Wally APRO5 1985

To: Dr. S. Bandak, London
T. A. Chandler, Bad Homburg
Dr. B. A. Gennery, Erl Wood
Dr. C. D. Hardison, Indianapolis
G. Mayr, Bad Homburg
E. R. Roberts, Indianapolis
S. A. Taurel, London
D. E. Thompson, Indianapolis
Dr. H. J. Weber, Bad Homburg
Dr. A. J. Weinstein, Indianapolis
Dr. Dr. J. F. Wernicke, Indianapolis
Dr. R. L. Zerbe, Indianapolis

cc: Dr. K.-C. Bamberg, Bad Homburg
S. Heymanns, Bad Homburg
B. von Keitz, Bad Homburg

EXHIBIT
WEBER 6

From: Dr. J. Schenk, Bad Homburg

Date: April 4, 1985/ja/mb

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Report on Fluoxetine Working Session
on April 29 and 30, 1985
Bad Homburg

Participants:
Professor Herrmann, Berlin
Dr. Kern (Mrs.), Berlin
S. Heymanns, Bad Homburg
B. von Keitz, Bad Homburg
Dr. J. Schenk, Bad Homburg

Objective of meeting:

To make Professor Herrmann and his co-worker familiar with fluoxetine data, so that he is in a better position to give best advice as a consultant to the company in the registration process of fluoxetine.

Data reviewed:

1. Original documentation submitted March 1, 84
2. Analysis of pooled studies fluoxetine vs. imipramine vs. placebo (protocol no. 27), submitted Oct. 26, 84.

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Outcome:

Professor Herrmann left an opinion of 21 type-written pages. The essential points are summarized as follows:

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A. EFFICACY

- Fluoxetine's onset of action later than that of imipramine
- initial potency inferior to that of imipramine
- overall response rate identical
- drop out rate because of lack of efficacy only slightly higher than on imipramine
- FLUOXETINE IS AN EFFECTIVE ANTIDEPRESSANT IN OUT-PATIENTS SUFFERING FROM PREFERABLY ENDOGENOUS DEPRESSION

B. SAFETY

- Initially only slightly higher incidence of signs of activation or no difference at all (compared to placebo)
- Imipramine and fluoxetine have both components, activation as well as initial sedation
- initial sedation more pronounced under imipramine (this is used therapeutically, but is a disadvantage on prolonged treatment, i. e. initial inferiority --- later superiority)

- Fluoxetine is unequivocally superior to imipramine with regard to lower anticholinergic side-effects

- Nausea more frequent than under imipramine, but no major cause for early discontinuations

- Fluoxetine causes a relevantly smaller incidence of drop outs because of side-effects

- STILL NOT RESOLVED IS THE FACT THAT SUICIDE ATTEMPTS HAVE BEEN OBSERVED MORE FREQUENTLY ON FLUOXETINE AS COMPARED TO IMIPRAMINE (ONLY EPIDEMIOLOGIC DATA OR LITERATURE ON OTHER ANTIDEPRESSANTS MAY HELP TO IDENTIFY, WHETHER IT HAPPENED BY CHANCE THAT INCIDENCE OF SUICIDE ATTEMPTS WAS ABNORMALLY HIGH ON FLUOXETINE, OR ABNORMALLY LOW UNDER COMPARATORS).

- EXCEPT NAUSEA FLUOXETINE'S SIDE-EFFECT SPECTRUM IS UNEQUIVOCALLY MORE FAVOURABLE THAN THAT OF IMIPRAMINE, BUT ACCORDING TO THE TODAY'S KNOWLEDGE THIS IS NEGATIVELY AFFECTED BY THE INCREASED SUICIDAL RISK.

C. BENEFIT/RISK RATIO

Not unequivocally positive.
THEREFORE IT IS OF GREAT IMPORTANCE TO DETERMINE CERTAIN TYPE OF PATIENTS WHO WILL BETTER RESPOND TO FLUOXETINE THAN TO IMIPRAMINE, SO THAT HIGHER RISK MIGHT BE ACCEPTABLE.

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D. PROBABILITY OF SUCCESS

The today's knowledge of data does not justify the judgement that there is a high probability of getting fluoxetine registered in Germany.

Reasons:

- Benefit/risk ratio as discussed above

- no studies in Europe and Germany

- NO EVIDENCE OF BENEFIT VERSUS RISK IN TREATMENT OF HOSPITALIZED PATIENTS, WHICH IS OF SPECIAL IMPORTANCE FOR THE INDICATION "ENDOGENOUS DEPRESSION" (TO DATE NO COMPANY HAS APPLIED FOR REGISTRATION WITHOUT HOSPITALIZED PATIENTS).

E. PREREQUISITES FOR SUCCESSFUL OUTCOME (= limited indication, i. e. mild to moderate endogenous depression plus precautionary statement concerning suicidal risk):

1) Plausible explanation for incidence of suicides/s. attempts
2) Positive results of Hippius' trial
3) Identification of certain patient type ("responder")

OUR (BAD HOMBURG) RECOMMENDATION WOULD BE THE FOLLOWING NOW:

1) Stick to the action plan of March 26
2) Do all analyses recommended by Professor Herrmann to establish the basis for a successful outcome
3) Make a new assessment of probability of success at the time new analyses, the Hippius report, and other expert opinions are available.

Professor Herrmann was asked to go through our reply to the BGA of October 24. This might probably change his opinion on the one or the other issue.

HOWEVER, BEAR IN MIND WITHOUT INPATIENT DATA, EVEN IF ALL OTHER DATA ARE SATISFACTORY, IT IS HERRMANN'S OPINION THAT WE AT BEST GET A LIMITED INDICATION APPROVAL, I. E. FOR MILD TO MODERATE DEPRESSION ONLY.

Dr. Johanna Schenk

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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 December 8, 1987

FROM R. M. Kapit

SUBJECT: Lilly's response re the BGA *RMK 12-8-87*

TO: File, NDA 18-936

On December 4, 1987, a letter from Dr. M. W. Talbott relayed Dr. Wernicke's response to a teleconference with Dr. T. Laughren and this reviewer regarding comments made by the German regulatory authority (the BGA) on the safety of Prozac.

The letter asserted that the German authorities never defined or documented the phrases "severe organ damage" or "unacceptable damaging effects", which were used in their communications to the company. The letter denies that any such organ damage has ever occurred in fluoxetine-treated patients.

The company asserts that all information made available to the BGA has been made available to the FDA, and to their knowledge, the FDA has used more sophisticated analyses in reviewing the data.

Conclusion: The BGA comments do not appear to reflect clinical events, since no such events have been reported to the FDA, and according to the company, we have received all information submitted to the BGA.

Recommendation: The comments by the BGA should not affect FDA's conclusion that NDA 18-936 is approvable.

Dist
NDA 18-936
HFN-120
HFN-120/TLaughren, TDeCicco, RKapit

12-8-87
I agree that the BGA comments do not raise any new concerns. I see 12-3-87 memo to file re: teleconference c Lilly.
Thomas P. Laughren, MD
GL, DNDP

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