4151

cc: Dr. D. M. Brennan
Dr. C. N. Christensen
Dr. L. Lemberger
Dr. C. E. Redman
Dr. P. Stark

June 16, 1982

Food and Drug Administration
Bureau of Drugs, HFD 120
Attention: Document Control Room 10B-45
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: IND 12274 - Compound LY110140 - Fluoxetine Hydrochloride
(Psychotropic Agent)

Reference is made to Dr. Paul Leber's letter dated May 17, 1982, pertaining to this notice.

One-year animal toxicity studies in the dog and rat have been completed. A summary of the findings is included in this submission. Detailed reports are in preparation and will be submitted in the near future.

We have carefully considered your recommendation regarding the disposition of patients as they complete the blind phase of the fluoxetine efficacy studies. The suggestion was made that the blind be maintained and that we "either routinely switch the patients to fluoxetine if they are appropriate candidates for the long-term exposure or continue patients on blind medication for the extended phase."

Our current procedure requires that the investigator report, by telephone, the final efficacy ratings on a given patient before he is provided with the drug assignment for that patient. Our data thus far indicate that fluoxetine has a lower incidence of certain adverse effects than the reference drugs; however, there is nothing discernibly unique about either the side effect profile or the improvement seen with fluoxetine or the other study drugs. Thus, we find it highly unlikely that breaking the code for completing patients would invalidate the "blind" with respect to others.

EXHIBIT
DOBBS 8

Pz 902 1557

If we were to assign, on a blinded basis, all eligible patients who have completed the blind phase to fluoxetine, there would be the following results:

- patients who had responded favorably while on placebo would then receive an investigational drug unnecessarily
- patients who had responded favorably while on the reference drug (imipramine, amitriptyline, or doxepine) would then be changed to another drug unnecessarily

Neither condition, in our view, is consistent with good medical practice. Further, no comparative data would be available thereafter.

Alternatively, if we were to continue, on a blinded basis, the assigned study drug, the trial would become open-ended. Analysis of the data would be fraught with difficulty as the drop-out rate increased.

Our protocols provide for the collection of information on both fluoxetine and the reference agents over extended periods of time. The intent is primarily for safety purposes. Patients who have responded unfavorably to either placebo or a reference drug may be switched to fluoxetine. Those who have responded well on fluoxetine or the reference drug may continue on the assigned drug. Admittedly, thereafter, the fluoxetine and reference drug groups are not randomly assigned. Nevertheless, we will acquire some comparative safety data over a time span of several months.

We would be glad to discuss these subjects with you if a meeting is thought desirable.

Very truly yours,

ELI LILLY AND COMPANY

Dorothy S. Dobbs, M.D.
Medical Advisor
Regulatory Affairs

DSD:lm

Enclosure

JHM AUG 24 1983

File _____

FU _____

Copy To _____

Pass To _____

August 24,1983

Dr. D. S. Dobbs
cc: Mr. D. A. Argay
Dr. C. N. Christensen
Dr. K. A. DeSanto
Dr. L. Lemberger
Dr. J. A. Marsden

RE: PACKAGE INSERT FOR FLUOXETINE

Attached are Dr. Lemberger's and my comments on the package insert for fluoxetine. We will be gald to meet with you to discuss any of these changes.

R. F. Bergstrom, Ph.D.
4808

Pz 364 2864

EXHIBIT

DOBBS 2

CLINICAL PHARMACOLOGY:

Page 2 - first paragraph - last sentence:

CHANGE: " ... would not be expected to affect noradrenergic ..."

TO: " ... would not be expected to directly affect noradrenergic ..."

COMMENT: The key word in this discription is directly. Indirect effects on the noradrenergic and dopaminergic neurons may be mediated by fluoxetine's direct effect on serotonergic neurons.

Page 3 - first paragraph - 2nd to last sentence:

CHANGE: " ... appeared in the urine and 16% in the feces."

TO: " ... appeared in the urine and 16% in the feces over a five week period."

COMMENT: Reporting the total excretion of radioactivity without reporting the time period over which the total excretion occurs may be misleading.

Page 3 - second paragraph - first sentence:

CHANGE: (omit first sentence completely). "Steady state levels are obtained ... "

TO: (replace first sentence with the following) Plasma levels of fluxetine and the desmethyl metabolite increase upon multiple dose administration until steady state levels are achieved and levels will persist for a prolonged period of time after discontinuation of therapy. Attainment of steady state levels requires a period of time roughly equivalent to five times the half life. When dosing regimens ...

COMMENT: In the clinical pharmacology section of the package literature it is important to make certain that the full ramifications of a long half life drug are appreciated. Although it was our suggestion to include a time to steady state in the original draft of the package literature, the essential prescribing information may be more meaningful if a more generic statement is included (omit the reference of 15 days or 25 days time to reach steady state). The generic statement pertaining to half life should include three salient points: (1) plasma levels of

fluoxetine and the desmethyl metabolite persist in plasma for a long time period after fluoxetine administration has ceased, (2) plasma levels of fluoxetine and the desmethyl metabolite will increase until steady state levels are achieved requiring a period of time roughly equivalent to five times the half life, and (3) changes in the dosage regimen for fluoxetine require an equivalent period of time for a new steady state to be achieved.

Page 4 - second paragraph - last sentence:

CHANGE: "However, with chronic administration there may be accumulation of unidentified metabolites in patients with impairment of renal function."

TO: "However, with chronic administration accumulation of fluoxetine or its metabolites may occur in patients with impairment of renal function."

COMMENT: In the package literature we should avoid the terminology "unidentified metabolites" as this statement may place a burden upon us at a future date to identify these metabolites or conduct further studies. Fluoxetine does have at the current time unidentified metabolites but work is continuing to make their structures known. The important point is to caution against the indiscriminate use of fluoxetine in renally impaired patients. In the new statement the word "accumulation" is to be interpreted to mean "above and beyond" the increase in levels that will normally occur for all patients. The intent is to remind the prescriber that use of fluoxetine in renally impaired individuals should be carefully monitored as for any drug being used in such patients.

PRECAUTIONS

Page 6 - first paragraph - add

ADD: A statement should be added that "Patients who are ~~with~~ ~~suicidal ideation~~ considered for possible suicide should be considered for hospitalization."

PULVULES™

(TRADEMARK)

FLUOXETINE HYDROCHLORIDE

DESCRIPTION

(Trademark) (fluoxetine hydrochloride, Lilly) is an antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy] propylamine hydrochloride, with the empirical formula of $C_{17}H_{18}F_3NO$ HCl. It has a molecular weight of 345.79. The structural formula is as follows:

Fluoxetine is a white to off-white crystalline solid that is soluble at a concentration of 60 mg/ml in water. Stability assays have shown fluoxetine to be stable for periods of 24 months when exposed to temperatures of 25°, 40°, or 50°C.

Each Pulvule contains fluoxetine hydrochloride equivalent to 20, 30, 40, or 60 mg fluoxetine.

CLINICAL PHARMACOLOGY

The mechanism of action of fluoxetine is not definitely known. The current hypothesis is that the clinical effects may be due to inhibition of the reuptake of serotonin into presynaptic neurons. In clinical studies, uptake of serotonin by platelets was decreased by greater than 60% after subjects had received 30 mg/day for one week. Animal studies suggest that therapeutic doses of fluoxetine, in contrast to tricyclic anti-depressants, would not be expected to affect noradrenergic or dopaminergic neurons.

In double-blind efficacy studies, statistically significant improvement (as measured by the Hamilton Psychiatric Rating Scale for Depression) was seen after one week in patients who received Trademark.

Fluoxetine is well absorbed following oral administration. Peak plasma levels of fluoxetine occur approximately 6 hours after the dose. Food causes a slight delay in the rate of absorption of fluoxetine but does not affect the extent of absorption. Fluoxetine may be administered with or without food.

One of the known metabolites of fluoxetine is desmethyl fluoxetine which is also a selective serotonin uptake inhibitor.

In normal volunteers, the half life of fluoxetine is about 3(±2 S.D.) days. The half life of the desmethyl metabolite is generally longer than that of the parent compound, i.e., approximately 7(±4 S.D.)

days. Both fluoxetine and its desmethyl metabolite exhibit a very large volume of distribution (approximately 20-45 L/kg) and have relatively low plasma clearances (approximately 20 L/hr for fluoxetine and 9 L/hr for desmethyl fluoxetine). Based upon radiolabeled disposition studies of fluoxetine in normal subjects, approximately 60% of the radioactivity appeared in the urine and 16% in the feces. However, fluoxetine is highly metabolized; thus, very little unchanged compound is excreted in the urine.

Steady state levels are obtained in approximately 15 days for fluoxetine and 25 days for desmethyl fluoxetine. When dosing regimens are changed, new steady state levels will not be achieved until a similar period of time has elapsed. The steady state levels of fluoxetine and desmethyl fluoxetine ultimately achieved are proportional to the daily dose administered; however, the plasma levels vary widely from individual to individual.

In normal subjects, the projected or observed steady state plasma levels of desmethyl fluoxetine were generally higher than or equal to those of fluoxetine. The reverse was observed for most of the depressed patients in whom steady state plasma levels were measured.

In vitro, fluoxetine is approximately 94% bound to human serum protein.

When single doses of fluoxetine were administered to healthy elderly subjects, pharmacokinetic profiles for fluoxetine and desmethyl fluoxetine were not significantly different from the profiles in younger normal subjects.

Single doses of fluoxetine administered to subjects with various degrees of renal impairment demonstrated similar disposition of fluoxetine and desmethyl fluoxetine for subjects with normal, moderately impaired, severly impaired, and no (anephric) renal function. However, with chronic administration there may be accumulation of unidentified metabolites in patients with impairment of renal function.

The electrocardiograms of 312 patients who received Trademark in double-blind trials were retrospectively evaluated; no conduction abnormalities were observed.

INDICATIONS AND USAGE

(Trademark) is indicated for the relief of symptoms of various depressive disorders and for the associated anxiety in both hospitalized and outpatient populations. Based on the classification of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (Third Edition)[1], the effectiveness of (Trademark) has been demonstrated in both types of Major Depression, i.e., Major Depression, Single Episode, and Major Depression, Recurrent.

A diagnosis of Major Depression is based upon the presence of a prominent and persistent dysphoric or depressed mood plus at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, loss of energy or excess fatigue, feelings of guilt or worthlessness, diminished ability to think or concentrate, and suicidal ideation or attempts.

The effectiveness of (Trademark) in long term use, i.e., up to one year, has been shown in extensions of the controlled clinical studies; these included 221 patients evaluated for at least six months of whom 71 continued for over one year. The physician should periodically re-evaluate the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

(Trademark) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

None.

PRECAUTIONS

General: The possibility of suicide in seriously depressed patients

is inherent in the illness and may persist until significant remission occurs. Therefore, in order to minimize the opportunity for overdosage, prescriptions should be written for the smallest number of capsules consistent with good patient management.

Information for Patients: Antidepressants may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or other machinery; the patient should be cautioned accordingly.

Laboratory Tests: Rarely, low white blood cell counts or elevated transaminase levels have been noted in patients receiving (Trademark) or placebo. Leukocyte and differential counts and determination of transaminase levels are recommended during therapy with (Trademark) if indicated by clinical signs and symptoms.

Drug Interactions: The safety of (Trademark) given concomitantly with monoamine oxidase inhibitors has not been established. Single doses of secobarbital, warfarin, diazepam, chlorothiazide, and tolbutamide were given alone, following a single dose of fluoxetine, and following seven daily doses of fluoxetine. The pharmacokinetics of these drugs were unaltered by the concurrent administration of fluoxetine; no consistent clinical effects were attributable to concurrent fluoxetine administration. However, the concomitant administration of (Trademark) and barbiturates or other central nervous system depressants may result in excess sedation.

Therapeutic Interactions: Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dietary administration of fluoxetine to rats for two years at levels equivalent to approximately 7.5 times the maximum recommended human dose produced no evidence of carcinogenicity.

Fluoxetine was shown to have no genotoxic effects based on the following mutagenicity assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow.

Two fertility studies conducted in rats at doses of approximately 5 and 9 times the maximum recommended human dose indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted and was probably associated with depressed maternal food consumption and weight gain.

(Multiples of the maximum recommended human dose are calculated on the basis of 80 mg/day in an individual weighing 60 kg.)

Pregnancy: Pregnancy Category B: No teratogenic effects were produced in rat fertility studies or in rat and rabbit teratology studies at doses of approximately 9 and 11 times respectively, the maximum recommended human dose. There are, however, no adequate and

well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (Trademark) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

It is recognized that the incidence of adverse drug reactions varies widely between studies of a given drug. Information presented in the table which follows is derived from double-blind placebo controlled studies of five or six weeks duration. The figures cited cannot be used to predict precisely the frequency of untoward events which may be observed in medical practice.

Adverse Experience	(Trademark)	Placebo
Number of Patients	302	291
	% of Patients Reporting	
Autonomic Nervous System		
Blurred vision	8	4
Constipation	6	4
Dry mouth	18	11
Cardiovascular System		
Hot flushes	2	1
Palpitation	2	1
Tachycardia	1	*
Digestive System		
Anorexia	6	2
Diarrhea	7	6
Dyspepsia	8	4
Nausea	23	10
Nausea and Vomiting	1	1
Abdominal Pain	1	3
Taste Change	5	1
Musculoskeletal System		
Musculoskeletal Aches & Pains	6	7
Central Nervous System		
Anxiety	8	4
Bruxism	1	*
Concentration Decreased	4	1
Confusion	2	1

Coordination Disturbance	1	*
Dizziness/Lightheadedness	13	6
Dreams Abnormal	1	1
Drowsiness	16	7
Energy Decreased	1	*
Headache	15	17
Hypersomnia	2	*
Insomnia	14	7
Irritability	1	2
Libido Decreased	1	*
Nervousness	15	7
Sensation Disturbance (e.g., numbness, burning, tingling)	3	3
Tremor	13	2
Respiratory System		
Sinus headache, congestion	1	3
Skin and Appendages		
Pruritis	2	2
Rash	15	2
Sweating, Excessive	12	3
Special Senses		
Tinnitus	2	1
Urogenital System		
Sexual Dysfunction (e.g., impotence, delayed ejaculation, decreased orgasm)	5	*
Urinary Frequency	3	*
Urination Impaired	1	*
Other		
Asthenia	7	3
Chills	2	*
Edema	1	*
Malaise	1	*

* = less than one percent

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported in association with the use of (Trademark): flatulence, menstrual abnormalities, hypertension and hypotension, psychosis, hallucinations, abnormal involuntary movement, ataxia, galactorrhea, anemia, leukopenia, and akathisia.

One patient, in whom fluoxetine was continued after rash and pruritis occurred, developed a severe skin rash accompanied by fever and hepatic dysfunction. Another patient had erythema multiforme.

Two patient experienced episodes which may have been convulsions.

In controlled clinical trials, the mean weight loss among fluoxetine patients was 2.5 to 3 pounds over five or six weeks. _____ percent of patients lost ≥5% of their body weight and __% gained ≥5%. Weight loss or, less commonly, weight gain may be viewed as desirable or adverse, depending on the patient's preexisting condition.

OVERDOSAGE

There is minimal clinical experience with acute overdosage with (Trademark). The oral LD_{50} in mice and rats was found to be 248 and 466 mg/kg, respectively. Animals treated with multiples of the human therapeutic dose (25 times and greater) developed hyperirritability and convulsions. The drug and its active metabolite have long half lives; therefore, supportive care may be required for several days. Hemodialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

Dosage should usually be started with 20 mg per day and may be increased by 20 mg increments daily. The usual adult daily dose is 20 to 80 mg, administered as a single daily dose or in two divided doses, preferably in the morning and/or at lunchtime. Doses above 80

mg per day are not recommended. In elderly patients, the total daily dose should rarely exceed 60 mg. Following remission, medication should be administered at the lowest dose consistent with maintaining clinical improvement.

HOW SUPPLIED

Pulvules:

20 mg (green and off-white)

30 mg (green and light yellow)

40 mg (green and dark yellow)

60 mg (green and pink)

National Drug Code xxxx

Store at controlled room temperature 15° - 30°C (59° - 86°F).

Caution: Federal law prohibits dispensing without prescription.

ANIMAL TOXICOLOGY

The subchronic and chronic administration of fluoxetine to mice, rats, and dogs has been associated with systemic phospholipidosis. The effect was shown to be reversible after chronic administration of approximately 7.5 times the maximum recommended human dose (i.e., 80 mg/day) of fluoxetine for one year in rats and dogs. Systemic phospholipidosis has been demonstrated in animals with a number of other cationic amphiphilic drugs including chlorphentermine, imipramine, and zimelidine[2]. The significance of this finding for man is not known.

REFERENCES

1. Williams, J.B.W., Ed: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association, May, 1980.

2. Lullmann-Rauch, R. (1979). Drug-induced lysosomal storage disorders, in: Lysosomes in Biology and Pathology, vol. 6, pp. 49-130. Dingle, Jacques, and Shaw (eds.). North-Holland, Amsterdam.

ELI LILLY AND COMPANY, Indianapolis, Indiana 46285 U.S.A. Literature issued xxxx, 1983

EXHIBIT

6

OAA 0121 14:40GMT
IN04 0068 15:55GMT 06/26/84

ZCZC OAA121 GE1006
QL IND1
.GE1EL 06261440

ASHBROOK, EM (IND1) *IND1* 31/2
HARDISON, CD (IND1) *IND1* 22/3
STARK, P (IND1) *IND1* 31/2 ***
CC.: ARGAY, DA (IND1)
BANDAK, S (HQPA)
GODWIN, S (HQPA)
HEYMANNS, S (GE1)
VON KEITZ, B (GE1)
KOESTENBERGER, S (GE1)
KUSMIEREK, J (ERL)
SPICKSCHEN, I (GE1)
STEINMEYER, HB (GE1)
THOMPSON, WL (IND1) *IND1* 31/2
WAEGER, A (GE1)
WEINSTEIN, AJ (IND1) *IND1* 31/2
WOLD, J (ERL)
ZERBE, RL (IND1) *IND1* 31/2
:

BAD HOMBURG JUNE 26, 1984 GLA
TELEX NO. 005

RE.: FLUOXETINE - REGISTRATION GERMANY

THIS IS TO CONFIRM, WHICH ADDITIONAL DATA HAVE BEEN IDENTIFIED TO BE ESSENTIAL DURING OUR DISCUSSION AT THE BGA (JUNE 15, 84). ALL THE ISSUES WERE SUBJECT TO VARIOUS DISCUSSIONS WITH MEDICAL / MARKETING PERSONS ON THE OCCASION OF THE FLUOXETINE SYMPOSIUM / 14 TH C.I.N.P. CONGRESS:

1. EFFICACY DATA ON PATIENTS OF NON-ENDOGENOUS SUBTYPE, THIS COULD HELP US TO ACHIEVE THE ''REACTIVE DEPRESSION'' CLAIM.

2. THE BGA STATED THAT THERE IS A DISAGREEMENT BETWEEN PATIENT'S AND DOCTOR'S JUDGEMENT OF EFFICACY, SINCE IN THEIR OPINION THE PATIENT'S IMPRESSION IS MORE IMPORTANT, WE HAVE TO DEMONSTRATE CORRELATION BETWEEN SCL 58 AND HAMD AND CGI AND PGI RESP. (PERHAPS BY GRAPHS ?).

3.A A CRITICAL ISSUE FOR THE BGA IS SAFETY IN LONG-TERM TREATMENT. PATIENT NUMBERS OF 218 AND 74 TREATED FOR MORE THAN ONE HALF AND ONE YEAR RESP. MAY POSSIBLY NOT SATISFY OUR AUTHORITIES. THEIR CONCERNS ARE LEUKOPENIA / AGRANULOCYTOSIS, HEPATOTOXICITY

AND POSSIBLE DAMAGE DUE TO PHOSPHOLIPIDOSIS (CONCERNING THE LATTER SEE 15).
SINCE THE DATA BASE HAS BEEN ENLARGED DURING THE PAST YEAR THE QUESTION IS, WHETHER YOU COULD PROVIDE US WITH THE RESP. SAFETY DATA ON INCREASED PATIENT NUMBERS.

B EVALUATION OF RECURRENCIES DURING LONG-TERM TREATMENT.

4. IN THE CONTROLLED TRIALS WE HAD ALL THE CONTRAINDICATIONS OF TRICYCLIC COMPARATORS (E.G. GLAUCOMA, URINARY RETENTION, SEVERE CARDIOVASCULAR DISEASE, ETC.) AS EXCLUSION CRITERIA. WE HAVE TO DEMONSTRATE - PERHAPS BY ANALYSIS OF OPEN TRIALS - THAT FLUOXETINE IS SAFE IN SUCH PATIENTS. OTHERWISE WE WILL HAVE TO NAME THOSE EXCLUSION CRITERIA ALSO AS CONTRAINDICATIONS IN THE PACKAGE INSERT.
THE SAME APPLIES TO SERIOUS SUICIDAL RISK, BIPOLAR ILLNESS, HYPERTENSIVE PATIENTS TREATED WITH CERTAIN ANTIHYPERTENSIVE DRUGS, HISTORY OF SEIZURES, HYPERTHYROIDISM.

5. POOLED IN-PATIENT DATA

6. ANALYSIS OF PRETREATMENT WITH OTHER ANTIDEPRESSANTS, NEUROLEPTIC DRUGS, OR TRANQUILIZERS (TO DEMONSTRATE THAT ONE WEEK OF WASH-OUT WAS SUFFICIENTLY LONG).

7. THE BGA EXPLAINED THEIR RESERVATIONS REGARDING CNS SIDE-EFFECTS
I
THERE HAVE BEEN A FEW PATIENTS COMPLAINING OF PSYCHOSIS AND HALLUZINATIONS.
PLEASE PROVIDE US WITH DETAILED REPORT, WHETHER THOSE PATIENTS SUFFERED FROM ''PSYCHOTIC DEPRESSION'', WHETHER THE HALLUZINATIONS DEVELOPED DURING TREATMENT OR HAVE PERHAPS BEEN PRESENT ALREADY AT START OF TREATMENT, OR WHETHER THOSE EVENTS MAY INDEED BE INTERPRETED BY ''AGGRAVATION OF DISEASE''.

8. PLEASE CONFIRM THAT A TOLERANCE TO FLUOXETINE DID NOT DEVELOP (DOSE OVER TIME) AND WITHDRAWAL SYMPTOMS HAVE NOT BEEN OBSERVED AFTER LONG-TERM TREATMENT (LONG ELIMINATION HALF-LIFE)

9. ALL KINDS OF SAFETY DATA WE HAVE ON CONCOMITANT INTAKE OF NEUROLEPTIC OR OTHER ANTIDEPRESSANT DRUGS.

10. COMPARATIVE USE OF CONCOMITANTLY TAKEN HYPNOTICS AND BENZODIAZEPINES IN AGITATED / RETARDED FLUOXETINE PATIENTS VERSUS AGITATED / RETARDED PATIENTS ON COMPARATORS.
REASON: THE BGA SUSPECTS FLUOXETINE TO BE A STIMULATING / ACTIVATING DRUG (SIDE-EFFECT PROFILE, SUICIDES, SUICIDE ATTEMPTS).

11. WE HAVE TO EVALUATE THE APPROXIMATE TREATMENT DURATION UNTIL ANTIDEPRESSANT EFFICACY USUALLY BECOMES EVIDENT (FOR PACKAGE INSERT INFORMATION).

12. THE BGA STATED THAT DUE TO THE ACCUMULATION OF FLUOXETINE WE SHOULD CONSIDER TO RECOMMEND A LOWER MAINTENANCE DOSE AFTER HAVING ACHIEVED A CERTAIN RELIEF OF ACUTE SYMPTOMS.
THEY ADVISED TO GIVE CLEAR INSTRUCTIONS CONCERNING DOSE-

ADJUSTMENT WITH TIME.

13. WE SHOULD CLEARLY DEFINE THE MAXIMUM DURATION OF TREATMENT WHICH WE ARE GOING TO RECOMMEND.

14. AS WE ALREADY EXPLAINED BY OUR TELEX TO DR. ZERBE OF JUNE 8, '84 WE NEED A CAREFUL ANALYSIS OF SUICIDES AND SUICIDE ATTEMPTS: PATIENT BY PATIENT, SYMPTOMATOLOGY / SEVERITY UPON ENTRY INTO THE STUDY AND WEEK BY WEEK UNTIL THE EVENT OCCURRED, DOSE OF FLUOXETINE, SIDE-EFFECTS, ETC
THIS IS A VERY SERIOUS ISSUE IN THE OPINION OF THE BGA.
IT MIGHT WELL BE THAT WE WILL HAVE TO RECOMMEND CONCOMITANT TRANQUILIZER INTAKE FOR THE FIRST 2 OR 3 WEEKS IN THE PACKAGE LITERATURE.

15. THE MOST IMPORTANT ISSUE IS THE LUNG AND EYE FINDINGS DURING FLUOXETINE TREATMENT.
THE BGA STATED THAT WE DID NOT APPLY NEWER TECHNIQUES (E.G. SCANNING, TOMOGRAPHY, BIOPSY) TO SUBSTANTIATE, WHETHER THE CHANGES FROM NORMAL TO ABNORMAL WERE DRUG RELATED OR NOT. THE BGA CANNOT RULE OUT A DAMAGE SIMILAR TO THAT SEEN IN ANIMALS DUE TO PHOSPHOLIPIDOSIS.

ACTIONS, WHICH COULD HELP IN A NOT VERY PROMISING SITUATION:

A) OBTAIN OPINIONS FROM OPHTHALMOLOGIST AND PULMONOLOGIST, WHO HAVE EXAMINED FLUOXETINE PATIENTS.
B) PROVIDE DETAILED REPORT ON LYMPHOCYTE INVESTIGATIONS.
C) INVOLVE PROFESSOR LUELLMANN.

PLEASE EXCUSE IF THERE ARE SOME OF THE ISSUES ALREADY COVERED BY THE DATA WE RECEIVED IN THE MEANTIME.
WE HAD NOT ENOUGH TIME TO GO THROUGH IN DETAIL.
WE APPRECIATE ALL THE HELP WHICH WAS SPONTANEOUSLY OFFERED BY THE INDIANAPOLIS AND LONDON / ERL WOOD GROUPS OF STATISTICIANS, MEDICAL AND MARKETING COLLEAGUES.
NEVERTHELESS IT WILL BE A DIFFICULT EXERCISE FOR A FINAL SUCCESSFUL OUTCOME.

REGARDS
SCHENK, J (GE1)
WEBER, HJ (GE1)

#06261443
NNNN

Recd.
File Discard
Follow Up
Pass to JLC
GTB
LDH
Return To:
M. E. Amundson

May 28, 1982

Dr. L. Lemberger
Dr. P. Stark
cc: Dr. M. E. Amundson
Dr. D. M. Brennan
Dr. C. N. Christensen
Dr. C. E. Redman

Re: IND 12274 - Compound LY110140 - Fluoxetine Hydrochloride (Psychotropic Agent)

Attached for your information is a letter dated May 17, 1982, from the Food and Drug Administration regarding the above IND.

A response to FDA has been drafted and will be forwarded in the near future.

Dorothy S. Dobbs
(3424)

lm
Attach.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 12,274

MAY 17 1982

Lilly Research Laboratories
Attention: Dorothy S. Dobbs, M.D.
307 East McCarty Street
Indianapolis, Indiana 46285

Gentlemen:

Please refer to your communications dated March 25 and April 12, 1982 pertaining to your Notice of Claimed Investigational Exemption for a New Drug for Fluoxetine HCl (LY 110140), IND 12,274.

We have reviewed your requests to amend protocols 26, 28, and 36 to (1) enable responders to continue treatment on an open-label basis for an "indefinite period of time", (2) eliminate the chest X-ray requirement for protocol 26, and (3) extend the duration of open-label study No. 36 from eight to 48 weeks. We have no objection to the elimination of the chest X-ray. However, without the necessary supporting animal studies, clinical exposure to fluoxetine should not exceed six months duration. We will require the submission of animal toxicity studies in two species of six months duration or greater.

We also recommend that when patients complete the blind phase of a trial, you maintain the blind and either routinely switch the patients to fluoxetine if they are appropriate candidates for the long-term exposure or continue patients on blind medication for the extended phase. Comparative data will be to your advantage, and breaking the code at the end of individual trials may invalidate the controlled conditions. That is, investigators may learn to associate certain side effects or improvement with one treatment or another.

Your cooperation and prompt response will be appreciated.

Sincerely yours,

Paul Leber, M.D.
Director (Acting)
Division of Neuropharmacological
Drug Products
Bureau of Drugs

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

December 17, 1984

Food and Drug Administration
Center for Drugs and Biologics
Division of Neuropharmacological
Drug Products (HFN-120)
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: NDA 18-936
"TRADEMARK", fluoxetine hydrochloride

Reference is made to the telephone conversation of October 22, 1984, between Dr. Hilary Lee and the undersigned at which time additional information was requested regarding concomitant drugs taken by patients who were enrolled in the controlled clinical trials of fluoxetine.

The requested information is appended.

Very truly yours,

ELI LILLY AND COMPANY

Dorothy S. Dobbs, M.D.
Medical Advisor
Clinical Investigation
and Regulatory Affairs
(Neuroendocrinology)

Attachment

cc: Dr. Hilary Lee (HFN-120)

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Request: To provide additional summary information about concomitant medications used in the controlled studies

The following tables (1-22) show by study and for individual patients the "allowed psychotropics" (those permitted by the protocols), the "disallowed psychotropics", and "other CNS effect medications" (incorporates those suggested by the FDA reviewer).

The "allowed psychotropics" included benzodiazepine (not specified), temazepam, clonazepam, clorazepate, diazepam, lorazepam, nitrazepam, oxazepam, alprazolam, prazepam, chlordiazepoxide, flurazepam, and chloral hydrate.

The "disallowed psychotropics" included amphetamine, Combid, prochlorperazine, Eskatrol, meprobamate and aspirin, meprobamate, hydroxyzine, thiothixene, butabarbital, cocaine, ethchlorvynol, doxepin, amitriptyline, imipramine, Fiorinal with codeine, carisoprodol/phenacetin/aspirin, and Pabalon Forte.

The "other CNS effect medications" included propranolol, cimetidine, Fiorinal, meperidine, diphenhydramine, phenylpropanolamine HCl, and phenylpropanolamine and caffeine.

Please note that the categories of other medications are not mutually exclusive, i.e., a given patient may be included in more than one.

TABLE 1

Dr. L. F. Fabre - Protocol 19
Reference Fluoxetine NDA 18-936:1.30/068-069

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chloral hydrate	X		
	placebo	eskalith		X	
	placebo	chloral hydrate, oxazepam	X		
	placebo	chloral hydrate	X		
	fluoxetine	chloral hydrate, oxazepam	X		
	placebo	chloral hydrate	X		
	placebo	chloral hydrate, diazepam	X		
	fluoxetine	oxazepam, dyphenhydramine	X		X
	fluoxetine	chloral hydrate, amitriptyline	X	X	
		TOTAL	8	2	1

TABLE 2

Dr. K. Rickels - Protocol 25
Reference Fluoxetine NDA 18-936:1.31/069-070

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate, diazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	cimetidine			X
	placebo	chloral hydrate, meprobamate and aspirin, fiorinal	X	X	X
	placebo	chloral hydrate, chlordiazepoxide	X		
	placebo	diazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate, diazepam	X		
	placebo	diazepam			
	fluoxetine	cimetidine			X
	fluoxetine	chloral hydrate	X		
		TOTAL	11		3

TABLE 3

[redacted] - Protocol 24
Reference Fluoxetine NDA 18-936:1.61/090, 093

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chloral hydrate	X		
	placebo	meprobamate		X	
	fluoxetine	propranolol			X
	placebo	propranolol			X
	fluoxetine	lorazepam, doxepin	X	X	
		TOTAL	2	2	2

TABLE 4

Dr. J. D. Bremner - Protocol 20
Reference Fluoxetine NDA 18-936:1.42/071-072

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	hydroxyzine, diphenhydramine		X	X
	imipramine	clorazepate	X		
	fluoxetine	chlordiazepoxide	X		
	fluoxetine	flurazepam	X		
	imipramine	diazepam	X		
	imipramine	diazepam	X		
	fluoxetine	diazepam	X		
	imipramine	diazepam	X		
	fluoxetine	diazepam	X		
	imipramine	diazepam	X		
	imipramine	cimetidine			X
	imipramine	diazepam	X		
	imipramine	propranolol			X
		TOTAL	10	1	3

TABLE 5

Dr. H. L. Manco - Protocol 22
Reference Fluoxetine NDA 18-936:1.45/072-074

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	amitriptyline	chloral hydrate, flurazepam	X		
	amitriptyline	chlordiazepoxide, cimetidine	X		X
	fluoxetine	chloral hydrate, flurazepam	X		
	fluoxetine	flurazepam	X		
	fluoxetine	diazepam, propranolol	X		X
	fluoxetine	diazepam	X		
	amitriptyline	diazepam, flurazepam	X		
	amitriptyline	oxazepam	X		
	amitriptyline	diazepam	X		
	fluoxetine	oxazepam	X		
	fluoxetine	chloral hydrate, clorazepate	X		
	amitriptyline	chloral hydrate, chlordiazepoxide, flurazepam	X		
	fluoxetine	chlordiazepoxide, oxazepam	X		
	amitriptyline	chloral hydrate, chlordiazepoxide, flurazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	chlordiazepoxide, flurazepam	X		
	fluoxetine	chlordiazepoxide	X		
	amitriptyline	chlordiazepoxide	X		
	fluoxetine	chloral hydrate, diazepam, flurazepam	X		
	fluoxetine	chloral hydrate, chlordiazepoxide, flurazepam, thiothixene	X	X	
	amitriptyline	chloral hydrate, chlordiazepoxide, flurazepam, diphenhydramine	X		X
	fluoxetine	chloral hydrate, chlordiazepoxide, flurazepam	X		

TABLE 5 (continued)

Dr. H. L. Masco - Protocol 22
Reference Fluoxetine NDA 18-936:1.45/072-074

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chlordiazepoxide, flurazepam	X		
	amitriptyline	chlordiazepoxide	X		
	fluoxetine	cimetidine			X
	fluoxetine	flurazepam	X		
	amitriptyline	flurazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	flurazepam	X		
	amitriptyline	flurazepam	X		
	fluoxetine	diazepam, flurazepam	X		
	amitriptyline	flurazepam, oxazepam	X		
	fluoxetine	chlordiazepoxide, clorazepate	X		
	amitriptyline	diazepam, flurazepam, Noctec	X		X
		TOTAL	33	1	5

TABLE 6

Dr. J. P. Feighner - Protocol 23
Reference Fluoxetine NDA 18-936:1.46/075-077

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	amitriptyline	lorazepam	X		
	fluoxetine	flurazepam	X		
	amitriptyline	lorazepam, Fiorinal	X		X
	amitriptyline	propranolol			X
	fluoxetine	butabarbital		X	
	amitriptyline	lorazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate, chlordiazepoxide	X		
	amitriptyline	clorazepate	X		
	fluoxetine	chloral hydrate, diazepam	X		
	amitriptyline	diazepam	X		
	fluoxetine	chloral hydrate	X		
		TOTAL	11	1	2

TABLE 7

Dr. G. Chouinard - Protocol 26
Reference Fluoxetine NDA 18-936:1.47/074-075

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	cimetidine			X
	fluoxetine	diazepam	X		
	amitriptyline	diazepam	X		
	fluoxetine	diazepam	X		
	amitriptyline	diazepam	X		
	amitriptyline	diazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	diazepam	X		
	amitriptyline	diazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	diazepam	X		
	amitriptyline	diazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	oxazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	diazepam	X		
	amitriptyline	diazepam, flurazepam	X		
	amitriptyline	diazepam	X		
		TOTAL	17		1

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TABLE 8

Dr. J. P. Feighner - Protocol 27
Reference Fluoxetine NDA 18-936:1.32/119-124

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	placebo	propranolol			X
	fluoxetine	Fiorinal			X
	imipramine	Fiorinal			X
	imipramine	chloral hydrate	X		
	fluoxetine	diazepam	X		
	placebo	chloral hydrate	X		
	imipramine	chloral hydrate, flurazepam, propranolol	X		X
	fluoxetine	doxepin, diphenhydramine		X	X
	fluoxetine	flurazepam, diphenhydramine	X		X
	placebo	chloral hydrate	X		
	placebo	propranolol			X
	imipramine	flurazepam, oxazepam	X		
	imipramine	flurazepam	X		
	imipramine	flurazepam	X		
	placebo	chloral hydrate, cimetidine, propranolol	X		X
	fluoxetine	flurazepam	X		
	imipramine	flurazepam	X		
	imipramine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	placebo	chloral hydrate	X		
	placebo	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	placebo	flurazepam	X		
	imipramine	flurazepam, cimetidine	X		X
	placebo	flurazepam	X		
	fluoxetine	flurazepam	X		

TABLE 8 (continued)

Dr. J. P. Feighner - Protocol 27
Reference Fluoxetine NDA 18-936:1.32/119-124

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	placebo	cimetidine			X
	placebo	chloral hydrate, meperidine	X		X
	placebo	chloral hydrate	X		
	imipramine	diphenhydramine			X
	placebo	flurazepam	X		
	fluoxetine	diazepam, flurazepam	X		
	placebo	flurazepam	X		
	imipramine	cimetidine			X
	fluoxetine	chloral hydrate, flurazepam	X		
	fluoxetine	propranolol			X
	placebo	flurazepam	X		
	placebo	chloral hydrate, clorazepate, flurazepam, diphenhydramine, Fiorinal	X		X
	imipramine	flurazepam	X		
	imipramine	diazepam	X		
	imipramine	flurazepam	X		
	imipramine	flurazepam	X		
	placebo	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	fluoxetine	flurazepam	X		
	placebo	cimetidine			X
	imipramine	chloral hydrate	X		
	fluoxetine	flurazepam	X		
	fluoxetine	flurazepam, diphenhydramine	X		X
	placebo	flurazepam	X		
	imipramine	flurazepam, cimetidine	X		X
	imipramine	flurazepam	X		
	imipramine	cimetidine			X
	fluoxetine	chloral hydrate	X		

TABLE 8 (continued)

Dr. J. P. Feighner - Protocol 27
Reference Fluoxetine NDA 18-936:1.32/119-124

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	imipramine	flurazepam, diphenhydramine	X		X
	fluoxetine	meperidine			X
	fluoxetine	prochlorperazine, cimetidine		X	X
	fluoxetine	chloral hydrate	X		
	imipramine	flurazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	chloral hydrate, flurazepam	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	placebo	flurazepam, hydroxyzine	X	X	
	placebo	chloral hydrate, Fiorinal	X		X
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
		TOTAL	56		23

TABLE 9

Dr. J. B. Cohn - Protocol 27
Reference Fluoxetine NDA 18-936:1.34/121-126

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	diphenhydramine			X
	placebo	propranolol			X
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	Fiorinal			X
	placebo	phenylpropanolamine HCl			X
	fluoxetine	Parafon Forte		X	
	placebo	cimetidine			X
	imipramine	propranolol			X
	placebo	cimetidine			X
	placebo	cimetidine			X
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate, flurazepam	X		
	imipramine	cimetidine			
	fluoxetine	propranolol			X
		TOTAL	4	1	10

TABLE 10

Dr. J. D. Bremner - Protocol 27
Reference Fluoxetine NDA 18-936:1.36/081-083

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	flurazepam	X		
	placebo	chloral hydrate, flurazepam	X		
	fluoxetine	flurazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	imipramine	flurazepam	X		
	imipramine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	chloral hydrate, flurazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	flurazepam	X		
	fluoxetine	flurazepam	X		
	imipramine	chloral hydrate, flurazepam	X		
	fluoxetine	flurazepam	X		
	imipramine	cimetidine, propranolol			X
	fluoxetine	flurazepam			
	fluoxetine	cimetidine			X
	fluoxetine	cimetidine			X
	placebo	flurazepam	X		
	imipramine	flurazepam	X		
	imipramine	flurazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	propranolol			X
	imipramine	flurazepam, carisoprodol/ phenacetin/aspirin, cimetidine	X	X	X
		TOTAL	23	1	5

TABLE 11

Dr. D. L. Dunner - Protocol 27
Reference Fluoxetine NDA 18-936:1.37/089-093

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	imipramine	diphenhydramine			X
	fluoxetine	chloral hydrate, flurazepam	X		
	fluoxetine	diphenhydramine			X
	fluoxetine	diazepam	X		
	placebo	Parafon Forte		X	
	fluoxetine	chloral hydrate	X		
	imipramine	cimetidine			X
	placebo	Parafon Forte		X	
	imipramine	prazepam	X		
	placebo	Parafon Forte		X	
	placebo	chloral hydrate	X		
		TOTAL	5	3	3

TABLE 12

Dr. B. I. Grosser - Protocol 27
Reference Fluoxetine NDA 18-936:1.39/094-096

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	imipramine	flurazepam	X		
	placebo	flurazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	fluoxetine	flurazepam	X		
	imipramine	propranolol			X
	imipramine	flurazepam, cocaine	X	X	
	fluoxetine	flurazepam, cimetidine	X		X
	placebo	cimetidine			X
	fluoxetine	flurazepam	X		
	placebo	flurazepam			
	fluoxetine	flurazepam	X		
	fluoxetine	cimetidine			X
	placebo	prochlorperazine		X	
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	flurazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	placebo	cimetidine			X
		TOTAL	15		5

TABLE 13

Dr. F. S. Abuzzahab - Protocol 27
Reference Fluoxetine NDA 18-936:1.40/088-090

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	placebo	meperidine			X
	imipramine	cimetidine			X
	fluoxetine	diphenhydramine			X
	fluoxetine	chlordiazepoxide	X		
	placebo	temazepam	X		
	fluoxetine	temazepam, cimetidine	X		X
	fluoxetine	temazepam	X		
	imipramine	clonazepam	X		
	fluoxetine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	flurazepam	X		
	imipramine	temazepam	X		
	placebo	chloral hydrate, flurazepam	X		
	imipramine	flurazepam	X		
	imipramine	flurazepam, cimetidine	X		X
	imipramine	flurazepam	X		
	fluoxetine	chloral hydrate, flurazepam	X		
	imipramine	flurazepam	X		
	imipramine	flurazepam	X		
	fluoxetine	diphenhydramine			X
	placebo	flurazepam	X		
	fluoxetine	imipramine			
	imipramine	chloral hydrate	X		
	placebo	flurazepam	X		
	placebo	chloral hydrate	X		

TABLE 13 (continued)

Dr. F. S. Abuzzahab - Protocol 27
Reference Fluoxetine NDA 18-936:1.40/088-090

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	flurazepam	X		
	imipramine	flurazepam	X		
	placebo	flurazepam	X		
	imipramine	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	placebo	chloral hydrate	X		
		TOTAL	26	1	6

TABLE 14

[redacted] - Protocol 27
Reference Fluoxetine NDA 18-936:1.61/091, 092, 094

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	placebo	chloral hydrate	X		
	fluoxetine	cimetidine			X
	placebo	flurazepam	X		
		TOTAL	2	-	1

TABLE 15

Dr. J. P. Feighner - Protocol 29
Reference Fluoxetine NDA 18-936:1.43/076-078

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	diphenhydramine			X
	imipramine	flurazepam	X		
	imipramine	flurazepam	X		
	imipramine	alprazolam, flurazepam, propanolol	X		X
	imipramine	flurazepam	X		
	imipramine	flurazepam, dyphenhydramine	X		X
	fluoxetine	flurazepam	X		
	fluoxetine	chloral hydrate, chlordiazepoxide, flurazepam	X		
	imipramine	chloral hydrate	X		
	fluoxetine	flurazepam, cimetidine	X		X
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate, prochlorperazine	X	X	
	imipramine	chloral hydrate, diphenhydramine	X		X
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate, Parafon Forte	X	X	
	fluoxetine	flurazepam, cocaine	X	X	
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	diphenhydramine			X

TABLE 15 (continued)

Dr. J. P. Feighner - Protocol 29
Reference Fluoxetine NDA 18-936:1.43/076-078

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	imipramine	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	flurazepam	X		
	fluoxetine	cimetidine			X
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate, flurazepam, hydroxyzine, meperidine	X	X	X
	fluoxetine	diazepam, flurazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
		TOTAL	15	4	8

TABLE 16

Dr. J. M. Davis - Protocol 29
Reference Fluoxetine NDA 18-936:1.44/076-077

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	imipramine	flurazepam	X		
	fluoxetine	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate, flurazepam	X		
	imipramine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate, flurazepam, cimetidine	X		X
	imipramine	propanolol			X
	fluoxetine	chloral hydrate, flurazepam	X		
	fluoxetine	flurazepam	X		
	imipramine	flurazepam, cimetidine	X		X
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
	fluoxetine	chloral hydrate, cimetidine	X		X
	fluoxetine	diazepam	X		
	imipramine	propanolol			X
	fluoxetine	prochlorperazine		X	
	fluoxetine	chloral hydrate	X		

TABLE 16 (continued)

Dr. J. M. Davis - Protocol 29
Reference Fluoxetine NDA 18-936:1.44/076-077

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	imipramine	chloral hydrate, hydroxyzine, meperidine	X	X	X
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	imipramine	chloral hydrate	X		
		TOTAL	25	2	6

TABLE 17

Dr. A. Kiev - Protocol 31
Reference Fluoxetine NDA 18-936:1.48/072-073

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	flurazepam, propanolol	X		X
	fluoxetine	flurazepam	X		
	fluoxetine	benzodiazepine, flurazepam	X		
	fluoxetine	cocaine		X	
	fluoxetine	diazepam, flurazepam	X		
	fluoxetine	diazepam	X		
	fluoxetine	flurazepam	X		
	doxepin	hydroxyzine		X	
	fluoxetine	flurazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	flurazepam	X		
		TOTAL	10	2	1

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TABLE 18

Dr. H. L.Masco - Protocol 31
Reference Fluoxetine NDA 18-936:1.49/080-083

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	chloral hydrate, flurazepam	X		
	fluoxetine	flurazepam	X		
	doxepin	flurazepam	X		
	doxepin	Parafon Forte		X	
	fluoxetine	flurazepam, diphenhydramine	X		X
	doxepin	diazepam, flurazepam	X		
	doxepin	flurazepam	X		
	fluoxetine	chlordiazepoxide, flurazepam	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	doxepin	chloral hydrate	X		
	fluoxetine	chloral hydrate, flurazepam	X		
	fluoxetine	chloral hydrate	X		
	doxepin	chloral hydrate	X		
	doxepin	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	fluoxetine	Parafon Forte		X	
	doxepin	Parafon Forte		X	
	fluoxetine	chloral hydrate	X		
	fluoxetine	chloral hydrate, propanolol	X		X
	doxepin	propanolol			
	doxepin	chloral hydrate, flurazepam	X		
	doxepin	flurazepam, Fiorinal with codeine, cimetidine	X	X	X

TABLE 18 (continued)

Dr. H. L.Masco - Protocol 31
Reference Fluoxetine NDA 18-936:1.49/080-083

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	doxepin	propanolol			X
	fluoxetine	chloral hydrate, Parafon Forte	X	X	
	doxepin	flurazepam	X		
	doxepin	chloral hydrate	X		
	fluoxetine	propanolol			X
	doxepin	chloral hydrate	X		
	fluoxetine	chloral hydrate, cimetidine, propanolol	X		X
	fluoxetine	flurazepam	X		
	fluoxetine	chloral hydrate, cimetidine	X		X
		TOTAL	21	5	8

TABLE 19

Dr. J. P. Feighner - Protocol 33
Reference Fluoxetine NDA 18-936:1.50/076-078

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	doxepin	chloral hydrate	X		
	doxepin	flurazepam, ethchlorvynol, propanolol	X	X	X
	fluoxetine	flurazepam	X		
	doxepin	flurazepam	X		
	doxepin	flurazepam, propanolol	X		X
	fluoxetine	flurazepam	X		
	doxepin	flurazepam	X		
	doxepin	flurazepam	X		
	doxepin	flurazepam	X		
	fluoxetine	flurazepam	X		
	doxepin	propanolol			X
	fluoxetine	flurazepam	X		
	doxepin	flurazepam	X		
	fluoxetine	flurazepam	X		
	doxepin	propanolol			X
	fluoxetine	cimetidine			X
	doxepin	flurazepam	X		
	doxepin	chloral hydrate	X		
	doxepin	flurazepam	X		
	doxepin	flurazepam	X		
	fluoxetine	diphenhydramine			X
	fluoxetine	chloral hydrate	X		
	doxepin	diphenhydramine			X
	fluoxetine	flurazepam	X		
	fluoxetine	flurazepam	X		
	doxepin	flurazepam	X		
		TOTAL	21	1	7

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TABLE 20

Dr. J. B. Cohn - Protocol 33
Reference Fluoxetine NDA 18-936:1.51/104-107

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine	propanolol			X
	fluoxetine	cimetidine			X
	doxepin	chloral hydrate	X		
	doxepin	cimetidine			X
	fluoxetine	diphenhydramine			X
	fluoxetine	propanolol			X
	fluoxetine	propanolol			X
	fluoxetine	chloral hydrate, propanolol	X		X
	doxepin	chloral hydrate	X		
	fluoxetine	chloral hydrate	X		
	doxepin	chloral hydrate	X		
	doxepin	chloral hydrate	X		
		TOTAL	6	-	7

TABLE 21

Dr. K. Rickels - Protocol 35
Reference Fluoxetine NDA 18-936:1.52/082-083

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine QD	Fiorinal			X
	fluoxetine QD	cimetidine			X
	fluoxetine BID	propanolol			X
	fluoxetine BID	chloral hydrate, flurazepam	X		
	fluoxetine BID	chloral hydrate, diphenhydramine	X		X
	fluoxetine BID	chloral hydrate	X		
	fluoxetine QD	chloral hydrate	X		
	fluoxetine BID	diphenhydramine			X
	fluoxetine BID	flurazepam, propanolol	X		X
	fluoxetine QD	flurazepam	X		
	fluoxetine QD	flurazepam	X		
	fluoxetine QD	flurazepam	X		
	fluoxetine BID	flurazepam	X		
	fluoxetine BID	flurazepam	X		
	fluoxetine QD	cimetidine			X
	fluoxetine BID	flurazepam	X		
	fluoxetine BID	chlorhydrate, flurazepam	X		
	fluoxetine QD	diphenhydramine			X
	fluoxetine QD	chloral hydrate,hydroxyzine	X	X	
		TOTAL	13	1	11

TABLE 22

[redacted] Protocol 35
Reference Fluoxetine NDA 18-936:1.53/079-080

Pt. No.	Study Drug	Concomitant Meds	Allowed Psych	Disallowed Psych	Other CNS Effect Meds
[redacted]	fluoxetine QD	hydroxyzine		X	
	fluoxetine BID	cimetidine			X
	fluoxetine BID	chloral hydrate, meperidine	X		X
	fluoxetine QD	chloral hydrate, doxepin	X	X	
	fluoxetine QD	chloral hydrate	X		
	fluoxetine BID	chloral hydrate	X		
	fluoxetine QD	chloral hydrate, flurazepam	X		
	fluoxetine BID	chloral hydrate, flurazepam	X		
	fluoxetine BID	propanolol			X
	fluoxetine QD	propanolol			X
	fluoxetine BID	Fiorinal, propanolol			X
	fluoxetine QD	chloral hydrate	X		
	fluoxetine BID	chloral hydrate	X		
	fluoxetine QD	chloral hydrate, flurazepam	X		
	fluoxetine QD	flurazepam	X		
	fluoxetine QD	chloral hydrate	X		
	fluoxetine BID	chloral hydrate	X		
	fluoxetine QD	flurazepam	X		
	fluoxetine BID	chloral hydrate, hydroxyzine	X	X	
	fluoxetine QD	diphenhydramine			X
	fluoxetine BID	temazepam	X		
	fluoxetine QD	Parafon Forte		X	
	fluoxetine QD	chloral hydrate	X		
	fluoxetine QD	chloral hydrate	X		
	fluoxetine BID	chloral hydrate, diphenhydramine	X		X
		TOTAL	18	4	7