Memorandum of Telephone Call

Date: September 25, 1997

NDA: 20-822

Subject: Missing narratives, data discrepancies

Firm: Forest Labs

Drug: Citalopram

Point of Contact: Kathryn Bishburg, Pharm.D.

Phone number: (212) 224-6866

I telephoned Dr. Bishburg regarding the following:

I couldn't find narrative summaries on the following patients with serious adverse events: Study 96902, #102; Study 93401, #1097; Study 92302, #5149; study 95201, #217; study 88701, #1230; study 94406; #S164; Study 96902 (#125, 309).

On p. 242 of the ISS volume, it states that there is information on 12 citalopram overdoses from Group 1 and 8 from Group 3 studies, then refers to a summary of these in Panel 6.3-9, which though contains only 19 patients. I asked her to clarify which is correct. I thanked her and the conversation ended.

/S/

Susan Molchan, M.D.
September 25, 1997

cc: NDA#20-822
HFD-120/GDubitsky
TLaughren
PDavid

Memorandum of Telephone Call

Date: September 8, 1997

NDA: 20-822

Subject: Studies classified as Group 3

Firm: Forest Labs

Drug: Citalopram

Point of Contact: Kathryn Bishburg, Pharm.D.

Phone number: (212) 224-6866

Dr. Bishburg was telephoned and an inquiry was made regarding the sponsor's August 21, 1997 response to the July 28 fax, item 1. The July 28 request asked that we be sent the study numbers of the 118 studies classified as Group 3 in the ISS. There were discrepancies between some of the numbers provided and the listing of studies in ISS volume 1.294. Two of the studies (92413 and 95201) noted on the August 21 list were labelled as ongoing in the ISS (and not labelled as Group 3). Another study (7908) was not found in the ISS list. In addition,three studies listed in the ISS (90A, 7809, and 84-N-0084) as Group 3 studies were not mentioned on the August 21 list.

In addition, I asked Dr. Bishburg about discrepancies in patient exposure year data in the ISS. On p. 98 of the ISS PEY for study 89422 (citalopram) is given as 11.48, but on p. 117, it is given as 102.03; for study 89303 (placebo) PEYs given are 6.86 and 5.86.

I also asked about discrepancies between the mortality table (8.1.1.2 in vol. 295) and the death line listing in the ISS and the mortalty rate table in the ISS (p. 117).

I thanked her and the conversation ended.

/S/

Susan Molchan, M.D.
September 8, 1997

cc: NDA#20-822
HFD-120/GDubitsky
TLaughren
PDavid

MEMORANDUM

TO: Forest Laboratories, Inc.
ATTN: Kathryn Bishburg, Pharm.D.
Associate Director, Regulatory Affairs
909 Third Avenue
New York, New York 10022-4731

FROM: Food and Drug Administration
Center for Drug Evaluation & Research
Division of Neuropharmacological Drug Products
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-822: Citalopram HBr
Request for Information

DATE: August 14, 1997

Please provide us with the following information regarding the two placebo-controlled, long-term studies, 89304 and 89305:

1) For study 89304, a table depicting the number of patients in-study by visit for each treatment group (see Table 1 below).

TABLE 1:
PATIENTS IN-STUDY BY VISIT (STUDY 89304)

Treatment Groups	ITT	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
CIT	152						
PLAC	74						

2) For both studies 89304 and 89305, Panel 4.3.6-2, on page 133 of the Integrated Summary of Effectiveness, displays the cumulative percentage of patients who relapsed by visit for each treatment group; please provide the numerators and denominators used to calculate each percentage in that Panel.

3) For both studies 89304 and 89305, the mean and median times to relapse for each treatment group.

Your timely response to this request is appreciated. Should any questions arise, please contact Dr. Dubitsky at (301)594-2850.

/S/

Gregory M. Dubitsky, M.D.
Medical Reviewer

/S/ 8-15-97

Thomas P. Laughren, M.D.
Team Leader
Psychiatric Drug Products Group

cc: HFD-120/SMolchan
GDubitsky
TLaughren
PDavid

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-822

Drug:	Citalopram	
Sponsor:	Forest Laboratories	
Date:	July 8, 1997	
Telephone:	(212) 421-7850	
Conversation Between:	Agency	Firm
	Robin Huff, pharmacology reviewer	Keith Rotenberg Executive Director, Reg Affairs
	Glenna Fitzgerald, Team Leader	Ron Filler, Toxicologist

RE: Clarification of histopathology table entries

A copy of the histopathology table for the rat carcinogenicity study, with indecipherable entries highlighted, was faxed to the sponsor on July 7, 1997. In our telcon, Dr. Filler indicated that subentries without descriptive phrases indicated that the study pathologist did not rate the severity (or diffuseness) of the particular pathology. He presumed that all entries could be added to determine the total number of animals with the pathology (irrespective of severity etc.), but was not certain. Dr. Rotenberg indicated that they would contact to determine if this was in fact the case. Five minutes later, Dr Rotenberg called to confirm that the total number of animals affected was the sum of all subentries (i.e., no animal was assigned to more than one subentry). Written confirmation should be requested.

The sponsor was also informed that they had sent two copies of the histopathology table for decedents in the 1 year rat study, but had omitted the gross pathology table. They indicated that the omitted table would be faxed as soon as possible.

/S/

Robin A. Huff, Ph.D.

cc: 20822A
HFD-120
/G. Fitzgerald 7/9/97
/R. Huff
/P. David

Memorandum of Telephone Call

Date:	June 18, 1997
NDA:	20-822
Subject:	Response to inquiries on Group II data locations
Firm:	Forest Labs
Drug:	Citalopram
Point of Contact:	Kathryn Bishburg, Pharm.D.
Phone number:	(212) 224-6866

Dr. Bishburg was telephoned and the following two inquiries were made:

1) The location of the Group II case report forms for dropouts and SAEs, with volume numbers.

2) The location of narrative summaries for Group II SAEs and dropouts, with volume numbers

She responded for 1) above, that the CRFs were with the specific Group II study reports, and that these were located only in Section 6, volumes 1.52-1.81.

She responded for 2) above, that the Group II narrative summaries were in the ISS, Appendix 8.10.16.4.3, which is located in volume 468, 10-51704. She noted that the same appendix should be in section 8 as well but couldn't locate it there.

I thanked her and the conversation ended.

/S/

Susan Molchan, M.D.
June 19, 1997

cc: NDA#20-822
HFD-120/GDubitsky
TLaughren
PDavid

MEMORANDUM OF TELECON

DATE: January 5, 1997

APPLICATION NUMBER: NDA 20-822

DRUG NAME: citalopram HBr

BETWEEN:

Name: Kathryn Bishburg, Pharm.D.
Phone: (212) 224-6820
Representing: Forest Pharmaceuticals

AND

Name: Paul David /S/
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request additional biopharmaceutic information

At the request of Dr. Iftekar, I contacted Dr. Bishburg to request that the following additional information be submitted to this pending NDA:

1. Please provide data on urinary excretion of citalopram in renally impaired patients (Study 90103).

2. Please tabulate the data according to age groups (Study 84-N-0082). Pool data from age groups from 51 years to 90 years and then compare with young (50 years or less) from other single dose PK studies.

3. From single dose studies identify male and female PK data and then compare for gender differences (collect data for 12 or more subjects in each group).

4. Is there any single dose, dose proportionality studies available?

Dr. Bishburg acknowledged understanding of the above, and stated that she would provide this information as soon as possible.

cc:
NDA 20-822
HFD-120/Div file
HFD-120/PLeber/TLaughren/GDubitsky/SMolchan
HFD-860/MIftekar/CSahajwalla
HFD-120/PDavid
TELECON

7/3/97 -
LSI

MEMORANDUM

TO: Forest Laboratories, Inc.
ATTN: Kathryn Bishburg, Pharm.D.
Associate Director, Regulatory Affairs
909 Third Avenue
New York, New York 10022-4731

FROM: Food and Drug Administration
Center for Drug Evaluation & Research
Division of Neuropharmacological Drug Products
Psychiatric Drug Products Group
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-822: Citalopram HBr
Request for Information

DATE: July 3, 1997

We request that you provide us with the following items to facilitate the clinical review of your NDA for citalopram.

1) Please complete the attached efficacy tables for studies 85A (Attachment 1) and 91206 (Attachment 2). The comparisons of least squares adjusted mean changes from baseline are acceptable. Note that, with respect to the HAM-D data, we ask that the 24-item HAM-D and 21-item HAM-D analyses be provided for studies 85A and 91206, respectively. The data for 91206 may include the Borison center.

2) In section 8.9.4.1.3-6 of the Integrated Summary of Efficacy (ISE), the tables which display the completion rates by visit (e.g., Table A2 for study 85A) seem to indicate that the number of randomized patients comprise the intent-to-treat (ITT) population, whereas the text of the ISE defines the ITT as those patients who had 1) a baseline assessment and 2) at least one follow-up assessment (see volume 1.282, page 73754). Please explain this discrepancy and incorporate any corrections into the tables requested under 1) above.

3) Also with respect to section 8.9.4.1.3-6, we notice that the tables of efficacy results contain numbers of patients (N's) that appear to be inconsistent with the number of patients in the trial at various timepoints. For example, regarding study 85A, Table 10.0 lists N's for the presumed LOCF analysis of 76 for citalopram and 75 for placebo. These are considerably smaller than the N's for the number of patients with at least one post-baseline assessment in Table A2, namely 82 for citalopram and 87 for placebo. Additionally, the corresponding tables for studies 91206, 89306, and 86141 contain observed-cases (OC) dataset N's that

frequently are less than the number of patients in-study. For instance, while there were 128 patients in the 20mg dose group who completed week 1, the N's in the OC analyses for each of the major variables is 126 or less at week 1 for this group. Please explain the above discrepancies and, if the submitted figures are incorrect, please incorporate corrections into the tables requested under 1) above.

4) Please provide a graphic display of the by-center efficacy results for study 85A and study 91206. We would like to suggest that this consist of a histogram which depicts, for each center, the LOCF mean change from baseline to endpoint in HAM-D 24- or 21-item total score for the citalopram group minus that of the placebo group, along with the 95% confidence interval for this mean difference. An example is provided as Attachment 3.

5) With reference to the efficacy analyses for study 91206 excluding the Borison center, which is presented as Appendix 6.0 to the ISE, Tables 4.2.1a and 5.2.1a are not adequately labeled. The following should be clearly indicated in the tables:

a) dataset used (LOCF or OC).

b) timepoint (presumably week 6).

c) headings for the two columns of t-test p-values (presumably one is based on a parametric analysis and one a non-parametric analysis).

6) For study 89304, kindly provide a display of the mean citalopram dose by each visit (for example, see the third table under Attachment 1).

7) Kindly perform an analysis of the effects of demographic variables (age, gender, and race) on the incidence of common and likely drug-related adverse events, i.e., those events occurring at a frequency ≥ 5% in the citalopram group and ≥ twice the placebo rate in the Group 1 placebo-controlled, short-term study pool. We ask that you use the following methodology; we have used gender as an example. For the identified adverse events, calculate the relative risks for males (RR_m) and females (RR_f) with reference to placebo and their respective 95% confidence intervals within this pool of studies. Then compute the ratios of the relative risks of females to males (RR_f/RR_m). Next, compute odds ratios for each subgroup and also a common odds ratio (using the Mantel-Haenszel method), along with 95% confidence intervals. Finally, test the homogeneity of the odds ratios between the subgroups for each selected adverse event using the Breslow-Day Chi-Square and provide the p-values. Please submit results as shown in the two tables in Attachment 4. Similar analyses should be carried out for age effects by comparing 2 age subgroups (e.g. <65 and ≥65 years old)

and for race effects by comparing 2 race subgroups (e.g. Caucasian and non-Caucasian) for these same adverse events.

8) Please assess those events identified as being common and likely drug related in study 91206, as defined under item 7) above, for dose-relatedness in this fixed dose study. Kindly use an appropriate trend test (e.g., Exact Permutation test) across the four active dose groups (10, 20, 40, and 60mg), excluding placebo.

9) Please provide the adverse event dictionary resulting from your coding of investigator terms to preferred terms. This should be provided in two formats: one alphabetically by investigator term and one alphabetically by preferred term.

10) The submitted Master Table of Studies appears to have excluded many Group 2 studies. Please forward a list of all Group 2 studies, including a brief description of each trial (i.e. study objective, design, dose, and number of patients exposed to citalopram).

11) Please provide narrative summaries for Group 2 citalopram patients who dropped out due to an adverse event. We are unable to locate these summaries within the clinical section of the NDA.

12) Kindly provide the following data displays for the Group 2 patients:

a) patient enumeration by treatment group.

b) demographic characteristics by treatment group.

c) dose and duration table for citalopram patients.

The desired formats for these displays are shown in Attachment 5.

13) Table 8.1.6.4.2.1.1 on page 79592, volume 1.300, enumerates patients from Group 1 placebo-controlled studies who had potentially clinically significant vital sign changes. We request the following regarding this table:

a) a revision of this table to provide the breakdown of each abnormal parameter into the number of patients with outlying high values and the number of patients with outlying low values separately; the submitted table appears to present the total number of patients with abnormal values, with high and low measures combined.

b) then, prepare a line listing of the citalopram patients with potentially clinically significant changes for each abnormality, as enumerated in the above revised table; for example, a listing of those citalopram-treated patients with a outlying high sitting systolic blood pressure.

14) Please provide a line listing of all Group 1 patients, by treatment group, who dropped out due to an abnormal laboratory, vital sign, or ECG finding. This table should clearly reflect the nature of the specific finding leading to premature discontinuation (e.g., hypokalemia, decreased standing systolic blood pressure, QTc prolonged).

15) Please provide readable copies of foreign labeling from all countries where citalopram is currently marketed. Non-English labeling should be translated.

Your timely response to this request is appreciated. Should any questions arise, please contact either Dr. Molchan or Dr. Dubitsky at (301)594-2850.

/S/

Gregory M. Dubitsky, M.D.
Medical Reviewer

/S/

Thomas P. Laughren, M.D.
Team Leader
Psychiatric Drug Products Group

cc: HFD-120/SMolchan
GDubitsky
TLaughren

ATTACHMENT 1

Study: 85A Demographic Characteristics							
Treatment Groups	ITT (N)	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
CIT							
PLAC							

Study: 85A Patient Completion Rates by Visit						
Treatment Groups	Number Randomized	Intent-to-Treat Sample	ITT Patients In-Study [n(%)]			
			Wk 1	Wk 2	Wk 3	Wk 4
CIT						
PLAC						

Study: 85A Dosing Information				
Treatment Groups	Mean Citalopram Dose (mg/day) by Visit			
	Wk1	Wk2	Wk3	Wk4
CITALOPRAM				

ATTACHMENT 1

Study: 85A
Mean Change from Baseline in HAM-D 24-Item Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
CIT										
PLAC										
2-sided p-values for pairwise comparisons										
CIT vs PLAC										

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
CIT										
PLAC										
2-sided p-values for pairwise comparisons										
CIT vs PLAC										

ATTACHMENT 1

Study: 85A
Mean Change from Baseline in HAM-D Depressed Mood Item

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
CIT										
PLAC										
2-sided p-values for pairwise comparisons										
CIT vs PLAC										

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
CIT										
PLAC										
2-sided p-values for pairwise comparisons										
CIT vs PLAC										

ATTACHMENT 1

Study: 85A
Mean Change from Baseline in CGI-Severity Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week									
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
CIT										
PLAC										
2-sided p-values for pairwise comparisons										
CIT vs PLAC										

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week									
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ
CIT										
PLAC										
2-sided p-values for pairwise comparisons										
CIT vs PLAC										

ATTACHMENT 2

Study: 91206

Demographic Characteristics

Treatment Groups	ITT (N)	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
CIT 10mg							
CIT 20mg							
CIT 40mg							
CIT 60mg							
PLAC							

Study: 91206

Patient Completion Rates by Visit

Treatment Groups	Number Randomized	Intent-to-Treat Sample	ITT Patients In-Study [n(%)]					
			Wk 1	Wk2	Wk3	Wk4	Wk5	Wk6
CIT 10mg								
CIT 20mg								
CIT 40mg								
CIT 60mg								
PLAC								

ATTACHMENT 2

Study: 91206
Mean Change from Baseline in HAM-D 21-item Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week													
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

ATTACHMENT 2

Study: 91206
Mean Change from Baseline in HAM-D Depressed Mood Item

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week													
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

ATTACHMENT 2

Study: 91206
Mean Change from Baseline in MADRS Total Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week													
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

ATTACHMENT 2

Study: 91206
Mean Change from Baseline in CGI-severity Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

Treatment Groups	Treatment Week													
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

OBSERVED CASES ANALYSIS

Treatment Groups	Treatment Week													
	Baseline		Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	X	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg														
CIT 20mg														
CIT 40mg														
CIT 60mg														
PLAC														
2-sided p-values for pairwise comparisons														
10mg vs PLAC														
20mg vs PLAC														
40mg vs PLAC														
60mg vs PLAC														

ATTACHMENT 2

Study: 91206
Mean CGI-improvement Score

LAST OBSERVATION CARRIED FORWARD ANALYSIS

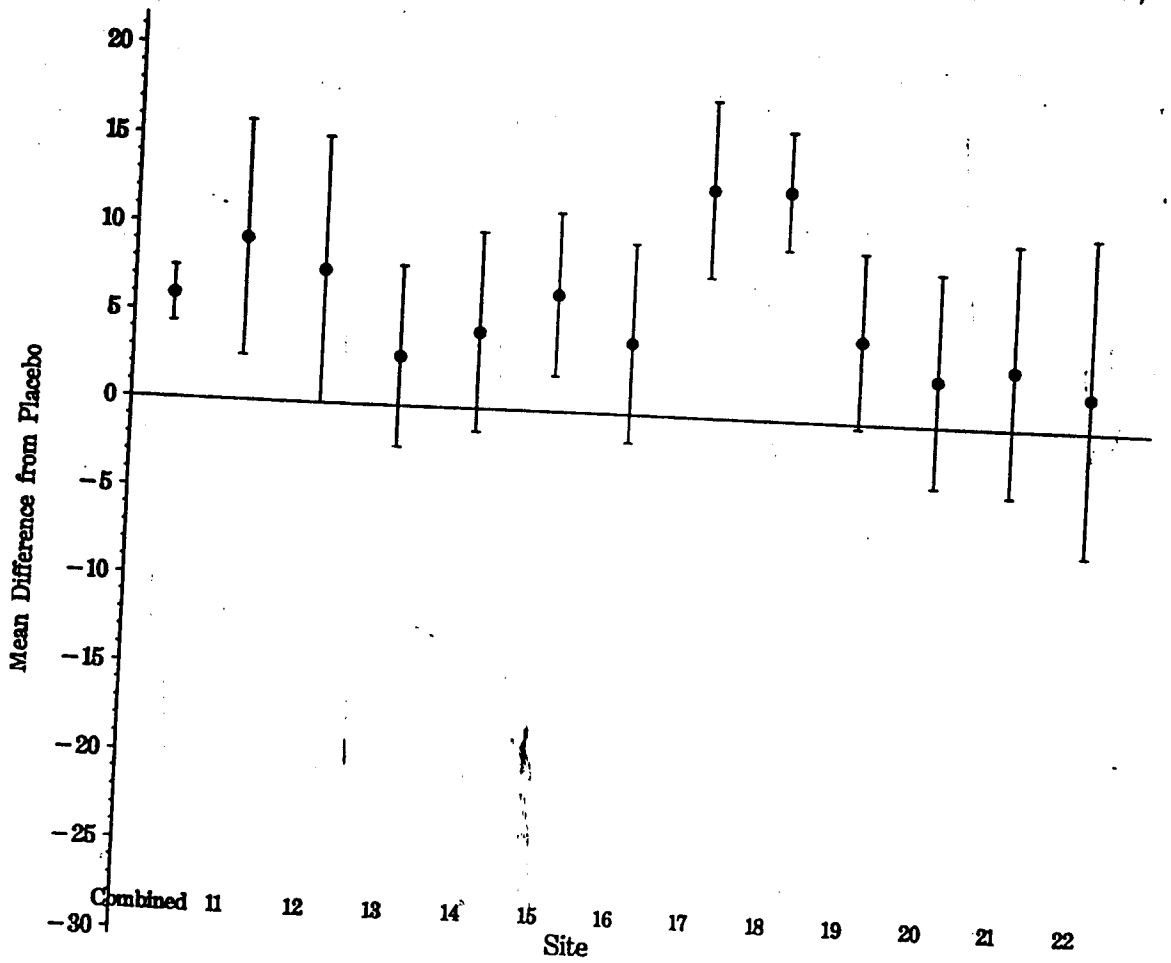
Treatment Groups	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg												
CIT 20mg												
CIT 40mg												
CIT 60mg												
PLAC												
2-sided p-values for pairwise comparisons												
10mg vs PLAC												
20mg vs PLAC												
40mg vs PLAC												
60mg vs PLAC												

OBSERVED CASES ANALYSIS

Treatment Groups	Wk 1		Wk 2		Wk 3		Wk 4		Wk 5		Wk 6	
	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ	n	Δ
CIT 10mg												
CIT 20mg												
CIT 40mg												
CIT 60mg												
PLAC												
2-sided p-values for pairwise comparisons												
10mg vs PLAC												
20mg vs PLAC												
40mg vs PLAC												
60mg vs PLAC												

ATTACHMENT 3

By Center Display of the Mean Difference Between Citalopram and Placebo (with 95% Confidence Intervals)
Using the HAM-D Total Score Change from Baseline to Endpoint (LOCF)



ATTACHMENT 4

RELATIVE RISK AND CONFIDENCE INTERVALS FOR SELECTED STUDY EVENTS									
Adverse Event	MALES				FEMALES				RR = RR_f+RR_m
	Citalopram (n=) N (%)[1]	Placebo (n=) N (%)	RR_m[2]	95% C.I.	Citalopram (n=) N (%)	Placebo (n=) N (%)	RR_f[3]	95% C.I.	

1 N = number of patients with the event, % = (N ÷ n) × 100%.
2 RR_m = relative risk for male patients (citalopram/placebo).
3 RR_f = relative risk for female patients (citalopram/placebo).

ODDS RATIOS BY GENDER FOR SELECTED ADVERSE EVENTS						
Adverse Event	Odds Ratios[1]		Common Odds Ratio[2]	95% C.I.	Breslow-Day[3]	
	Males	Females			$\chi^2(1)$	p-value

1 Odds ratios computed with reference to placebo patients.
2 Common Odds Ratios computed using the Mantel-Haenszel method.
3 Breslow-Day test for homogeneity of the odds ratios.

ATTACHMENT 5

Patient Enumeration by Study Type: All Group 2 Subjects			
Study Type	Citalopram	Placebo	Active Control
Single Dose			
Multiple Dose			
Total			

Demographic Characteristics: All Group 2 Subjects			
	Citalopram (N=)	Placebo (N=)	Active Control (N=)
Age (years)			
Mean (SD)			
Range			
Sex N(%)			
Female			
Male			
Race N(%)			
White			
Non-white			

ATTACHMENT 5

Number (Percent) of all Subjects Receiving Citalopram According to Mean Daily Dose and Duration of Therapy in Group 2 Studies *					
Duration of Exposure (Days)	Citalopram Mean Dose (mg/day)				Total N (%)
	<20	20-39	40-60	>60	
≤1					
2-7					
8-14					
15-30					
>30					
Total N(%)					

* Each Group 2 citalopram patient should be enumerated in only one cell, according to mean daily dose and total duration of exposure.

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 4, 1997
Time: 3:00 PM
Location: WOCII 4th Floor Conference Room
Application: NDA 20-822; Forest; Citalopram Hydrobromide Tablets
Type of Meeting: Conference Call
Meeting Chair: Gregory Dubitsky, MD
Meeting Recorder: Paul David, RPh

FDA Attendees: Gregory Dubitsky, MD, Japo Choudhury, PhD, Paul David, RPh
Forest Attendees: Kathryn Bishburg, Pharm.D. - Regulatory Affairs; Jia-Yeong Tsay, PhD - Statistician

Meeting Objectives:
The meeting was requested by the Agency to request additional statistical analyses in order to review this pending NDA.

Discussion Points:
The Agency requested an analysis of the treatment-by-center interactions for the two long-term studies (89304 and 89305) in this NDA. These analyses should include both the graphical display of treatment effect size by center as well as the p-values from the ANOVA for treatment-by-center interaction.

The sponsor may combine smaller centers into one but this grouping must have some rationale, e.g., group by country, province, hospitalized vs. outpatients, etc. in order to attain ~~more~~ meaningful data.

Since both studies use the MADRS to measure efficacy outcome, this should be the measurement used in this analysis.

Decisions (agreements) reached:
Forest stated that they could provide this information.

Unresolved issues or issues requiring further discussion:
None.

Action Items:
Forest will provide the above information.

Minutes Preparer: /S/
Paul A. David , R.Ph.
Project Manager, DNDP

Chair Concurrence: /S/
(or designated signatory)

cc: Original NDA 20-822
HFD-120/Div. File
HFD-120/David
HFD-120/Leber/Laughren/Dubitsky/David
HFD-710/Choudhury/Sahlroot
rd:12/08/97pd
rev:12/08/97jc;gd
ft:12/08/97pd
Doc #CITALOPRAM/NDA/12-04-97.MM

MEETING MINUTES

MEMORANDUM

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

DATE: April 30, 1998

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-822
Celexa, citalopram hydrobromide
Sponsor: Forest Laboratories

SUBJECT: Addendum to April 8, 1998 memorandum

Retinal Degeneration in Rats

In the two year rat carcinogenicity study there was an increase in both the incidence and severity of retinal degeneration/atrophy, only in high dose rats receiving 80 mg/kg/day (13 times the maximum recommended human daily dose of 60 mg on a mg/m^2 basis). The no-effect dose was 24 mg/kg/day (4 times the MRHD on a mg/m^2 basis). The effect was more pronounced in males than females, primarily due to a very high control incidence in females. There was not a similar finding in the one year rat study, 18 month mouse study, or one year dog study.

It was suggested by the sponsor, and their pathology consultant Dr. F.J.C. Roe, that the retinal degeneration resulted from increased light penetration into the eye because of treatment-related mydriasis. Although mydriasis was not seen in the carcinogenicity study, it was apparently seen in a rat teratology study (at doses of 70 and 140 mg/kg), and in two dog studies and a rabbit study. Albino rats lack the protection from light-induced retinal damage offered by pigment in the choroidal layer, and are at greater risk than pigmented animals of developing retinal atrophy after chronic exposure to normal levels of light. Retinal atrophy in albino rats has also been observed in carcinogenicity studies conducted with other drugs reviewed in this Division (two dopamine agonists, one NMDA receptor antagonist). Sponsors of those drugs have done, or are doing, studies which compare the onset and severity of retinal toxicity in drug treated albino rats with effects in drug treated pigmented rats. In those experiments the animals are subjected to an enhanced light level in order to be able to observe retinal toxicity in sub-chronic studies. While the finding with citalopram could be light-related, no studies were conducted to examine mechanism.

It is recommended that the finding of retinal degeneration be added to labeling, as follows:

Animal Toxicology:
Pathologic changes (degeneration/atrophy) were observed in the retina of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m^2 basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20 and 10 times, respectively, the maximum recommended daily human dose on a mg/m^2 basis)

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

/S/
Glenna G. Fitzgerald, Ph.D.

NDA 20-822
c.c. /Div. File
/Leber/Laughren/Molchan/Huff/Fitzgerald/David

MEMORANDUM

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

DATE: April 8, 1998

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-822
Celexa, citalopram hydrobromide
10,20,40,60 mg (base) tablets
Sponsor: Forest Laboratories

SUBJECT: Approvability for Pharmacology and Toxicology

The pharmacology and toxicology studies submitted to this NDA for Celexa, a specific serotonin reuptake inhibitor indicated for the treatment of depression, have been reviewed by Dr. Barry Rosloff and Dr. Robin Huff and are adequate to support an approvable action.

During the development of this drug two serious animal toxicology issues were encountered, both of which had an effect on the progress of clinical trials: 1) sudden, unexplained deaths in a chronic dog toxicity study and 2) teratogenic findings, including cardiovascular defects, in a rat teratology study. The first of these, sudden deaths in dogs, necessitated the suspension of clinical trials from July, 1985 until April, 1990. Because of the finding of teratogenicity (in a repeat study conducted because the first study was inadequate), the inclusion of women of childbearing potential was precluded from the beginning of development in 1983 until December, 1991.

Sudden Death in Dogs

During a 1 year dog toxicity study, 5 of 10 high dose dogs receiving 8 mg/kg/day (about 4 times the maximum human daily dose of 60 mg on a surface area basis) were found dead within 2 to 3 hours post-dosing during weeks 17, 18, 27, 27 and 31. The deaths were sudden and unexpected since the dogs were in generally good condition prior to death. No cause of death could be determined from gross and histopathologic evaluation. It was known that dogs were susceptible to the toxic effects of citalopram. Acute doses of 20 mg/kg produced mydriasis, restlessness, anxiety, tachycardia, a

highly labile heart rate, convulsions and death; in a 3 month study, 10 mg/kg/day produced similar signs and death by week 7. However, in a 6 month study at 8 mg/kg/day, in which plasma levels of citalopram were somewhat higher than those measured in the 1 year study, no deaths occurred. It was considered that the sudden deaths in the 1 year study could be due to convulsions, which had been observed in acute studies, or possibly to cardiac effects, which are known to occur at high doses with drugs of this class. Also, there had been slight QT prolongations in the dogs in the 1 year study, although EKGs were not measured until 24 hours after dosing so relatively acute effects were not seen.

To address this issue of sudden deaths the sponsor conducted a special cardiovascular toxicity study in dogs (Dr. Rosloff's review of that study is excerpted on pages 17 - 20 of Dr. Huff's review). That study was an acute intravenous study in which four groups of dogs received either saline, citalopram (10 mg/kg/hr), di-desmethyl citalopram (2.5 mg/kg/hr) or both drug and metabolite. The di-desmethyl metabolite, DDCT, is prominent in dogs and is present at very low levels in humans. Ventricular arrhythmias were seen in both groups receiving citalopram, CT, but not in the group receiving DDCT alone. This was thought to occur secondary to excessive CNS stimulation due to parent drug. There was prolongation of the QT interval in both groups receiving DDCT but not in the group receiving CT alone. But most important, there were **fatal** ventricular arrhythmias in the group receiving CT plus DDCT, leading to the assumption that deaths resulted from an interaction between the effect of DDCT on QT prolongation and the CNS effects of CT which resulted in centrally mediated ventricular arrhythmias. Plasma levels of drug and metabolite indicated that **both** CT and DDCT must be above a certain threshold before lethality occurs, and that if only one was above that threshold death did not occur (see figure on page 18 of Dr. Huff's review). Also, plasma levels in the acute i.v. study which were associated with lethality were similar to those in the 1 year study that were associated with lethality. It can be seen in the same figure that plasma levels of CT and DDCT obtained in humans receiving 40 mg of citalopram a day are well below those associated with lethality in dogs (data not available for 60 mg but would still be well below critical levels since kinetics are linear). It is also noted that humans have a much greater CT/DDCT ratio than dogs, thus presumably making them less susceptible to any interaction of the two.

From the results of this special cardiovascular study in dogs, the sponsor concluded that the mechanism for the lethality had been determined to be a fatal interaction between high plasma levels of both CT and DDCT, and that there is no risk to humans since they have very low levels of the DDCT metabolite. While this may be true, it has not been definitively established, and there remain questions that have not been addressed. These issues are discussed by Dr. Rosloff (see pages 19 - 20 of Dr. Huff's review). They include the following: 1) the role of the mono-desmethyl metabolite, formed in both dogs and humans, was not addressed, 2) why did an essentially acute effect take 4 to 8 months to be expressed in the 1 year dog study, since steady state

levels of the metabolite should have been reached in 2 weeks, 3) what role does differences in species sensitivity play (does lethality occur in monkeys that also have high levels of DDCT), and 4) what role did the rapid rate of rise of plasma levels in the acute i.v. study play. With respect to the last issue, it would have been useful for the sponsor to conduct a study in dogs with EKG monitoring, giving 8 mg/kg/day orally to a steady state level of both parent and metabolite, to see if cardiac arrhythmias occur as they did in the i.v. study.

There have apparently not been effects reported in the clinical data base similar to the toxicities observed in dogs (pronounced CNS effects or cardiac arrhythmias, QT prolongation), and the findings in dogs have been placed in an Animal Toxicology section of labeling. However, it should be emphasized that the mechanism for the sudden deaths in dogs has not been definitively determined to be a "fatal interaction" between plasma levels of CT and DDCT, and it cannot therefore be concluded that there is no risk to humans because they have very low plasma levels of DDCT.

Teratogenicity

Because the original rat teratology study was conducted at doses which were too low (high dose of 40 mg/kg of salt, 32 mg/kg of base) the sponsor was asked to conduct a repeat study using higher doses. That study, submitted Feb 21, 1989 used 40 as the low dose and 70 and 140 mg/kg as mid and high doses (32, 56, 112 mg/kg of base). There was an increase in abnormalities at high dose, a dose which was associated with some maternal toxicity, but it is not thought that the developmental toxicity observed may be attributed to maternal toxicity. In addition to an increase in post-implantation loss and a decrease in fetal weight, teratogenic effects were seen, particularly involving skeletal defects and defects of the cardiovascular system (cardiac septal defect, absence of septum between pulmonary veins and right atrium, etc). (Dr. Rosloff's review* of that study is excerpted in Dr. Huff's review, pages 23 - 24). At a June 19, 1990 meeting with the sponsor and their consultants to review the safety of citalopram in women of childbearing potential, the sponsor was informed that citalopram could not be used in WCBP until the teratology issue was resolved. At that meeting authorized the FDA to discuss the teratology findings with countries where the drug is marketed; there is no record to indicate that that was done. It was noted that labeling in Belgium notes no evidence for teratogenicity and labeling in Denmark and Finland do not mention the subject. The sponsor did state that the cardiac abnormalities were not due to maternal toxicity, but argued that it was generally known that most drugs can cause terata with sufficient dosage. They cited the fact that fluoxetine was not tested at comparably high doses, and indicated their intention to perform another rat teratology study with the possible inclusion of a fluoxetine group.

On November 22, 1991 the final report of the second repeat teratology study (with no

fluoxetine group), which used the same doses as the previous study, was submitted (Dr. Rosloff's review* of that study is excerpted in Dr. Huff's review, pages 24 - 26). In that study no effects on the heart were observed; however, other anomalies were observed, both visceral and skeletal. Both studies showed an increase in post-implantation loss and a decrease in fetal weight and increased fetal abnormalities at high dose. The types of fetal abnormalities did not in general overlap between the studies, except that sternal abnormalities were prominent in both studies. In both studies there were many individual abnormalities which were not greatly increased in incidence but indicated a widespread drug effect. The reason(s) for the different results are not evident. Different laboratories conducted the studies, and there were different suppliers for the rats. In the second study, drug was made up every four days rather than daily as had been done for the first study, so stability may have played a role in the absence of cardiac effects. In addition to repeating the study, the sponsor hired consultants to re-examine the slides from the first study. Although there were differences in interpretation, the revised data still indicated an effect on the heart and other structures as originally reported.

It was concluded that, despite reanalysis of the slides and data from the first study, and performance of a second study using the same doses which produced different results, there was still concern about the potential teratogenic effects of citalopram. At a December 10, 1991 meeting with the sponsor they were informed that they could enter WCBP in clinical trials, but that the results of the second study did not negate the findings from the first study and labeling would reflect the teratogenic findings. The sponsor was also asked to provide better pharmacokinetic data for drug and metabolites in pregnant rats (Cmax, AUC, half life) and their fetuses in order to obtain exposure data to compare to human exposures. The information submitted consisted of plasma levels at 2 hours, with no information about Tmax. Therefore, for purposes of labeling, body surface area comparators are used. This may be a more relevant measure anyhow, since we have no information about whether parent or metabolites are the toxic entities.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Citalopram was mutagenic in two tester strains in the Ames test in the absence, but not the presence of metabolic activation. It was clastogenic in an *in vitro* assay (Chinese hamster lung cells) in the presence and absence of metabolic activation. In carcinogenicity studies in mice (18 months) and rats (24 months) the only relevant finding was a treatment related increased incidence of small intestine carcinoma, a relatively rare tumor, in rats receiving the low and middle doses. Those doses are equivalent to the human dose and four times higher on a body surface area basis. A no effect dose was not established in that study.

There was no CDER statistical review of the study, but the sponsor was asked to analyze the data, not including the high dose group. That analysis has not been received, but the finding is included in labeling because, not only is it a rare tumor, but the incidence (8/200) fell outside the sponsor's historical control data (5/400). It was concluded by the CAC that the finding of 2/50 kidney carcinomas in middle dose female rats was probably not treatment related. Limited and out of date historical control data from the sponsor show a rate of 4/223. We believe the finding not to be significant and have not included it in labeling. The CAC-EC report is attached.

The three generation study which assessed fertility and reproductive performance in rats (Segment 1) was conducted prior to GLP regulations. While that does not in and of itself make the study unacceptable, there are other reasons that make it fall far short of current standards. Primarily, inadequate doses were studied, a fact that was conveyed to the sponsor at the time of the review, and inadequate numbers of treated animals were evaluated. The Segment 3 aspect of the study was subsequently conducted separately and is adequate.

Recommendations

This NDA is approvable for Pharmacology and Toxicology with the attached recommended labeling

/S/

Glenna G. Fitzgerald, Ph.D.

*Dr. Rosloff's reviews of the two rat teratology studies, including figures and tables, are available in IND and are dated April 14, 1989 and December 9, 1991.

Attachments:
Recommended labeling
CAC-EC report
NDA 20-822
c.c.
/Div. File
/Leber, Laughren, Molchan, Rosloff, Huff, Fisher, Fitzgerald, David

4 Page(s) Redacted

DRAFT LABELING