CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: June 22, 2004

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Gepirone, NDA 21-164, ER Tablets for MDD

TO: File

I concur with the Division's view that NDA 21-164 is not approvable. The thorough failure of 4/5 ER studies, some at the dose that was successful in study 134001, is impressive and 134004 gave a result numerically worse than placebo and almost significantly worse than Prozac. [I can't find any reference to the dose used in this study, but it appears that no serious D/R study has been conducted.] Also, and given the history of success of studies of this design, study 28709, a randomized withdrawal study, also failed once the 37 excluded patients were put back (including 5 gepirone relapses). Such failures are very unusual for effective agents. There thus seems real doubt as to whether gepirone is effective and no doubt that its effectiveness has not been shown. It is certainly possible that the variable blood levels associated with gepirone's 3A4 metabolism are part of the difficulty. It is conceivably a case where a D/R study accompanied by blood levels and an attempt at a C/R analysis could be useful.

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/s/

Robert Temple
6/22/04 04:20:40 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: March 13, 2002

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: NDA 21-164 (Gepirone, Organon)

TO: Director, Division of Neuropharmacologic Drug Products, HFD-120

I concur in the NA action, but I have a few comments (and have modified the letter somewhat):

1. I am troubled by the lack of any D/R information. Failure of studies with doses < 40 mg/day may give some idea of the dose needed for effectiveness (although there were many failures at higher doses as well and note that many patients in some of the "positive" studies didn't get to 40 mg), but we have little or no data within the dose range where gepirone might work. I therefore believe the additional ER study should study several fixed doses, such as 40, 80, 120. You could refer to ICH-E4, a U.S. adopted guideline. It also seems at least possible that the mixed success is a result of substantial PK variability. It would not be a bad idea to get trough blood levels to allow at least a retrospective look at C/R relationships. I could possibly be dissuaded from this view if there were some persuasive reason to titrate everyone from (say) 20 mg, but even in that case you need to know what dose to go to.

2. Whether a molecule is effective or not does not necessarily tell you that a particular dosage form and dose work, although assurance can perhaps be gained by PK modeling. In the present case, the marginal results suggest at a minimum that dose could matter a lot. I believe the additional study needed should therefore use the to-be-marketed product, i.e., the ER form. Note (Table 1) that some of the $\leq$ 40 mg studies (105-057, 105-078) had mean doses (30-34 mg) not so different from the higher dose studies [03A7A-003 (mean 41); 03A7C-001B (mean 33); 03A7A-002 (mean 40); 03A7C-001A-2490 (mean 47); 03A7C-001A-2486 (mean 47)]; so not much about dose seems clear, and not all the low dose (<40 mg) failures can be dismissed.

3. We need to pin down which of the Clin Pharm deficiencies are really needed. I have removed the request for an in-vitro study of 3A4 interactions (they already have a in – vivo study of ketoconazole) but left in a request to study 3A4 induction (the letter says in vitro but I don't believe there is such a method). Do we now insist on such a study of all drugs (I believe current guidance does not say this). As induction of 3A4 would lead to lower gepirone blood levels over time (it's 3A4 metabolized), perhaps blood levels over time in the further study would be sufficient.

Robert Temple, M.D.

cc:
Orig.
HFD-120
HFD-120/P David
HFD-101/R Behrman
HFD-101/R Temple
draft:sb/3/12/02
final:sb/3/13/02
filename:Gepirone_MM_Mar02.doc

Table 1
18 placebo-controlled

		(approx) n/gp	Dose	Result
	ER			
	CN 105-052, 053, 064	15-35	--	Active failed (053 NS as pooled, though one center SS)
	CN 105-057	150	2-4, 5-10, 10-20, 20-40 (mean 34)	D/R, but no dose worked
--	CN 105-078	45	10-50 (mean 30); 20-100 (mean 53)	Failed (no active)
--	CN 105-083	40	10-50 (mean 30); 20-100 (mean 57)	Failed (no active)
*	134001	100	20-80 (mean 70)	HamD 17 – p=0.018
--	134002	105	20-80 (mean 68)	Failed
	IR			
	CN 105-037, 029, 028	20-60	--	Active control failed
	CN 105-043, 022	60, 70	$\leq$ 40 mg (mean 17, 15)	Cpos for fluoxetine
	03A7C-001A-2486	40	5-45 (mean 22); 10-80 (mean 47)	"Pos," but very high D/O (>70%)
--	03A7C-001A-2496	40	5-45 (mean 25); 10-90 (mean 47)	Failed (no active)
*	03A7A-003	30	10-90 (mean 41)	Baseline HamD = 13.7-.8; Pos HamD 17, p=0.009; but ? patients
*	03A7C-001B	70	5-45 (mean 21) 10-90 (mean 33)	Pos but driven by 1 small study site
*	03A7A-002	35	10-90 (mean 40)	Rand WD; failed 1° endpoints

*Submitted as positive
-Failed (dose $\geq$ 40, no failed active control)

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/s/

Sandra Benton
3/13/02 09:59:39 AM
TECHNICAL

Robert Temple
3/14/02 06:45:32 PM
MEDICAL OFFICER