = not enough information, non-fatal

A subject was considered to have suicidal behavior or ideation if the event was assigned a Columbia rating of 1-4, and a suicidal behavior event if the event was assigned a rating of 1-3. Columbia ratings of 5-9 were considered non-events. Relative risk ratios and 95% CI were calculated in relation to subjects who received placebo and in relation to those receiving another active control.

In addition, the sponsor's analysis included the results of an analysis of change from baseline in the suicide questions from the Hamilton Depression rating scale (HAMD, suicide item), and Montgomery-Asberg Depression rating scale (MADRS, item 10) at the 8-week time point.

There were a total of 3 completed suicides; 2 subjects were treated with gepirone ER. In addition, there were 13 subjects reported to have suicidal attempts; 7 were from gepirone ER treated group, 2 in gepirone IR, 1 in imipramine, 2 in paroxetine and 1 in placebo.

In all the Phase II/III studies included in the PSRAE analysis, 2143 subjects received gepirone ER, 1527 subjects received gepirone IR, 2450 received placebo, 457 received fluoxetine, 142 received paroxetine, and 220 received imipramine. Based on the grouping of Columbia rating categories, examination of the risk ratios suggested that treatment with gepirone (ER, IR, or ER+IR) did not statistically significantly increase the risk of suicidal behavior or ideation (categories 1-4) relative to placebo or to another active control. When gepirone ER was compared to placebo in suicidal behavior (categories 1-3) and suicidal attempt, there were 5 patients with suicide behavior (total count of 8 suicide behaviors) in a total of 2143 gepirone ER patients compared none in a total of 2450 placebo patients ($p=0.022$; Fisher's exact test). There were 4 patients with suicide attempt among a total of 2143 gepirone ER patients compared to none in a total of 2450 placebo patients ($p=0.048$; Fisher's exact test).

In the controlled Phase II/III studies included in the PSRAE analysis, 1723 subjects received gepirone ER, 1393 subjects received gepirone IR, 2292 received placebo, 457 received fluoxetine, 142 received paroxetine, and 220 received imipramine. There were 3 patients with suicide behavior and 2 suicide attempts in a total of 1723 gepirone ER patients compared none in a total of 2292 placebo patients. It did not seem to have increased the suicidal behavior ($p=0.08$) and suicide attempt ($p=0.12$) for gepirone ER compared to placebo.

The sponsor's proposed labeling includes the standard antidepressant box warning on suicidality in children and adolescents. If we decide to approve this drug, we should modify the language including recently updated adult suicidality data.

5.2.3 Conclusion Regarding Safety Data

Overall, this submission revealed no new safety concerns. There were no outstanding safety issues to be resolved based on our prior reviews of safety data of this drug.

6.0 WORLD LITERATURE

The sponsor has provided a brief literature review for the period of 2003-2006 in this submission. Based on Dr. Hearst's review, the literature search results are consistent with the safety data of gepirone as presented in this submission.

7.0 FOREIGN REGULATORY ACTION

I am not aware of any post-marketing experience with this drug in any foreign country.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC. However, we will be discussing this application at CDER regulatory briefing scheduled on 10/19/07.

9.0 DSI INSPECTIONS

DSI Inspection was requested for 2 U.S. sites (Dr. Beilski #701 and Dr. Weiss #706) in their conduct of study FKGBE-007. These two sites were selected because of their significant

contribution to study outcome. DSI found data from these inspected sites acceptable in support of this NDA.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

This submission contains revised labeling in a new PLR format. I will not provide any labeling comments since I am recommending a non-approvable action. If a decision was made to approve this drug, the sponsor's proposed language would need further modification.

11.0 CONCLUSION AND RECOMMENDATION

I believe that the sponsor has not provided convincing data to support the conclusion that gepirone ER is efficacious in the treatment of MDD. I recommend that the Agency issue a non-approval letter.

Although the FDA regulation does not require us to consider efficacy and safety of this drug comparable to available products to treat depression, I agree with Dr. Hearst that by approving gepirone ER, it would expose patients taking this drug to delay treatment with another approved antidepressant with demonstrated evidence of efficacy.

At the time completing this memo, Dr. Hearst has not finalized his clinical review. My comments were based on his draft clinical review. Based on my communication with Dr. Hearst, I do not anticipate that items discussed in his final version of clinical review would change my conclusion and recommendation. If my conclusion changes upon receipt and review of completed clinical review, addendum to this memo will be generated.

Cc:
NDA21-164
HFD-130/Laughren/Mathis/Hearst/Grewal

File: NK/N21164/Memo_gepirone ER_MDD_102007

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this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin
10/19/2007 12:09:18 PM
MEDICAL OFFICER

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 20, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

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 12-23-03 response to our 3-15-02 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.

This NDA was most recently submitted 5-18-01, and a nonapprovable letter was issued 3-15-02. I refer the reader to my 5-5-02 memo for a detailed summary of the very complicated development and regulatory history for this product. Prior to the 5-18-01 submission of this NDA, we had 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. At the time of issuing the 3-15-02 letter, however, we did not consider any of the 3 candidates for IR studies to be positive. We subsequently modified our view on IR study 03A7A-003, and did consider that a positive study (see minutes for 7-3-02 meeting with sponsor), but not the other two IR studies. At the 7-3-02 meeting, the sponsor 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, they would have sufficient efficacy data for filing the application.

However, in a 4-17-03 package outlining their proposed response to our 3-15-02 nonapprovable letter, we learned that study 134004 failed to distinguish either active drug (gepirone and fluoxetine) from placebo. They claimed, however, that their randomized withdrawal study (28709) was positive, and argued that this combination of two positive short-term studies and one positive long-term study should be sufficient to file the application. In a 7-14-03 telcon, we agreed only that we would likely be willing to file such an application, without reaching any agreement that this combination of studies would be sufficient. Part of the difficulty was a preponderance of negative studies for gepirone in the application, making the overall program very weak indeed.

The other reason for issuing a nonapprovable letter for the 5-18-01 application was a failure to provide sufficient longer-term safety data at relevant doses. Based on an overview of the accumulated efficacy data, we considered the possibly effective dose range to be 40-80 mg/day. The sponsor clearly did not have sufficient longer-term safety data in this range.

The sponsor has sought to respond to the deficiencies in the 5-18-01 application by submitting (1) efficacy data from their randomized withdrawal study (28709), and (2) longer-term safety data at relevant doses. They have also submitted responses to a number of other deficiencies noted in the 3-15-02 letter to be important, but not the basis for the nonapprovable action.

As noted, this response to our 3-15-02 nonapprovable letter was submitted 12-23-03. The efficacy data for this application were reviewed by Earl Hearst, M.D., from the clinical group, and Dr. Roswitha Kelly, from biometrics. The clinical safety data were also reviewed by Earl Hearst.

We decided not to take gepirone ER to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

The chemistry group has similar concerns to those of OCPB regarding the new tablet shape. The sponsor has not adequately documented why they made the change, i.e., what problem this change was intended to fix, and whether or not the change has succeeded. As noted by OCPB, at the very least they will need to provide dissolution data for the new shape vs the original shape. I

The history of the proposed names for gepirone ER and the agency responses to these proposed names is somewhat complicated, and still unresolved. Most recently, we have informed the sponsor (4-27-04) that their most recent proposal, “Alriza,” is unacceptable.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology deficiencies that would preclude the approvability of this product.

4.0 BIOPHARMACEUTICS

Our 3-15-02 nonapprovable letter included a number of comments, requests, and recommendations regarding OCPB issues, and the 12-23-03 response addressed most of these concerns. This part of the response has been reviewed by Sally Yasuda, Ph.D, from OCPB. One issue that has not yet been resolved is the 40 and 60 mg strength tablets, because of the sponsor's decision to change the tablet shape. They would need dissolution studies comparing these tablet forms to the original forms. Dr. Yasuda also has several recommendations for phase 4 studies, if this drug were to be approved. Based on the results of new data submitted by the sponsor, Dr. Yasuda has made a number of recommendations for labeling changes. However, given the remaining concerns about inadequate efficacy, we have not yet incorporated these changes into a labeling proposal, since we are not recommending an approvable action.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

As noted under background, the two positive short-term trials for gepirone coming out of the 5-18-01 application, one for IR (03A7A-003) and one for ER (134001), were derived from a total of 18 short-term placebo controlled trials. While we accepted the explanations for many of these trials failing, we noted in the 3-15-04 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 short-term ER studies having a positive outcome was noted to be a concern. This was the basis for our indicating that an additional "robustly positive" ER study would be needed. As noted, the most recent ER study (134004) has in fact failed, both for fluoxetine and gepirone. However, it is of concern that the results for gepirone are actually numerically worse than placebo, while the results for fluoxetine are numerically superior to placebo. In fact, the p-value for the fluoxetine/gepirone contrast on the primary outcome (HAMD-25) almost reaches statistical significance ($p=0.068$). Thus, the net result for short-term ER studies is now only one of five positive, with the additional finding of gepirone essentially being beaten by fluoxetine in this most recent ER study. Given this very marginal picture for the gepirone short-term efficacy data, a robustly positive result for the randomized withdrawal study became even more pressing.

The efficacy review for this resubmission focused exclusively on the results for the randomized withdrawal study (28709).

5.1.2 Study 28709

This was a multicenter study [29 European centers (Germany, France, Poland, Finland, Turkey)]. This was a typical randomized withdrawal study in depression, 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 ≤ 8 , at week 8 or week 12) were randomized to either continue on gepirone (at the same dose that was associated with a “response”) or switch to placebo, with a 40-44 week period of observation for relapse (defined as a HAMD-17 ≥ 16 , or discontinuation due to lack of efficacy as determined by the investigator). The total period of participation for any individual patient was to have been 1 year. This trial recruited adult patients (≥ 18) who met DSM-IV criteria for major depressive disorder (MDD). During the open label phase, patients were titrated up to 40 mg of gepirone by day 4, and were then titrated within a range of 40-80 mg/day for the remainder of that phase. The double-blind phase involved the random assignment of responding patients (1:1) to either gepirone (at their last dose during the open label phase) or placebo. Patients were then observed for relapse over the next 40-44 weeks.

The primary outcome was the proportion of patients who had relapsed at the end of the observation period, and the primary analysis was 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 postbaseline efficacy evaluation.

There was an excess of females compared to males (about 68% female), the mean age was about 45, and patients were almost entirely Caucasian white (about 99%).

Out of a total of $n=303$ patients who completed the open label phase, $n=250$ were randomized and had at least one dose of assigned medication and at least one efficacy assessment during postbaseline, i.e., the ITT population ($n=126$ to gepirone and $n=124$ to placebo).

The overall rates of discontinuation prior to reaching the 40-44 week endpoint were as follows:

Gepirone:	71/126 (56%)
Placebo:	70/124 (56%)

According to the sponsor’s analysis, the results on the primary endpoint, rate of relapse at endpoint, favored gepirone:

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

However, there were two important problems with the sponsor’s analysis:

-5 patients on gepirone who appear to have had relapses, but were not included in the sponsor's analysis:

-Prior to unblinding the data, the sponsor identified 5 gepirone patients who appeared to have met relapse criteria, since they appeared to have been discontinued due to worsening of depression, but had not been so designated on the CRF (Note: discontinuation due to lack of efficacy was one of two criteria for relapse). In fact, there is an internal company memo indicating that these patients would be redefined as having relapsed, and they were so redefined. Subsequent to unblinding and analysis, the sponsor found that these patients scores had not met the ≥ 16 criterion, but it was too late to query investigators, since they had also been unblinded. Nevertheless, the sponsor then decided to exclude the patients as relapsers, on the grounds that the redefinition had not been done for 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

-Comment: Both Drs. Hearst and Kelly consider it inappropriate for the sponsor, after the fact, to have not included these patients as relapsers, when they had already been quite reasonably reclassified as relapsers by the sponsor prior to unblinding the data. It is difficult not to reach the conclusion that their change of heart had a lot to do with the fact that the analysis on the primary endpoint lost statistical significance with this redefinition. In any case, it seems obvious to me that, on face, 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, I agree that the appropriate analysis is the one that includes these 5 patients as having relapsed.

-Failure to include all ITT patients in the analysis:

-The sponsor excluded 32 patients from the analysis (CMH) because they came from centers that had patients in only 1 treatment arm, or had no relapses. More appropriate grouping of centers yields nonsignificant results: p=0.10, with grouping small centers; p=0.08, with grouping by country. These results are negative, even with the sponsor's exclusion of the 5 patients as relapsers that we feel should be included. When these 5 patients are included in these analyses with appropriate grouping of centers, the results are as expected, far from significant (p=0.33 and p=0.31, respectively, for groupings by small center and by country).

-Comment: These results provide additional reasons for rejecting the sponsor's analysis.

The results 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 even less significant, i.e., p=0.28.

As noted by Dr. Kelly, the time to relapse analysis is the more appropriate analysis, and the one that we always recommend for this type of study. The CMH analysis of proportion relapsed does not properly address censored patients, in that it implicitly treats them as successes.

Given the negative outcome for this study, no exploratory analyses looking at the effect of age, sex, and race were done.

Comment: Both Drs. Hearst and Kelly considered this a negative study, and I agree. Thus, it does not, in my view, provide any additional support for the effectiveness of gepirone in MDD.

5.1.3 Comment on Other Important Clinical Issues Regarding Gepirone ER for MDD

Evidence Bearing on the Question of Dose/Response for Efficacy

There were no data in this resubmission pertinent to the question of dose response for efficacy. This was also the case for previous submissions of this NDA.

Clinical Predictors of Response

As noted, given the negative outcome for this study, no exploratory analyses looking at the effect of age, sex, and race were done.

Size of Treatment Effect

Effect size is not relevant, given the negative outcome for the only study submitted in support of this application.

Duration of Treatment

Even if this study had been positive, it would not have provided evidence of longer-term effectiveness, given the very short period of time in responder status prior to randomization.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, not provided sufficient evidence to support the claims of short-term and longer-term antidepressant efficacy for gepirone ER. Based on earlier discussions with the sponsor, we had agreed that a single positive short-term trial with the ER formulation, in the face of independent evidence for the antidepressant efficacy of the IR formulation, would be sufficient to support a claim for the antidepressant efficacy of the ER formulation. The sponsor has not, in my view, provided such evidence. It is true that they have provided evidence from 2 short-term studies, however, with different formulations (1 for IR and 1 for ER). We have never accepted this level of evidence to support a short-term claim, and it remains my view that such data would not be sufficient to support a claim for gepirone ER, since it does not meet my requirement for a “bridge” between the 2 formulations. Nevertheless, we did agree to file the application, given the sponsor’s claim that they had a positive longer-term study, but with no guarantee that we would

consider this additional study as sufficient to support these claims. Given the negative outcome on study 28709, I continue to feel that the evidence in support of an antidepressant claim for this drug is not adequate to justify an approvable action. Furthermore, as the negative data continue to accumulate, it becomes difficult to advise the company about what further work they might do to address such a preponderance of negativity. At this point, I 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.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The development program for gepirone extended over a long period of time, and ownership transferred twice. In addition, there was a shift in focus from an initial program with the IR formulation to a later program focusing on the ER formulation. The earlier data were generated by the BMS program, and the more recent data by Organon.

This development program, including all patients exposed to both the IR and ER formulations, in a total of 75 clinical studies, up through the 6-23-03 cutoff date for this resubmission, contained 4862 subjects exposed to 1 or more doses of gepirone. With this resubmission, the sponsor has addressed our concern about longer-term safety data. They have provided safety data for n=732 patients exposed to gepirone for ≥ 6 months (including n=497 at modal doses of ≥ 40 mg/day), and also safety data for n=260 patients exposed to gepirone for ≥ 12 months (including n=170 at modal doses of ≥ 40 mg/day). They have also addressed our concerns about coding of adverse event data and pooling strategies. The mean age of patients was roughly 40, with less than 2-3% >65 . Patients were predominantly Caucasian, and about 2/3 female.

5.2.2 Sponsor’s Responses to Safety Issues Raised in 3-15-02 Nonapprovable Letter

In addition to a requirement for longer-term safety data in our 3-15-02 letter (one of two deficiencies that were the basis for the nonapprovable action), we asked for a safety update, including requests for a number of specific concerns to be addressed.

5.2.2.1 Overview

Based on the resubmitted safety data, the adverse event profile included the following adverse events that emerged as being likely drug-related, both for overall adverse event incidence and with regard to events leading to discontinuation, were dizziness, nausea, and vomiting. Little can be said about dose relatedness for adverse events, since the studies were all flexible dosing. There were no consistent effects on vital signs, at least in the sitting position. Generally there was no suggestion of gepirone related changes in chemistry, hematology, or urinalysis.

5.2.2.2 Additional Adverse Events Issues for Which FDA Sought Responses from Organon in the 3-15-02 Non-Approvable Letter

Dizziness

In the 3-15-02 letter, we asked for additional analyses of data for the event “dizziness.” We asked for a characterization of this event over time, and also for a discussion of the relationship of this event, if any, to syncope, objectively measured orthostatic changes, and accidental injury.

Response: The sponsor explored for relationships among “dizziness” and the other events mentioned by searching across the entire database for such events occurring in temporal association in patients. While there were occasional such pairings, there was no pattern of findings to suggest that dizziness was explained by orthostatic changes. Most instances of dizziness occurred early in treatment and appeared to be dose-related. There was no indication of worsening of dizziness over time in patients who had more than 1 episode.

ECG Changes

In the 3-15-02 letter, we asked for additional analyses of ECG data, in particular, data for outliers (≥ 30 msec change from baseline and ≥ 60 msec change from baseline).

Response: There was no clinically meaningful difference between gepirone ER patients and placebo patients in mean change from baseline or proportions of patients meeting the ≥ 30 msec change from baseline or ≥ 60 msec change from baseline criteria.

Weight Changes

In the 3-15-02 letter, we asked for additional analyses of weight data, in particular, data for the gepirone ER depression trials.

Response: While there was a statistically significant increase in weight for gepirone ER vs placebo at the ≥ 40 mg level, both for mean change from baseline and proportion of patients meeting criteria for a clinically significant increase, the changes were small and of doubtful clinical significance.

Lack of Sexual Dysfunction

In the 3-15-02 letter, we asked for more information on how information was collected on sexual functioning.

Response: They claim to have shown in active and placebo-controlled trials an excess risk of sexual dysfunction for the active controls (SSRI and imipramine groups) vs placebo, but no difference with placebo for gepirone, both based on spontaneous reporting and with the Derogatis Interview for Sexual Function Self Report. If we can confirm these findings, some mention of such results in labeling may be justified.

Suicidal Ideation/Suicide Attempt

Because there was a slight excess of risk for these events in GIR/GER patients vs pbo, we asked the sponsor to adjust for time at risk with total person time.

Response: There continued to be an excess of suicidal ideation even with adjustment for time, i.e., 0.07 per PY for gepirone vs 0.04 per PY for placebo. An evaluation of suicidality based on the HAMD and MADRS suicide items did not reveal any greater risk for gepirone.

Allergic Reaction

There were concerns about the possibility of allergic reactions to GIR/GER, based on a severe case of hepatosplenomegaly associated with fever, rash, transaminitis, and eosinophilia, along with AE rates for the BMS ph 2-3 trials suggesting a slight excess of events that may indicate allergic reaction, i.e., arthralgia and myalgia. We asked the sponsor to explore for this possibility.

Response: They developed a case definition for allergic reaction and looked for such occurrences, along with changes in eosinophil count, across a variety of study groupings. There was no signal emerging suggestive of a risk of such reactions for gepirone.

Follow-Up for Patient with Evidence of Hepatic Dysfunction

We asked for followup information on a patient who developed transaminitis during treatment with gepirone.

Response: The sponsor provided followup on this patient, who was treated for about 3 months. Just before stopping treatment, his SGOT/PT were modestly elevated (52/93). Gepirone was stopped on (b) (6), and 6 days later, there was substantial increase (148/393). Levels were back to normal by 2 months post-stopping (24/41). There was one other patient who experienced significant hepatitis 15 days after starting gepirone (biopsy showed necrosis and mild intrahepatic cholestasis). Few other details were available on this patient, other than that he recovered after stopping. That case was complicated by coadministration of acetaminophen and apparently numerous other psychotropic drugs.

Comment: Overall, the controlled trials data do not show a transaminitis with this drug, and these isolated cases are difficult to interpret.

5.2.2.3 Conclusions Regarding Safety of Gepirone ER

There are no safety findings that would preclude the approvability of gepirone ER.

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

We found the literature review in the 5-18-01 submission to be inadequate, and we asked in the 3-15-02 letter that the sponsor more fully address the published literature, including a comprehensive review and commentary on the findings. In response, they provided citations to 617 published papers. Dr. Hearst reviewed this material and agreed with the sponsor's conclusion that there were no important new safety findings identified in this material that would impact on approvability or on labeling.

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.

9.0 DSI INSPECTIONS

It is my understanding that an inspection has been conducted for the randomized withdrawal study (28709), however, we have not, at this point, received a final report.

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 and outlines what would be needed for an approvable application.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Organon has not submitted sufficient data to support the conclusion that gepirone ER is safe and effective in the treatment of MDD. Thus, I recommend that we issue the attached nonapproval letter.

cc:

Orig NDA 21-164 (Gepirone ER)

HFD-120

HFD-120/TLaughren/RKatz/EHearst/PSDavid

HFD-100/RTemple

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/s/

Thomas Laughren
5/20/04 11:11:34 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 5, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

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 5-18-01
original submission.]

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 5HT_{1A} 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. These transfers of ownership resulted in several disruptions in the flow of the development program. There were several critical milestones in the further development of this product:

3-14-94: EOP2 Meeting

-We discussed with sponsor generally what would be needed to establish efficacy of ER formulation, given the existing database with IR; we also discussed completion of PK program, and pharm/tox requirements.

3-20-98: PreNDA Meeting

-We first became aware at this point of the preponderance of negative studies for the IR formulation, and discussed some of possible reasons for this outcome. The focus of this meeting was mostly on the standard requirements for filing the NDA and on format issues. Subsequent to this meeting we worked with sponsor to provide more advice on the filing.

9-30-99: Original Submission of NDA & Refusal to File (RTF)

-This was the original submission of this NDA for gepirone ER in MDD. 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 met on 11-18-99 to consider the fileability of this application, It was noted that 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. While there had been discussion of this trial at the 3-20-98 preNDA meeting, the critical facts regarding the analysis plan had not been made clear. Consequently we issued a RTF letter on 11-30-99.

2-2-00: Post RTF Planning Meeting

-We met with the sponsor on this date to discuss their plans for 2 additional identical trials with the ER formulation in MDD: 134001 & 134002. We generally endorsed this program.

5-18-01: Resubmission of NDA

-The NDA was resubmitted on this date, including the data from the additional ER studies. We met on 7-9-01 to consider the fileability of this application. While a number of problems were identified in the ISS, we agreed that the application was fileable.

10-11-01: Notification of Safety Deficiency

-It had been determined at this point in the review of the safety data that there was a significant deficiency in the requirement for long-term safety data. In fact, they had only 124 exposed patients for 6 months and only 35 for 1 year. Thus, we informed the sponsor of our concern about this deficiency. They indicated that they will have the required long-term data and planned to submit them in a March, 2002 safety update.

As noted, the original NDA 21-164 for gepirone ER was submitted 5-18-01. A safety update was submitted 9-18-01. The efficacy data for this application were reviewed by Earl Hearst, M.D., from the clinical group, and Drs. Roswitha Kelly/Kooros Mahjoob, from biometrics. The clinical safety data were reviewed by Tarek Hammad, M.D., from the safety group.

We decided not to take gepirone ER to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

There are some minor deficiencies that have been communicated to the sponsor. I am not aware of any CMC deficiencies that would preclude an approvable action.

The history of the proposed names for gepirone ER and the agency responses to these proposed names is somewhat complicated. The sponsor had originally proposed the name “(b) (4)” in a 1-16-97 amendment. We responded in a 6-10-97 letter with a rejection of this name, on the basis of it being “fanciful and misleading.” The sponsor proposed another name, “Ariza,” in a 11-2-99 amendment, and initially we accepted this proposal in a 8-25-00 letter, based on a review by OPDRA. However, in a subsequent followup review by OPDRA, they found this name unacceptable, due to possible confusion with the drug “Arava.” We issued a letter 1-14-02 indicating that we now considered the name “Ariza” unacceptable. We have had no further communication with the sponsor regarding a name as of this time.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology deficiencies that would preclude the approvability of this product.

4.0 BIOPHARMACEUTICS

Both the parent drug, gepirone, and the 3'OH-gepirone metabolite appear to have pharmacological activity relevant to the psychotropic effects of this drug, and therefore, plasma levels of both moieties are pertinent. Steady-state gepirone levels are attained in 2 to 4 days with daily dosing with gepirone ER. While dose proportionality studies with gepirone ER did not suggest any disproportionate increases in plasma concentration with dose, there was very high inter- and intra-subject variability that may mask any lack of dose proportionality. In fact, clearance was decreased by ½ at the higher gepirone ER doses. There is extensive first pass metabolism, and a prominent food effect, with a 62% increase in Cmax when gepirone ER is given with a high fat meal. More information is needed regarding the effects of meals with lesser fat content. 3A4 accounts overwhelming for the clearance of gepirone, with a very minor role for 2D6. Co-administration of ketoconazole is contraindicated with gepirone, (b) (4)

(b) (4) Clearance is reduced in patients with hepatic or renal compromise, and dose reduction is recommended in these groups. (b) (4)

Since the 40, 60, and 80 mg strengths have not been shown to be bioequivalent to the 20 mg strength, OCPB is recommending that these higher strengths not be approved. Our action letter notes a number of deficiencies that need to be addressed before any final action could be taken.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were a total of 4 short-term, placebo-controlled trials of gepirone ER (134001) or IR (03A7A-003; 03A7C-001-B; 03A7A-002) in major depressive disorder that were the focus of the efficacy review for this NDA (3 were typical, 8-week acute studies, and 1 was a randomized withdrawal study). These studies were reviewed by Earl Hearst, M.D., from the clinical group, and by two reviewers, Kooros Mahjoob, Ph.D. and Roswitha Kelly, Ph.D., from the biometrics group.

It should be noted that these 4 trials come from a much larger set of clinical trials of gepirone ER or IR in MDD, i.e., 24 in all. Of these 24 trials, 18 were placebo controlled and 6 were uncontrolled.

Thus, there were 14 placebo-controlled trials (7 with gepirone IR and 7 with gepirone ER) that were not the focus of our review, and these studies merit some discussion. All 14 were 6 to 8 week acute studies, and several explanations were given for considering them as not relevant for detailed review, in addition to their failure to show a benefit for gepirone.

-The following 6 of these studies had an active control group, at an adequate dose for that drug, that also failed to beat placebo, and thus could reasonably be considered failed studies:

- CN105-052 (ER)
- CN105-053 (ER)
- CN105-064 (ER)
- CN105-037 (IR)
- CN105-029 (IR)
- CN105-028 (IR)

-Another problem was likely the lower doses used in many of the initial studies with gepirone IR. In fact, none of the studies with maximum doses of ≤ 40 mg/day had positive results for gepirone. The studies considered positive by the sponsor, except for 03A7C-001-B, targeted gepirone doses in a range of 40 mg to some higher dose. Thus, ≤ 40 mg might be considered a threshold for considering studies as possibly irrelevant for an efficacy determination. Several of the studies having these dosing limits overlap with the studies considered above as failed for other reasons, and so I will add here only the 3 studies having these dosing limitations and not being considered failed otherwise:

- CN105-057 (ER)

CN105-043 (IR)

CN105-022 (IR)

It may be noted that study CN105-022 was, in fact, a positive study for fluoxetine, however, it was likely not an adequate test for gepirone due to the inadequate dosing.

-1 other study, 03A7C-001A-2486 (IR), was particularly difficult to interpret due to an unusually high dropout rate. This was an 8-week study that actually appeared to show significance for gepirone in the LOCF analyses, however, the overall rate of dropouts was almost 70%, which is extremely unusual for a depression trial of this length, and it raises significant questions about the conduct of this study. Thus, both the primary reviewers and the sponsor considered this an uninterpretable study, and I am inclined to agree.

-The following remaining 4 studies were, in my view, adequate by design, including gepirone dose, duration, population studied, assessment methods, and study conduct otherwise, to be considered relevant to the efficacy of gepirone, and yet all 4 failed to show a benefit for gepirone. While I agree that these studies are not readily interpretable, I still think they need to be considered as negative trials for gepirone, and therefore, should be considered in the overall benefit assessment for this drug.

CN105-078 (ER)

CN105-083 (ER)

03A7C-001A-2496 (IR)

APPEARS THIS WAY ON ORIGINAL

5.1.2 Summary of Studies Considered by the Sponsor and/or Primary Reviewers to be Pertinent to Efficacy Claims

5.1.2.1 Study 134001

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (5 US sites) comparing gepirone ER, in a dose range of 20 to 80 mg/day on a qd schedule in the am, and placebo, in adult outpatients meeting DSM-IV criteria for MDD. Patients were initiated at 20 mg qd, with an increase to 40 mg qd on day 4, and then increases of 20 mg/day each week, depending on tolerability and therapeutic response, up to a maximum dose of 80 mg/day. Patients were to be maintained on a minimum dose of 40 mg qd. There were roughly 100 patients per each of the 2 groups in the sample analyzed (n=204), with the % completing to 8 weeks ranging from 73 to 76%. The patients were about 61% female, about 73% Caucasian, and the mean age was 40 years. The mean modal gepirone ER dose was 68 mg qd.

While the assessments included MADRS, HAMD-28, CGI, and others, the primary outcome was change from baseline to endpoint in HAMD-17 total score, and I will limit my comments to that outcome. The LOCF analysis of the usual modified ITT population was considered primary, but OC was also done. ANOVA (with treatment, center, and their interaction as terms) was the statistical model employed. The LOCF analysis for HAMD-17 was significant ($p=0.018$), as were the OC analyses for all time points beginning with week 2, and most of the secondary endpoints:

Efficacy Results on HAMD-17 Total Score for 134001(LOCF)

	Baseline HAMD-17	) Baseline HAMD-17[P-value(vs pbo)]
Gepirone ER (20-80)	22.7	-9.0
Placebo	22.8	-6.8

Drs. Kelly/Mahjoob conducted additional analyses, i.e., ANCOVA with baseline HAMD-17 as covariate, both LOCF and OC, and MMRM. They used the ICH-E9 preferred approach of first testing a model without an interaction term for treatmentXcenter, and only if significant, adding this term to the model. All revealed consistently positive results for HAMD-17.

Comment: Both Drs. Hearst and Kelly/Mahjoob considered this a positive study, and I agree.

5.1.2.2 Study 03A7A-003

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (1 US site:Quitkin) comparing gepirone IR, in a dose range of 10 to 120 mg/day on a bid schedule, and placebo in adult outpatients meeting RDC criteria for major, minor, or intermittent depression, and who had an atypical profile. For this study, the “atypical” profile was defined to include patients who maintained “mood reactivity” despite the depression, and who had had one or more of the following features: (1) increased appetite or weight gain, (2) oversleeping, (3) severe fatigue with “leaden paralysis,” or (4) hypersensitivity to rejection. Importantly, subjects needed only a HAMD-21 score ≥ 10 to qualify for this study. It was not clear how dosing commenced or how the titration proceeded. There were roughly 30 patients per each of the 2 groups in the sample analyzed (n=60), with the % completing to 8 weeks ranging from 57 to 63%. The patients were about 35% female, about 95% Caucasian, and the mean age was 39 years. Dr. Hearst indicates at one point in his review (p.53) that 76% of patients met RDC criteria for MDD, but elsewhere (p.65), he indicates that only 65% of patients met RDC criteria for MDD. The mean modal dose for gepirone IR was 48 mg qd.

While the assessments included MADRS, HAMD-28, CGI, and others, the coprimary outcomes were change from baseline to endpoint in HAMD-17 total score and CGI percent responders (defined as a 1 [very much improved] or 2 [much improved]), and I will comment primarily on these outcomes. The LOCF analysis of the usual modified ITT population was considered primary, but OC was also done. ANOVA (with treatment, center, and their interaction as terms) was the statistical model employed for HAMD-17. CMH was the statistical model employed for CGI percent responders. The overall analysis for HAMD-17 was significant (p=0.009), as was the analysis for CGI percent responders (p=0.009). The OC and secondary analyses were also generally significant. Apparently, results on the primary endpoints for the subgroup of patients who met RDC criteria for MDD also significantly favored gepirone over placebo.

Efficacy Results on HAMD-17 Total Score for 03A7A-003 (LOCF)

	Baseline HAMD-17	) Baseline HAMD-17[P-value(vs pbo)]
Gepirone IR (10-120)	13.8	-6.7
Placebo	13.7	-2.7

Efficacy Results on CGI Percent Responders for 03A7A-003 (LOCF)

	Percent Responders [P-value(vs pbo)]
Gepirone IR (10-120)	57%
Placebo	23%

Drs. Kelly/Mahjoob conducted additional analyses, i.e., ANCOVA with baseline HAMD-17 as covariate, both LOCF and OC, and MMRM. They used the ICH-E9 preferred approach of first testing a model without an interaction term for treatmentXcenter, and only if significant, adding this term to the model. All revealed consistently positive results for HAMD-17.

Comment: Dr. Hearst considered this a positive study. However, Drs. Kelly/Mahjoob did not consider this a positive study, for the following reasons: (1) they considered the dropout rate of about 40% too high to consider these data reliable, (2) they considered the sample sized unusually small for a depression trial, and (3) there was mention of an interim analysis in the protocol, however, it was not clear whether or not this analysis was ever actually conducted. I do not agree with the objections posed by Drs. Kelly/Mahjoob to this trial, however, I feel there is another reason to reject this as a study in support of a claim in MDD. While the results on the coprimary and various secondary endpoints were impressively positive, I am greatly troubled by the population recruited. While a majority of patients reportedly met RDC criteria for MDD, 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 it 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 my 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 I think the relatively low HAMD-17 scores are reflective of the diversity of patients in this sample. In fact, many of these patients likely overlap 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. Thus, while I consider this a positive study, I do not consider it a study that can support a claim of effectiveness in MDD. The sponsor, of course, may choose to challenge this objection,. If they do, they need to be very clear in describing how it was assured that patients did meet criteria for MDD, for those who did, and we might then ask for an additional analysis of the subgroup of patients who could have been reasonably considered to meet the criteria for MDD.

5.1.2.3 Study 03A7C-001-B

This was a randomized, double-blind, parallel group, 8-week, fixed-flexible dose study (3 US sites) comparing gepirone IR, in two dose ranges [low (5-60 mg/day) or high (10-120 mg/day), on a bid schedule], and placebo in adult outpatients meeting RDC criteria for major depressive disorder. While it is unclear exactly how dosing commenced in this study, subsequent dosing was apparently titrated within these dose ranges depending on tolerability and therapeutic response. There were roughly 70 patients per each of the 3 groups in the sample analyzed (n=206), with the % completing to 8 weeks ranging from 46 to 58%. The patients were about 55% female, about 93% Caucasian, and the mean age was 42 years. Mean modal doses for the low and high dose groups were 28 mg/day and 42 mg/day, respectively.

While the assessments included MADRS, HAMD-28, CGI, and others, the coprimary outcomes were change from baseline to endpoint in HAMD-17 total score and CGI percent responders (1 or 2 on CGI-I), and I will comment primarily on these outcomes. The LOCF analysis of the usual modified ITT population was considered primary, but OC was also done. ANOVA (with treatment, center, and their interaction as terms) was the statistical model employed for HAMD-17. CMH was the statistical model employed for CGI percent responders. Dunnett's approach was used to adjust for multiple comparisons of active drug groups with placebo. The overall analysis for HAMD-17 was significant (p=0.015 for 5-60 and p=0.001 for 10-120), as was the analysis for CGI percent responders (p=0.018 for 5-60 and p=0.05 for 10-120). [Note: Technically, the CGI-PR results are not significant for the 10-120 group, since 0.05 would not meet the Dunnett's criterion p-value.]:

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

	Baseline HAMD-17	) Baseline HAMD-17	[P-value(vs pbo)]
Gepirone IR (5-60)	23.4	-10.0	0.018
Gepirone IR (10-120)	24.4	-11.3	0.001
Placebo	24.1	-6.4	

Efficacy Results on CGI Percent Responders for 03A7C-001-B (LOCF)

	Percent Responders	[P-value(vs pbo)]
Gepirone IR (5-60)	59%	0.018
Gepirone IR (10-120)	55%	0.050
Placebo	39%	

Drs. Kelly/Mahjoob conducted additional analyses, i.e., ANCOVA with baseline HAMD-17 as covariate, both LOCF and OC, and MMRM. They used the ICH-E9 preferred approach of first testing a model without an interaction term for treatmentXcenter, and only if significant, adding this term to the model. Using the ICH-E9 approach for HAMD-17 total score and for CGI-PR, they concluded that statistical significance is achieved only when the two gepirone IR dose groups are combined for comparison with placebo. The MMRM approach for HAMD-17 total score suggested an effect for the high dose group and the combined dose groups, but not the low dose group by itself.

Drs. Kelly/Mahjoob also conducted additional analyses adding the treatmentXcenter interaction term to the model, and found a significant interaction. In fact, it appears that the overall positive results are coming from 1 center, i.e., the smallest center (Cole).

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

Clearly the positive results are coming from the Cole center, which turns out to be only 1/3 the size of the other 2 centers, where there is little drug effect observed. 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). It should be noted that the finding of essentially no placebo effect in the Cole center is extremely unusual in depression trials, and therefore, is suspect.

Comment: Dr. Hearst considered this a positive study on the sponsor's protocol specified analyses. However, Drs. Kelly/Mahjoob expressed concern about both the weaker results on alternative analyses and the very unusual interaction. I share this concern, in particular, the concern about the finding that the overall positive outcome is clearly coming from a very small center in which placebo patients are showing no movement at all on the HAMD-17. Thus, I am inclined to reject the results from the Cole center and consider this an uninterpretable study that does not support the claim of efficacy in MDD.

5.1.2.4 Study 03A7A-002

Results from this study were submitted in support of a claim for the short-term efficacy of gepirone ER in MDD. This 5 center, US study began with the selection of patients meeting RDC criteria for MDD; n=134 patients meeting these criteria were treated in a 6-week, open label phase involving dosing with gepirone

IR in a dose range of 10-90 mg/day, on a bid basis. Responders were selected from this phase (n=70) for randomization, where response was defined as (1) a reduction of the HAM-D-17 to ≤ 12 or a $\geq 50\%$ reduction, and (2) a CGI-I of at least 5 (moderately improved). Randomization of these n=70 responders was either to continuation on gepirone IR, at the same dose being used at the time of completion of the 6-week phase, or to placebo, for the 6 week double-blind discontinuation phase (n=36 for gepirone IR and n=34 for placebo). Apparently the protocol did not specify a primary endpoint, but rather, identified change from baseline in HAM-D-17 and CGI-I responders as important endpoints. Although the study report refers to 6 different definitions of relapse as key endpoints, these endpoints were apparently defined long after the conduct and analysis of this trial.

Patients in this study were roughly half female, essentially all Caucasian, and the mean age was roughly 44 years. The mean modal gepirone IR dose in the double blind phase was 41 mg/day.

There were no statistically significant differences favoring gepirone IR over placebo on change from baseline in HAM-D-17 ($p=0.08$) or on CGI-I responder status ($p=0.24$). Again, these presumably were about as close as we can get to protocol specified primary outcomes.

The analyses for time to relapse utilized the log rank test. The analysis were based on the sample meeting our usual criteria for ITT.

The overall rates of discontinuation prior to reaching the 6 week nominal endpoint were as follows:

Gepirone 20-90:	15/36 (42%)
Placebo:	16/34 (47%)

The results on time to relapse favored gepirone 20-90 over placebo for 4 of the 6 definitions of relapse. In my view, none of the 6 definitions could be completely rejected as unreasonable. Thus, one is left with a 2:1 split in results, that only slightly favors gepirone IR.

Comment: Dr. Hearst considered this a positive study in support of a claim of longer-term efficacy for gepirone ER in MDD, apparently because he believed at the time of finalizing his review that one of the 6 definitions of relapse (one that resulted in a significant p-value) had been designated as the primary outcome. However, since we later discovered that time to relapse was not until much later considered as an important outcome, I do not feel it is appropriate to emphasize these outcomes. In any case, these analyses are not positive on 2 of the 6 definitions of relapse, which seem as reasonable as any of the others. The study was negative on the other outcomes identified in the protocol as important, if not primary. For these reasons, Drs. Kelly/Mahjoob did not consider this a positive study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Gepirone ER for MDD

Evidence Bearing on the Question of Dose/Response for Efficacy

In my view, there are no data in this application directly pertinent to the question of dose response for efficacy. Given the uniformly negative results in studies with a maximum dose of ≤ 40 , it's probably a reasonable conclusion that doses lower than 40 mg are not likely to be effective. However, it would be much preferable to have the finding of lack of effect below 40 mg/day in the same study in which doses above 40 mg/day were shown to be effective, i.e., a dose response study. If this drug were to be approved, the dosing instructions in labeling would need to focus on the titration approach utilized in whatever positive studies supported the approval.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender and age for the 3 short-term trials, and the 1 longer-term trial proposed by the sponsor as positive. While there were scattered differences in various subgroups across these 4 studies, there were no consistent patterns to suggest a preferential response in one subgroup over another, in my view. However, there was also likely not adequate power to detect such differences.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the HAM-D-17 observed in the 1 short-term study that I consider positive was similar to that seen in other positive antidepressant trials.

Duration of Treatment

In my view, there are no data in this application pertinent to the question of longer-term efficacy.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, not provided sufficient evidence to support the claim of short-term antidepressant efficacy for gepirone ER. Based on earlier discussions with the sponsor, we had agreed that a single positive short-term trial with the ER formulation, in the face of independent evidence for the antidepressant efficacy of the IR formulation, would be sufficient to support a claim for the antidepressant efficacy of the ER formulation. The sponsor has not, in my view, provided such evidence.

I am in agreement with Drs. Kelly/Mahjoob/Hearst regarding the short-term gepirone ER study (134001). I also consider this to be a positive study in support of gepirone ER in MDD. However, I do not feel that any of the 3 gepirone IR studies proposed by the sponsor as support for the MDD claim can, in fact, be considered positive studies in support of this claim.

-Study 03A7A-003: As I've indicated, it's not clear to me what population was actually studied in this admittedly positive study. In my view, there is serious question about whether or not the population studied could have met the usual criteria for MDD, based on the HAM-D-17 baseline scores, despite the assertion

that most did meet MDD criteria. Thus, I consider this an uninterpretable trial with regard to the efficacy of gepirone in MDD.

-Study 03A7C-001-B: I agree with Drs. Kelly/Mahjoob that the very striking treatment by center interaction, i.e., the interaction revealing that the overall positive outcome from this trial derives entirely from the smallest center with a placebo response rate that is so low that it falls far outside the norm for this kind of trial, is a fatal flaw in the results that cannot be overlooked. Thus, I consider this another uninterpretable trial.

-Study 03A7A-002: Despite the flawed design of this unusual study, it may have provided some indication of antidepressant activity, had the appropriate outcomes been designated as primary in the protocol. However, as I've indicated, the outcomes that were designated in the protocol as important did not yield positive results, and for the more appropriate outcomes defining various states of relapse, only some of these yielded positive results, and all were post hoc. Thus, I consider this another uninterpretable study.

It is unfortunate that these deficiencies regarding the IR studies were not recognized earlier in the process, e.g., at the initial refusal to file, however, we were dealing with summary data at the time, rather than the more complete reports that were necessary to fully recognize these problems. In addition, the primary focus was on the inadequacies in study 53, the 1 ER study considered by the sponsor to be positive at that time. The sponsor, of course, may wish to challenge this conclusion that none of these 3 gepirone IR studies can count in support of the efficacy of gepirone ER in MDD. Of these 3 studies, only 03A7A-003 might conceivably withstand such a challenge, however, and that would still yield only 1 positive study for each of the IR and ER formulations. In my view, that still would not be sufficient to support a claim for gepirone ER, since it does not meet my requirement for a "bridge" between the 2 formulations.

Other Issues:

Drs. Kelly/Mahjoob raise a concern about the many negative trials in the overall development program for both the IR and ER formulations. I fully agree, as noted in my introductory comments to this efficacy discussion. I consider the following 3 gepirone ER studies to be negative (CN105-078; CN105-083; 134002) and also 1 gepirone IR study (03A7C-001A-2496). All 4 studies were, in my view, sufficiently adequate by design, including gepirone dose, duration, population studied, assessment methods, and study conduct otherwise, to be considered relevant to the efficacy of gepirone, and yet all 4 failed to show a benefit for gepirone. While I agree that these studies are not readily interpretable, I still think they need to be considered as negative trials for gepirone, and therefore, should be considered in the overall benefit assessment for this drug. Thus, in summary, of 5 studies that appear, on face, to be relevant for consideration of the efficacy of gepirone, 1 of 4 gepirone ER studies yielded a positive result, and a fifth study, for gepirone IR, failed to yield a positive result. Generally we have found that, overall, roughly half of antidepressant trials that appear to be adequate by design fail to beat placebo, even for drugs that we know are effective. Thus, this result for gepirone, i.e., 1 of 5 relevant studies being positive, while of concern, is not a result that would lead one to conclude that gepirone is ineffective as an antidepressant.

Nevertheless, in my view, 1 additional positive study for the ER formulation would be both necessary and persuasive of the antidepressant efficacy for this formulation.

Drs. Kelly/Mahjoob also raise a concern about what they consider to be high dropout rates for the short-term trials. Our experience with antidepressant trials has been to expect fairly high rates of dropout, and I don't consider the rates for the gepirone trials generally excessive, with a few exceptions in some of the earlier trials. Some of the earlier high dropout rates may have been a result of intolerability for the gepirone IR, given the way it was being used. In fact, the dropouts are generally lower for the 1 positive study for the ER formulation (134001), in particular for adverse events. This formulation was developed to specifically address the tolerability findings with the IR formulation, and this is the formulation that will be marketed if this drug is to be approved.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The development program for gepirone extended over a long period of time, and ownership transferred twice. In addition, there was a shift in focus from an initial program with the IR formulation to a later program focusing on the ER formulation. The earlier data were generated by the BMS program, and the more recent data by Organon.

This development program, including all patients exposed to both the IR and ER formulations, up through the 9-18-01 safety update, contained 3,631 subjects exposed to 1 or more doses of gepirone. Of these exposures, 2,708 came from phase 2-3 studies. As noted, the long-term exposure was limited, with 227 exposed to a modal dose of ≥ 20 mg/day for at least 6 months, and 80 subjects exposed to a modal dose of ≥ 20 mg/day for 1 year. The mean age of patients was roughly 40, with less than 2-3% >65 . Patients were predominantly Caucasian, and about 2/3 female.

5.2.2 Adverse Event Profile for Gepirone ER

5.2.2.1 Overview

Based on the data available, given the noted deficiencies, the adverse event profile included the following adverse events with an incidence of $\geq 5\%$ or more for gepirone ER and at least twice the placebo rate include: dizziness, nausea, insomnia, paresthesia, and vomiting. These same events also led to discontinuation in some patients. Little can be said about dose relatedness for adverse events, since the studies were all flexible dosing. There were no consistent effects on vital signs, at least in the sitting position. There was a suggestion of an orthostatic effect of gepirone (see below under 5.2.2.2). Generally there was no suggestion of gepirone related changes in chemistry, hematology, or urinalysis, with 2

exceptions (see below under 5.2.2.2). Generally there was no suggestion of a gepirone related effect on ECG parameters.

5.2.2.2 Adverse Events of Particular Note for Gepirone ER

Dizziness

Dizziness was reported in 34% of gepirone ER exposed patients (vs 13% pbo) in ph2-3 depression trials and led to discontinuation in 2.3% (vs 0.4% pbo). Orthostatic changes also occurred more frequently in gepirone ER exposed patients (1% GER vs 0.4% pbo) in ph2-3 depression trials, and may have accounted for some of the reports of dizziness. We are proposing to emphasize this rather common AE in Precautions, given the implications for driving, etc.

Lack of Sexual Dysfunction

The sponsor has proposed a (b) (4) the apparent finding of no difference between GER and placebo in sexual dysfunction. However, it is not clear how sensitive the approach was for detecting sexual dysfunction, and in the absence of a sensitive method, I am not inclined to permit them to promote GER as a drug that is free of such effects. We will request more information regarding the method, and suggest a separate sensitive study (or studies) of sexual dysfunction to support such a claim.

Lack of Assessment for Discontinuation Emergent Symptoms

The sponsor suggests that there is no evidence for discontinuation emergent symptoms associated with stopping gepirone, however, it seems clear that there was no attempt, even in the randomized withdrawal study (002), to sensitively assess for such symptoms. Thus, it is unknown whether or not such symptoms occur.

Neutropenia in Absence of Leukopenia

Dr. Racoosin has discussed the unusual finding of a slight excess of low ANC's in gepirone ER (GER) pts vs gepirone IR (GIR) patients, in the absence of an effect on total WBC's. This finding is of unknown clinical significance, and may be spurious.

Hyperbilirubinemia

Dr. Racoosin has discussed the finding of an excess GIR/GER patients with slight increases in total bilirubin vs pbo. These generally were not persistent changes, and were not associated with transaminase increases or any apparent clinical findings. These changes are of unknown significance.

Allergic Reaction

Dr. Racoosin has discussed the possibility of allergic reactions to GIR/GER. This is based on a severe case of hepatosplenomegaly associated with fever, rash, transaminitis, and eosinophilia, along with AE rates for the BMS ph 2-3 trials suggesting a slight excess of events that may indicate allergic reaction, i.e., arthralgia and myalgia. We will ask the sponsor to explore for this possibility.

Weight Reduction

Although the sponsor proposes labeling language suggesting a slight weight loss for gepirone compared to a slight weight gain for placebo, apparently the data are not consistent, and we have asked in the action letter for additional analyses to try to clarify what data would best characterize the effects of gepirone on weight, for purposes of labeling.

Suicidal Ideation and Attempts

There was a slight excess of risk for these events in GIR/GER patients vs pbo, however, this may be explained by greater exposure time for GIR/GER patients. We will ask the sponsor to adjust for time at risk with total person time.

5.2.2.3 Conclusions Regarding Safety of Gepirone ER

While there are no safety findings that would preclude the approvability of gepirone ER for MDD, there are several critical deficiencies in the safety data that need to be addressed before a final action can be taken on this NDA:

- The minimum ICH criteria for long-term exposure data have not been met for gepirone.
- The safety data have not been presented in a manner that permits a separate characterization of the safety profile for the IR and ER formulations. This is clearly of interest, since it is the ER formulation that is to be marketed, and in fact, the ER formulation was presumably developed because of tolerability problems with the IR formulation.
- The data have not been presented in a manner that permits a pooling of the BMS and Organon data for safety analyses.
- The data have not been presented in a manner that permits a separation of safety findings in the depression population as distinct from other populations studied.
- The event “dizziness” has not been adequately explored, e.g., the time and severity course for this event, its relationship with orthostatic events, etc.
- The QTc data have not been adequately evaluated regarding the proportion of patients having changes from baseline of fixed magnitude, e.g., ≥ 30 or ≥ 60 msec.
- For 18% of adverse dropouts, the specific event(s) leading to dropout were not identified; there needs to be an effort to identify, where possible, these events.

- The literature review is inadequate, including only references to 286 published papers, with the actual paper being provided in only 21 instances, and with no commentary on the relevance to safety of any findings reported in these papers. We will ask the sponsor to more fully address this requirement.
- The sponsor will be notified/reminded of these deficiencies in the action letter.

5.3 Clinical Sections of Labeling

Although I am recommending a nonapproval action, we have included a draft of labeling with the package.

6.0 WORLD LITERATURE

As noted under Safety, the literature review is inadequate. We will ask the sponsor to more fully address this requirement.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, neither gepirone IR nor gepirone ER is marketed anywhere at this time. We will ask for an update on the regulatory status of gepirone ER in the nonapproval letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 domestic sites for each of the 3 short-term studies considered pivotal for this NDA. While some deficiencies were noted, overall, the data were deemed acceptable. However, due to the discovery of a discrepancy between the CRFs and the sponsor's data listing for patients at one of these 3 sites, there is an audit of the sponsor records ongoing to try to better understand these discrepancies. Thus, the DSI conclusion regarding this NDA is pending.

10.0 LABELING AND NONAPPROVAL LETTER

10.1 Labeling

As noted, we have proposed labeling, even though my recommendation is for a nonapproval action. .

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 and outlines what would be needed for an approvable application.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Organon has not submitted sufficient data to support the conclusion that gepirone ER is safe and effective in the treatment of MDD. Thus, I recommend that we issue the attached nonapproval letter.

cc:

Orig NDA 21-164 (Gepirone ER)

HFD-120

HFD-120/TLaughren/RKatz/JRacoosin/EHearst/THammad/PDavid

HFD-100/RTemple

DOC: MEMGPDEP.NA1

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

/s/

Thomas Laughren
3/5/02 05:10:37 PM
MEDICAL OFFICER

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: 12-18-99

FROM: Thomas P. Laughren, M.D. 
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Refusal to File NDA 21-164 for gepirone (for the treatment of depression)

TO: NDA 21-164

[Note: This memo should be filed with the 9-30-99 original submission of this NDA.]

Refer to an 11-15-99 review of the 9-30-99 submission (for filing purposes) by Susan Molchan, M.D., for additional details on this application, and to HFD-120's refusal to file letter, issued 11-30-99.

The sponsor has submitted an NDA for an extended release formulation of gepirone, including data from depression studies with both the immediate release (IR) and the extended release (ER) formulations. Since the IR and ER forms are unlikely to be bioequivalent, it seems clear that we would not be able to rely on efficacy data only from IR studies. This was noted at our 3-20-98 preNDA meeting with the sponsor. In general, it has been division policy to accept clinical evidence of efficacy from 1 additional study involving an ER formulation when a company has already demonstrated efficacy for an IR formulation. That policy would apply here as well.

In this submission, the sponsor identifies studies 003 and 001B as short-term studies of the IR formulation that support the antidepressant efficacy of the IR, as well as study 002, a relapse prevention trial involving the IR formulation as an additional source of support for the IR. On face, I would agree that these trials are of adequate design and, if positive as suggested by the sponsor, would support the IR.

The difficulty is with the ER data. There is only 1 study (53) that, on face, could provide support for the antidepressant efficacy of the ER formulation, since the other 2 credible ER studies, 78 and 83, were positive only on evaluable subset analyses, according to the sponsor. Thus, study 53 would need to be positive in order for this NDA to have any chance of approval. Unfortunately we were misled on the details of this study at the our 3-20-98 preNDA meeting. It was our clear impression from that meeting that this study was designed as 2 independent trials at 2 separate sites, and given

that primary plan, we agreed with the sponsor that there would be no basis for combining data from the 2 sites (see 3-20-98 minutes from that meeting). However, given that we did not have details from the protocol for that meeting, we cautioned that this issue would be a matter for review. As it turns out, the protocol for this study is quite clear that this was planned as a 2-center study with the intent of pooling the data, as in any multicenter trial. Since the sponsor seems to agree that the overall analysis of the data for this trial does not yield a positive outcome, there is no basis for proceeding to the analysis of the individual sites. Thus, on face, this study could not support the approvability of this NDA as a bridge from the IR data.

As noted, we informed the sponsor of this conclusion in our refusal to file letter dated 11-30-99.

cc:

Orig NDA 21-164

HFD-120/DivFile

HFD-120/TLaughren/RKatz/SMolchan/PDavid

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