

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

Trade Name: Prozac

Generic Name: fluoxetine HCl

Sponsor: Eli Lilly & Company

Approval Date: July 29, 2002

Indication: Treatment of bulimia

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APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

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APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

APPROVAL LETTER



NDA 18-936/S-061/065

NDA 20-101/S-027

NDA 20-974/S-001

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated February 22, 2001 (NDA 18-936/S-065, 20-101/S-027, and 20-974/S-001) and July 26, 2000 (NDA 18-936/S-065), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine HCl) capsules (NDA 18-936), Solution (NDA 20-101), and Tablets (NDA 20-974).

Reference is also made to Agency approvable letters dated December 20, 2001 (NDA 18-936/S-065, 20-101/S-027, and 20-974/S-001), and March 11, 2002 (NDA 18-936/S-061).

We acknowledge receipt of your submissions dated February 27, and May 6, 2002. Your submissions of February 27, and May 6, 2002 constituted a complete response to our December 20, 2001, and March 11, 2002 action letters.

Supplemental applications 18-936/S-065, 20-101/S-027, and 20-974/S-001 provide for the longer-term treatment of bulimia.

Supplemental application 18-936/S-061 provides for the treatment of panic disorder, with or without agoraphobia.

We note your agreement made in your May 6, 2002, submission to incorporate the proposed changes to labeling, verbatim, as requested in the Agency action letters dated December 20, 2001, and March 11, 2002. We additionally note your agreement in the May 6, 2002 submission to change the terminology from depression to major depressive disorder as requested in an Agency letter dated March 19, 2002.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDAs 18-936/S-061/S-065, 20-101/S-027, & 20-974/S-001." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Russell Katz
7/29/02 09:26:57 AM

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APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

OTHER ACTION LETTERS



Food and Drug Administration
Rockville MD 20857

NDA 18-936/S-065
NDA 20-101/S-027
NDA 20-974/S-001

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated February 22, 2001, received February 23, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine HCl) capsules (NDA 18-936), Solution (NDA 20-101), and Tablets (NDA 20-974).

We acknowledge receipt of your submissions dated June 14, July 24, and September 20, 2001.

These supplemental applications provide for one adequate and well-controlled relapse prevention trial in the (b) (4) of bulimia.

We have completed the review of this application, as amended, and it is approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

LABELING

We have made revisions to the 3 sections of labeling for which you have proposed language. Our proposed revisions for these 3 sections are as follows:

1. Under **CLINICAL TRIALS-Bulimia Nervosa:**

[The following paragraph should be inserted as the final paragraph in this subsection.]

(b) (4)

2. Under **INDICATIONS AND USAGE-Bulimia Nervosa:**

[The following paragraph should be inserted to replace the final paragraph in this subsection.]

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (see **Clinical Trials**, under **Clinical Pharmacology**). Nevertheless, the physician who elects to use Prozac for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **Dosage and Administration**).

3. Under **DOSAGE AND ADMINISTRATION-Bulimia Nervosa-Maintenance/Continuation Treatment:**

[The following paragraph should be inserted to replace the current language in this subsection.]

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (see **Clinical Trials**, under **Clinical Pharmacology**). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

In addition, all previous revisions as reflected in the most recently acceptable fluoxetine labeling (see Agency letter dated May 25, 2001) must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

We additionally refer to an Agency approvable letter dated July 12, 2001, for supplemental application 18-936/S-064. At the time of this action letter, the Agency informed Lilly of our intent to change the indication from the more broad terminology of depression to major depressive disorder. We would fully expect, once this labeling is agreed upon by the Agency and Lilly, that the final printed labeling for the above supplemental applications would also incorporate these changes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please provide a worldwide updated search of the postmarketing adverse events database regarding fluoxetine in bulimia, and also a literature update regarding safety in this population. This should include an updated estimate of use for drug marketed in other countries, and English translations of current approved foreign labeling in the pediatric patient population.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
12/20/01 02:42:52 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-706/S-034

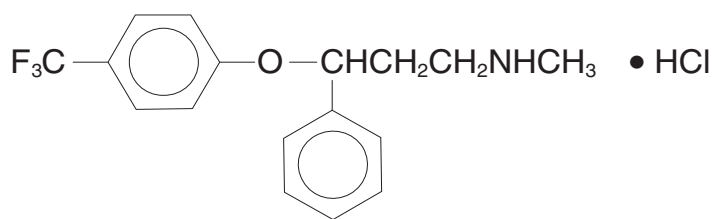
LABELING

PROZAC[®]

FLUOXETINE HYDROCHLORIDE

DESCRIPTION

Prozac[®] (fluoxetine hydrochloride) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem[™], fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of C₁₇H₁₈F₃NO•HCl. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule[®] contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10 mg and 20 mg Pulvules also contain F D & C Blue No. 1, and the 40 mg Pulvule also contains F D & C Blue No. 1 and F D & C Yellow No. 6.

Each tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10 mg tablet contains F D & C Blue No. 1 aluminum lake, and polysorbate 80.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

Prozac Weekly[™] capsules, a delayed release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

The antidepressant, antiobsessive-compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1 -adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion:

Systemic Bioavailability--In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule, tablet, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. Prozac Weekly capsules, a delayed release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate release formulations.

Protein Binding--Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1 -glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS).

Enantiomers--Fluoxetine is a racemic mixture (50/50) of R-fluoxetine and S-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The S-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism--Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, S-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to R- or S-fluoxetine. R-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism/Elimination--The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in Metabolism--A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs.

In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the four active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see Drug Interactions under PRECAUTIONS*).

Accumulation and Slow Elimination--The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac.

Weekly Dosing—Administration of Prozac Weekly once-weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared to once daily dosing (for fluoxetine: 24% [daily] to 164% [weekly] and for norfluoxetine: 17% [daily] to 43% [weekly]). Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20 mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady state fluoxetine

concentrations are approximately 50% lower following the once-weekly regimen compared to the once-daily regimen.

C_{max} for fluoxetine following the 90 mg dose was approximately 1.7 fold higher than the C_{max} value for the established 20 mg once daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90 mg once weekly dose and the last 20 mg once daily dose were separated by one week, C_{max} values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90 mg weekly dose and the last 20 mg once daily dose by one week (see Dosage and Administration).

Liver Disease--As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease--In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (see Use in Patients with Concomitant Illness under PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Age—

The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Clinical Trials:

Major Depressive Disorder—

Daily Dosing: The efficacy of Prozac for the treatment of patients with major depressive disorder (≥ 18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as

measured by the Hamilton Depression Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing Prozac 20 mg, and placebo have shown Prozac 20 mg daily, to be effective in the treatment of elderly patients (≥ 60 years of age) with major depressive disorder. In these studies, Prozac produced a significantly higher rate of response and remission as defined respectively by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤ 8 . Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤ 7 during each of the last 3 weeks of open-label treatment and absence of major depressive disorder by DSM-III-R criteria) by the end of an initial 12-week open treatment phase on Prozac 20 mg/day. These patients (N=298) were randomized to continuation on double-blind Prozac 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depressive disorder for 2 weeks or a modified HAMD-17 score of ≥ 14 for 3 weeks) was observed for patients taking Prozac compared to those on placebo.

Weekly dosing for maintenance/continuation treatment: A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded (defined as having a modified HAMD-17 score of ≤ 9 , a CGI-Severity rating of ≤ 2 , and no longer meeting criteria for major depressive disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with Prozac 20 mg once-daily. These patients were randomized to double-blind, once-weekly continuation treatment with Prozac Weekly, Prozac 20 mg once-daily, or placebo. Prozac Weekly once-weekly and Prozac 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared to placebo for a period of 25 weeks. However, the equivalence of these two treatments during continuation therapy has not been established.

*Obsessive Compulsive Disorder--*The effectiveness of Prozac for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once a day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. While there was no indication of a dose response relationship for effectiveness in Study 1, a dose response relationship was observed in Study 2, with numerically better responses in the two higher dose groups. The following table provides

the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined:

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies				
Outcome Classification	Placebo	Prozac		
		20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No Change	64%	41%	33%	29%
Minimally Improved	17%	23%	28%	24%
Much Improved	8%	28%	27%	28%
Very Much Improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Bulimia Nervosa--The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a day) or placebo. Patients in these three studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these three studies, Prozac 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg vs placebo was present as early as Week 1 and persisted throughout each study. The Prozac related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between Prozac 60 mg, and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

In a longer-term trial, 150 patients meeting (DSM-IV) criteria for bulimia nervosa, purging subtype, who had responded during a single-blind, 8-week acute treatment phase with Prozac 60 mg/day, were randomized to continuation of Prozac 60 mg/day or placebo, for up to 52 weeks of observation for relapse. Response during the single-blind phase was defined by having achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during the double-blind phase was defined as a persistent return to baseline vomiting frequency or physician judgement that the patient had relapsed. Patients receiving continued Prozac 60 mg/day experienced a significantly

longer time to relapse over the subsequent 52 weeks compared with those receiving placebo.

Panic Disorder—The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.

Study 1 (N = 180 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 42% vs. 28%, respectively.

Study 2 (N = 214 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percent of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% vs. 44%, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder--Prozac is indicated for the treatment of major depressive disorder. The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (see Clinical Trials *under* CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.

The efficacy of Prozac 20 mg once-daily in maintaining a response in major depressive disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving Prozac for extended periods should be reevaluated periodically (see Clinical Trials *under* CLINICAL PHARMACOLOGY).

The efficacy of Prozac Weekly once-weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection from relapse as that

provided by Prozac 20 mg daily (see Clinical Trials under CLINICAL PHARMACOLOGY).

The usefulness of the drug in patients receiving fluoxetine for extended periods should be reevaluated periodically.

Obsessive-Compulsive Disorder--Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bulimia Nervosa--Prozac is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa.

The efficacy of Prozac was established in 8 to 16 week trials for adult outpatients with moderate to severe bulimia nervosa, i.e., at least three bulimic episodes per week for 6 months (see Clinical Trials under CLINICAL PHARMACOLOGY).

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (see Clinical Trials under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder—Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see Clinical Trials under CLINICAL PHARMACOLOGY).

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 or more of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) fear of losing control; 10) fear of dying; 11) paresthesias (numbness or tingling sensations); 12) chills or hot flashes.

The effectiveness of Prozac in long-term use, that is, for more than 12 weeks, has not been established in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Prozac is contraindicated in patients known to be hypersensitive to it.

Monoamine Oxidase Inhibitors--There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY]) should be allowed after stopping Prozac before starting an MAOI.

Thioridazine—Thioridazine should not be administered with Prozac or within a minimum of 5 weeks after Prozac has been discontinued (see WARNINGS).

WARNINGS

Rash and Possibly Allergic Events--In US fluoxetine clinical trials as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Potential Interaction with Thioridazine—In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450IID6 isozyme activity. Thus, this study suggests that drugs which inhibit P450IID6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (see PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (see CONTRAINDICATIONS).

PRECAUTIONS

General

Anxiety and Insomnia--In US placebo-controlled clinical trials for major depressive disorder, 12% to 16% of patients treated with Prozac and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo.

Anxiety and nervousness were reported respectively in 15% and 11% of patients treated with Prozac 60 mg, and in 9% and 5% of patients treated with placebo.

Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (see Table 3, below).

Altered Appetite and Weight--Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with Prozac.

In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss.

In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with Prozac because of anorexia.

In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac, 60 mg, and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with Prozac, 60 mg, on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

Activation of Mania/Hypomania--In US placebo-controlled clinical trials for major depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of major depressive disorder.

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with Prozac and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania.

Seizures--In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Prozac should be introduced with care in patients with a history of seizures.

Suicide--The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between both OCD and major depressive disorder and bulimia and major depressive disorder, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD or bulimia.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites--Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Use in Patients With Concomitant Illness--Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (see Renal Disease under CLINICAL PHARMACOLOGY). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (see DOSAGE AND ADMINISTRATION).

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference With Cognitive and Motor Performance--Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients--Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests--There are no specific laboratory tests recommended.

Drug Interactions--As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY*).

Drugs Metabolized by P450IID6--Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the four active enantiomers is comparable between poor and extensive metabolizers (*see Variability in Metabolism under CLINICAL PHARMACOLOGY*).

Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (*see list below*), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see CONTRAINDICATIONS and WARNINGS*).

Drugs Metabolized by Cytochrome P450IIIA4--In an in vivo interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P450IIIA4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of P450IIIA4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of cytochrome P450IIIA4 activity is not likely to be of clinical significance.

CNS Active Drugs--The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly

administered drugs, using conservative titration schedules, and monitoring of clinical status (*see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY*).

Anticonvulsants--Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics--Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between serotonin specific reuptake inhibitors (SSRIs) and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia. For thioridazine, see CONTRAINDICATIONS and WARNINGS.

Benzodiazepines--The half-life of concurrently administered diazepam may be prolonged in some patients (*see Accumulation and Slow Elimination under Clinical Pharmacology*). Co-administration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Lithium--There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Tryptophan--Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors--*See CONTRAINDICATIONS.*

Other Drugs Effective in the Treatment of Major Depressive Disorder--In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY*, and *Drugs Metabolized by P450IID6 under Drug Interactions*).

Sumatriptan—There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

Potential Effects of Co-administration of Drugs Tightly Bound to Plasma Proteins--Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (*see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY*).

Warfarin--Altered anti-coagulant effects, including increased bleeding, have been reported when fluoxetine is co-administered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Electroconvulsive Therapy--There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility--There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

Carcinogenicity--The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose [MRHD] of 80 mg on a mg/m² basis), produced no evidence of carcinogenicity.

Mutagenicity--Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility--Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m² basis) indicated that fluoxetine had no adverse effects on fertility.

Pregnancy--Pregnancy Category C: In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the maximum recommended human dose [MRHD] of 80 mg on a mg/m² basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m² basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m² basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis). Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery--The effect of Prozac on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers--Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Pediatric Use--Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—U.S. fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients ≥ 65 years of age and 93 patients ≥ 75 years of age. The efficacy in geriatric patients has been established (see Clinical Trials under CLINICAL PHARMACOLOGY). For pharmacokinetic information in geriatric patients see Age under CLINICAL PHARMACOLOGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under PRECAUTIONS).

Hyponatremia--Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥ 60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Platelet Function--There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

ADVERSE REACTIONS

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical

trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials (excluding data from extensions of trials)--Table 1 enumerates the most common treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for Prozac and at least twice that for placebo within at least one of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US and non-US controlled trials. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who participated in US controlled clinical trials comparing Prozac with placebo in the treatment of major depressive disorder, OCD, or bulimia. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 1
MOST COMMON TREATMENT-EMERGENT
ADVERSE EVENTS: INCIDENCE IN US MAJOR DEPRESSIVE DISORDER,
OCD, BULIMIA AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL
TRIALS

	Percentage of patients reporting event							
	Major Depressive Disorder		OCD		Bulimia		Panic	
Body System/ Adverse Event	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2

Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence†	2	--	--	--	7	--	1	--
Abnormal ejaculation†	--	--	7	--	7	--	2	1

*Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

†Denominator used was for males only (N = 690 Prozac major depressive disorder; N = 410 placebo major depressive disorder; N = 116 Prozac OCD; N = 43 placebo OCD; N = 14 Prozac bulimia; N = 1 placebo bulimia; N = 162 Prozac panic; N = 121 placebo panic).

--Incidence less than 1%.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS:
INCIDENCE IN MAJOR DEPRESSIVE DISORDER, OCD, BULIMIA, and PANIC
DISORDER PLACEBO-CONTROLLED
CLINICAL TRIALS*

	Percentage of patients reporting event Major Depressive Disorder, OCD, bulimia, and panic disorder combined	
Body System/ Adverse Event†	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6

Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	—1
Thinking Abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	87	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	32	1

*Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

†Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo $\geq$ Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain/cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.

--Incidence less than 1%.

Associated with Discontinuation in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials)--Table 3 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH
DISCONTINUATION IN US MAJOR DEPRESSIVE DISORDER, OCD, BULIMIA
AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL TRIALS

Major Depressive Disorder, OCD, bulimia, and panic disorder combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic disorder (N=425)
--Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

*Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Events Observed in Prozac Weekly Clinical Trials—Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% vs. 3%, respectively) or taking Prozac 20 mg daily (10% vs. 5%, respectively).

Male and Female Sexual Dysfunction with SSRIs--Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to

underestimate their actual incidence. In patients enrolled in US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Events Observed In Clinical Trials--Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient treated with Prozac and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole--*Frequent*: chest pain, chills; *Infrequent*: chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare*: abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome*, photosensitivity reaction.

Cardiovascular System--*Frequent*: hemorrhage, hypertension, palpitation; *Infrequent*: angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare*: atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System--*Frequent*: increased appetite, nausea and vomiting; *Infrequent*: aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare*: biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System--*Infrequent*: hypothyroidism; *Rare*: diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System--*Infrequent*: anemia, ecchymosis; *Rare*: blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional--*Frequent*: weight gain; *Infrequent*: dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare*: alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System--*Infrequent*: arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare*: arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System--*Frequent*: agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent*: abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder†, psychosis, vertigo; *Rare*: abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System--*Infrequent*: asthma, epistaxis, hiccup, hyperventilation; *Rare*: apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages--*Infrequent*: acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare*: furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses--*Frequent*: ear pain, taste perversion, tinnitus; *Infrequent*: conjunctivitis, dry eyes, mydriasis, photophobia; *Rare*: blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System--*Frequent*: urinary frequency; *Infrequent*: abortion‡, albuminuria, amenorrhea‡, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation‡, fibrocystic breast‡, hematuria, leukorrhea‡, menorrhagia‡, metrorrhagia‡, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage‡; *Rare*: breast engorgement, glycosuria, hypomenorrhea‡, kidney pain, oliguria, priapism‡, uterine hemorrhage‡, uterine fibroids enlarged‡.

*Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.

† Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

‡ Adjusted for gender

Postintroduction Reports-- Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia

(including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class--Prozac is not a controlled substance.

Physical and Psychological Dependence--Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdose were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all six overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience--Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among six dogs purposely overdosed with oral fluoxetine, five experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see Management of Overdose*).

Management of Overdose--Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see Other Drugs Effective in the Treatment of Major Depressive Disorder under PRECAUTIONS*).

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION

Major Depressive Disorder--

Initial Treatment—

Adult--In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 mg to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see Liver Disease and Renal Disease under CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness under PRECAUTIONS*).

Maintenance/Continuation/Extended Treatment--It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing--Systematic evaluation of Prozac has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see Clinical Trials under CLINICAL PHARMACOLOGY*).

Weekly Dosing--Systematic evaluation of Prozac Weekly has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once-daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established. (*see Clinical Trials under CLINICAL PHARMACOLOGY*).

Weekly dosing with Prozac Weekly capsule is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (see CLINICAL PHARMACOLOGY).

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (see Clinical Trials *under* CLINICAL PHARMACOLOGY).

Obsessive-Compulsive Disorder--

Initial Treatment--In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (see Clinical Trials *under* CLINICAL PHARMACOLOGY). In one of these studies, no dose response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (i.e., morning) or b.i.d. schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended, however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see Liver Disease and Renal Disease *under* CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment--While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa--

Initial Treatment--In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (see Clinical Trials *under* CLINICAL PHARMACOLOGY). Only the 60 mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see Liver Disease and Renal Disease under CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness under PRECAUTIONS*).

Maintenance/Continuation Treatment-- Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (*see Clinical Trials under CLINICAL PHARMACOLOGY*). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Switching Patients to a Tricyclic Antidepressant (TCA):

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is co-administered or has been recently discontinued (*see Other Drugs Effective in the Treatment of Major Depressive Disorder under Drug Interactions*).

Switching Patients to or from a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Prozac before starting an MAOI (*see CONTRAINDICATIONS and PRECAUTIONS*).

Panic Disorder—

Initial Treatment—In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see Clinical Trials under CLINICAL PHARMACOLOGY*). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see Geriatric Use under PRECAUTIONS*), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see Liver Disease and Renal Disease under CLINICAL PHARMACOLOGY, and Use in Patients with Concomitant Illness under PRECAUTIONS*).

Maintenance/Continuation Treatment—While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition

and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

The following products are manufactured by Eli Lilly and Company for Dista Products Company.

Prozac® Pulvules®, USP, are available in:

The 10 mg* Pulvule is opaque green and green, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104**) - Bottles of 100

NDC 0777-3104-07 (PU3104**) - Bottles of 2000

NDC 0777-3104-82 (PU3104**) - 20 FlexPak™§ blister cards of 31

The 20 mg* Pulvule is an opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105**) - Bottles of 30

NDC 0777-3105-02 (PU3105**) - Bottles of 100

NDC 0777-3105-07 (PU3105**) - Bottles of 2000

NDC 0777-3105-33 (PU3105**) - (ID†100) Blisters

NDC 0777-3105-82 (PU3105**) - 20 FlexPak™§ blister cards of 31

The 40 mg* Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107**) – Bottles of 30

Liquid, Oral Solution is available in:

20 mg* per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120‡) - Bottles of 120 mL

The following products are manufactured and distributed by Eli Lilly and Company.

Prozac® Tablets are available in:

The 10 mg* tablet is green, elliptical shaped, and scored, with PROZAC 10 debossed on opposite side of score.

NDC 0002-4006-30 (TA4006) - Bottles of 30

NDC 0002-4006-02 (TA4006) - Bottles of 100

Prozac Weekly™ Capsules are available in:

The 90 mg* capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with "Lilly" on the cap, and "3004" and "90 mg" on the body.

NDC 0002-3004-75 (PU3004) – Blister package of 4

NDC 0002-3004-99 (PU3004) – Blister package of 12

*Fluoxetine base equivalent.

**Protect from light.

†Identi-Dose® (unit dose medication, Lilly).

‡Dispense in a tight, light-resistant container.

§FlexPak™ (flexible blister card, Lilly).

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

ANIMAL TOXICOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

Rx only

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Indianapolis, IN 46285, USA

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M

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

DATE: May 30, 2002

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

SUBJECT: Recommendation for Approval Action for
Prozac pulvules, oral solution, and tablets (fluoxetine) for the longer-term treatment of
bulimia

TO: File NDAs 18-936/S-065; 20-101/S-027; 20-974/S-011
[**Note:** This overview should be filed with the 2-27-02 response to our 12-20-01
approvable letter.]

In our 12-20-01 approvable letter, we requested several changes in labeling, and also: (1) foreign labeling, (2) a safety update to include postmarketing events, and (3) a literature update. The 2-27-02 submission adequately responded to these requests. Lilly agreed to our proposed labeling, with the exception of several very minor editorial changes, which are acceptable. Dr. Hearst has reviewed the other materials submitted, and concluded that no important new safety information that would impact on labeling was revealed. I agree. Thus, I recommend that this supplement can now be approved, with our mutually agreed upon labeling.

cc:
Orig NDA 20-415/S-009
HFD-120
HFD-120/TLaughren/RKatz/RGlass/PDavid

DOC: MMBULLT.AP1

Appears This Way on Original

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

/s/

Thomas Laughren
5/30/02 04:07:54 PM
MEDICAL OFFICER

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

DATE: December 10, 2001

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

SUBJECT: Recommendation for Approvable Action for
Prozac pulvules, oral solution, and tablets (fluoxetine) for the longer-term treatment of
bulimia

TO: File NDAs 18-936/S-065; 20-101/S-027; 20-974/S-011
[**Note:** This overview should be filed with the 2-22-01
original submissions.]

1.0 BACKGROUND

Prozac is currently approved and marketed for depression, OCD, and bulimia. These supplements provide data in support of a new claim for the three formulations of Prozac in the longer-term treatment of bulimia, at a dose of 60 mg/day. Prozac is the only drug approved for the treatment of bulimia. Since bulimia is a chronic condition requiring long-term treatment, the question of long-term efficacy of Prozac in this condition is clinically relevant.

We did not have any meetings or correspondence with Lilly regarding their program for obtaining longer-term efficacy data for the bulimia indication.

Since the proposal is to use the currently approved Prozac formulations, there was no need for chemistry, pharmacology, or biopharmaceutic reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Roberta Glass, M.D., from the clinical group. Yeh-Fong Chen, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The study supporting this supplement was conducted under IND 12,274. The original supplements for this expanded indication were submitted 2-22-01.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

As Prozac is already marketed, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Prozac is already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Prozac is already marketed, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Study HCIE

Results from study HCIE were submitted in support of this claim for the longer-term efficacy of Prozac in bulimia. This 16 center, US study began with a 1-2 week screening period to select patients meeting minimum baseline criteria for bulimia nervosa, purging subtype (DSM-IV) to enter an 8 week open Prozac 60 mg/day treatment period (n=232 received Prozac in this phase). Responders were selected from this phase (n=150) for randomization, where response was defined as a decrease of $\geq 50\%$ in vomiting frequency during 1 of the 2 weeks prior to randomization, compared to baseline. Randomization of these n=150 responders was either to continuation on Prozac 60 mg/day or to placebo, for the 52 week double-blind discontinuation phase (n=76 for Prozac and n=74 for placebo). The primary endpoints were time to relapse and relapse rate, at 52 weeks, where relapse was defined as a return to the baseline frequency of vomiting for two consecutive diary periods (4-10 days each). Time to relapse was defined as the number of days from the patient's randomization date to the date the patient met criteria for relapse or the date the patient was discontinued due to the physician's judgement that the patient had relapsed. There were 8 secondary outcomes. The primary analysis for relapse rate was CMH, and log-rank test for time to relapse.

Patients in study HCIE were roughly 98% female, mostly Caucasian, and the mean age was roughly 30 years.

There was a high overall rate of discontinuation prior to reaching the 52 week nominal endpoint, as follows:

Prozac:	63/76 (83%)
Placebo:	68/74 (92%)

The cumulative rates of discontinuation at 52 weeks due to relapse as defined in the protocol were as follows:

Prozac:	33%
Placebo:	51% p=0.32

However, the analysis of time to relapse was significant in favor of Prozac ($p=0.016$). [Note: The criterion p-value would be 0.025, given the most conservative bonferroni correction for the 2 primary endpoints.] Dr. Chen performed an additional analysis of time to all cause discontinuation (i.e., relapse plus any other reason for leaving early) before reaching 52 weeks, and this analysis even more strongly favored Prozac over placebo ($p=0.0002$).

All of the secondary outcomes, with the exception of the HAMD-17 total score, including frequency of binge eating, frequency of vomiting, CGI-S, Eating Disorder Inventory total score, and Yale-Brown-Cornell Eating Disorder Scale total score also statistically favored Prozac over placebo.

The sample was too homogeneous to do meaningful subgroup analyses.

Comment: While this study was positive on only 1 of the 2 specified primary outcomes, it was positive on time to relapse, the outcome that we usually accept as a basis for declaring studies of this design positive. Both Drs. Glass and Chen considered this a positive study in support of a claim of long-term efficacy for Prozac in bulimia, and I agree. I also agree with Dr. Glass' (b) (4)

5.1.2 Conclusions Regarding Efficacy Data

Study HCIE demonstrated a benefit of Prozac over placebo for the maintenance of response in patients with bulimia who demonstrated a response during an initial 8 week open label treatment period and were then observed for relapse during a 52-week followup period.

5.2 Safety Data

Dr. Glass' safety review of this supplement was based on n=232 patients who received Prozac in study HCIE. All patients received a dose of 60 mg/day. There were no unexpected safety findings among these patients, and no basis for changes in the labeling for Prozac from the standpoint of safety.

5.3 Clinical Sections of Labeling

We have modified the language in the 3 sections of labeling in which the sponsor has proposed changes, i.e., Clinical Trials, Indications, and Dosage and Administration. We have also added language changing the focus of the claim for this drug from "depression" to "major depressive disorder," as part of a class action for the antidepressant drugs approved within the last 15 years.

6.0 WORLD LITERATURE

To my knowledge, there was no pertinent literature to be reviewed.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Prozac is not approved for the longer-term treatment of bulimia anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we did not take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

9.0 DSI INSPECTIONS

Two sites from study HCIE were inspected, and data from both sites were judged to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling Attached to Approvable Package

Our proposed labeling for this new claim is included in the approvable letter.

10.2 Foreign Labeling

To my knowledge, Prozac is not approved for the longer-term treatment of bulimia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes our proposed labeling for this supplement.

11.0 PEDIATRIC RULE

Bulimia is generally viewed as a disorder having its onset in late adolescence or early adulthood. Dr. Glass has recommended that no pediatric testing of fluoxetine for bulimia is indicated at this time, and I agree. Nevertheless, we will include the standard language requesting the sponsor to justify a waiver.

12.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that Prozac is effective and acceptably safe in the longer-term treatment of bulimia. I recommend that we issue the attached approvable letter with our proposed labeling language for this expanded claim.

cc:

Orig NDA 20-415/S-009

HFD-120

HFD-120/TLaughren/RKatz/RGlass/PDavid

DOC: MMBULLT.AE1

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

/s/

Thomas Laughren
12/10/01 08:09:47 AM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 18-936, 20-101, 20-974
Sponsor: Lilly
Generic Name fluoxetine
Trade Name Prozac
Material Reviewed: Labeling submissions for bulimia relapse (S-065), PD indication (S-061), and the pediatric indication (S-064, MDD changes only)
Clinical Reviewer: Earl D. Hearst, M.D.

I. Review:

We have received a copy of Lilly's labeling incorporating the bulimia relapse, PD indication, and the pediatric indication (MDD changes).

Lilly agrees to the draft labeling contained in the FDA approvable letter for bulimia. The only changes are two minor editorial corrections in the language proposed in the approvable letter and other minor editorial changes throughout to bring the labeling into conformance with current Lilly standards. In the Clinical Trials section, (b) (4)

The basis for this draft labeling is the current approved Prozac labeling based on the Agency letter of May 25, 2001. Finally, the changes requested in the Agency approvable letter of July 12, 2001 for supplemental application 18-936/S-064 concerning the terms "depression" and "antidepressant" also been implemented.

In addition Lilly has changed the label as requested in the Prozac for panic disorder letter.

Lilly has confirmed that the changes are, verbatim, as that contained in the Agency AE letters for bulimia relapse, PD indication, and the pediatric indication (MDD changes). I have reviewed the changes and agree that they are as requested. I will deal with bulimia submission in more detail later in this review as this contained a safety update.

Foreign labeling: As requested in the approvable letter, Attachment 2 contains the Clinical Particulars sections of European Summary of Product Characteristics for 16 EU member states. The sponsor notes that (b) (4)

Thus, specific reference to this study and its results will not be found in these SPCs or other foreign labeling for fluoxetine.

Postmarketing adverse events: Contained in Attachment 3 is a report that contains the methodology of search, a brief statement of results and conclusions, and tables comparing adverse event information for patients taking fluoxetine for bulimia versus those taking it for other indications. This report was prepared by Lilly's pharmacovigilance group and concludes that the pattern of adverse events in patients with bulimia is not substantially different from that in other patient populations and no labeling changes are warranted based on this analysis.

Literature update: Attachment 4 contains search methodology, a bibliography and copies of the relevant articles for bulimia relapse with fluoxetine.

A search of the available medical literature was conducted to compile a list of pertinent publications discussing bulimia relapse along with fluoxetine therapy. This search included the search terms fluoxetine and bulimia in conjunction with relapse, recurrence, or long-term. The search evaluated publications from 1974 into January of 2002 utilizing the following databases: Embase, MEDLINE (combined representing 4900 biomedical journals), Derwent Drug Files (representing 1200 pharmaceutical journals), BIOSIS Previews (representing 6000 life sciences journals), PsychInfo (representing 1300 psychiatric journals), and SciSearch (representing approximately 5600 science, technology, and medical journals).

17 studies have been provided. I do not see any study that would affect the current labeling for Prozac.

DISTRIBUTION: Attachment 5 contains a summary of quantity of fluoxetine distributed in the US and foreign markets for the period December 1 2000 through November 2001, by product (pulvules, liquid, and tablets). This information is identical to that which will be provided in the fluoxetine annual report

for this period and is similar to that provided in annual reports for other years. Lilly does not track this use by indication.

Promotional Materials: Lilly does not plan to prepare promotional materials concerning the use of fluoxetine in bulimia, including the results of the study in relapse prevention. Thus, they feel there is nothing to submit to the Division or to the Division of Drug Marketing, Advertising, and Communications with regard to this supplement.

INTRODUCTION POSTMARKETING ADVERSE EVENTS

This report has been done in order to provide the FDA with a post-marketing review of adverse events reported in patients treated with fluoxetine for bulimia.

The report provides a cumulative review of all fluoxetine spontaneous adverse events, where the indication for use of fluoxetine has been reported as "bulimia" or "bulimia nervosa" in the Lilly global safety database from launch and up to a cut-off date of 15th January 2002. In addition, the report provides a comparison of adverse events reported in patients treated for bulimia with all other patients reported in the Lilly safety database.

Methodology

Spontaneous Adverse Event Data Sources

The Lilly Safety Database (b) (4) is a computerized safety database, implemented in 1998, but containing data from 1983, for the world-wide collection, storage and reporting of adverse events involving Lilly products. It includes serious and non-serious events reported spontaneously from post-marketing experience (including literature and regulatory reports) and clinical trial events described as "serious". The term "serious" refers to any adverse event that results in death, is life-threatening, is permanently or severely disabling, requires or prolongs inpatient hospitalization, results in congenital anomaly or is significant for any other reason.

Eli Lilly and Company have now changed to MedDRA Coding Dictionary Version 4.0. In this process Lilly has retrospectively re-coded all adverse events in the (b) (4) database to reflect a current MedDRA term. Some medical terms that do not exist in COST ART are available in MedDRA. Therefore, direct comparison with previous pharmacovigilance reviews performed in COSTART dictionary is not appropriate.

Database Search Criteria

The (b) (4) safety database was searched for all fluoxetine reports (spontaneous, clinical trial and post-marketing studies) in patients where the indication for fluoxetine were reported as bulimia to a cut-off date of 15th January 2002. Furthermore, the database was searched for adverse events occurring in all other patients.

The rate of adverse events for each MedDRA Preferred Term (PT) occurring in bulimia patients was compared to the rate of adverse events occurring in all other patients. Adverse event reports with unknown indication were excluded as these reports may have concerned bulimic patients. Finally, the ratio of adverse events occurring in bulimic patients to adverse events occurring in all other patients was calculated.

RESULTS

The search identified 742 adverse event reports associated with the use of fluoxetine in bulimic patients. There were 1442 adverse events reported in these 742 case reports. A line listing of these 742 adverse event reports are presented in Appendix 1.

A total of 166535 adverse events were identified for patients treated for all other indications than bulimia.

The number and rate of adverse events by MedDRA PT reported in patients treated with fluoxetine for bulimia and patients treated for all other indications are presented in appendix 2. In addition, the ratio of adverse events in bulimic patients to adverse events in patients with all other indications has also been presented.

Table 1 lists the MedDRA PTs that were reported with a ratio of bulimia to all other indications of greater than 1.00 and where the absolute relative rate of adverse events among bulimic patients were higher than 1.0%.

All other adverse events reported in bulimic patients have a absolute relative rate of less than 1.0 percent.

Table 1: MedDRA PTs Reported within bulimic patient of Greater than Reported in patients with other indications and an Absolute Rate $\geq 1.0\%$

MedDRA PT	Rate of Event within bulimic patients		Rate of Event within patients of all other indication		Ratio of bulimic patients to all other patients
	No.	%	No.	%	
Pregnancy NOS	45	3.12	2009	1.20	2.59
Rash NOS*	42	2.91	3982	2.39	1.22
Overdose NOS*	39	2.70	2045	1.23	2.20
Headache NOS	32	2.21	3488	2.09	1.08
Urticaria NOS*	24	1.66	1914	1.15	1.45
Convulsions NOS	20	1.39	1427	0.86	1.62
Weight increased NOS*	20	1.39	1833	1.16	1.19
Fatigue NOS*	19	1.31	1846	0.99	1.33
Pruritus NOS*	18	1.25	2011	1.21	1.03
Contusion*	17	1.18	470	0.28	4.18
Unintended pregnancy	16	1.11	1209	0.72	1.52
Arthralgia*	15	1.04	1317	0.79	1.31
Sweating increased*	15	1.04	1661	0.10	1.04

*Listed reaction according to fluoxetine labelling

All the MedDRA PTs included in table 1 with the exception of "pregnancy NOS", "overdose NOS" and "contusion" have been reported in bulimic patients with less than twice the rate of that reported in patients of all other indications. These events were reported proportionally higher in bulimic patients. However, the total number of adverse event_for each of these terms was relatively low. Therefore, the sponsor feels no conclusion can be drawn on the basis of these results.

The majority of events listed in Table 1 are listed adverse reactions according to the current fluoxetine labeling with the exception of "pregnancy NOS", "headache NOS", "convulsions NOS" and "unintended pregnancy".

I do not see any additional safety events which would effect the labeling.

II. Recommendation:

The safety update for bulimia does not materially effect the labeling. I recommend the labeling submitted be accepted for bulimia relapse prevwntion, PD indication, and the pediatric indication (MDD changes).

Earl D. Hearst, M.D.

Medical Reviewer

HFD_120

CC:file, tlaughren,ehearst,pdavid

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

/s/

Earl Hearst
5/29/02 02:35:03 PM
MEDICAL OFFICER

Thomas Laughren
5/30/02 01:07:06 PM
MEDICAL OFFICER
I agree that these supplements can now be approved.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION

NDA 18-936/SE8-065 (pulvule)
20-101/SE8-027 (oral solution)
20-974 (b) (4) (tablet)
Sponsor: Eli Lilly and Company
Date Submitted: February 22, 2001
User Fee Date: December 22, 2001

DRUG NAME

Generic Name: fluoxetine hydrochloride
Trade Name: Prozac[®]

DRUG CATEGORIZATION

Pharmacological Class: Selective Serotonin Reuptake Inhibitor
Proposed Indication: Bulimia, relapse prevention
Dosage Forms: 10 mg, 20 mg, 40 mg Pulvule
10 mg Tablet
20 mg/5 mL oral solution

REVIEWER INFORMATION

Medical Officer: Roberta L. Glass, M.D.
Review Completion Date: November 19, 2001

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

The current submission describes a placebo controlled 52 week relapse prevention study comparing the treatment of Prozac® (fluoxetine) and placebo in patients with bulimia nervosa who previously responded to Prozac® in an 8 week open label study. Although the sponsor was unable to demonstrate statistical significance for both identified primary efficacy variables (i.e. time to relapse & rate of relapse), the more important efficacy variable of time to relapse demonstrated statistical significance when comparing a Prozac® (fluoxetine) and placebo treatment group in this 52 week relapse prevention study. Because the time to relapse is clinically a more sensitive measure of altering the course of the illness of bulimia nervosa, (b) (4)

B. Recommendation on Phase 4 Studies and Risk Management Steps

Because bulimia nervosa often presents as a chronic illness, it would be beneficial for the sponsor to monitor the safety profile of Prozac® (fluoxetine) for a period of time beyond one year. Although there is no evidence to suggest cardiovascular difficulties in the short term acute studies, it would be reassuring to examine any long term effects on cardiovascular function with the long term use of Prozac® (fluoxetine); this is recommended in light of the fact that the sponsor did not monitor ECGs during this year long study.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Prozac® (fluoxetine), a selective serotonin reuptake inhibitor, is currently labeled for the indications of depression, obsessive compulsive disorder and bulimia nervosa. Formulations of Prozac® (fluoxetine) currently available are a pulvule (10 mg, 20 mg, 40 mg), a tablet (10 mg), and an oral solution (20 mg/5 mL). Because the labeling describes only a 16 week study for the maintenance/continuation treatment for bulimia nervosa, the sponsor was interested in expanding their claim of relapse prevention, and, thus, submitted the current supplement describing a 52 week placebo controlled relapse prevention study. There were 232 patients enrolled in the acute open label phase of the study. The 150 patients determined to be responders at the end of the acute phase were randomized to the 52 week relapse prevention phase (n=76 for the Prozac® treatment group). This NDA supplement incorporates a total exposure of Prozac® (fluoxetine) for up to approximately 48 patient years.

B. Efficacy

Efficacy for the use of Prozac® (fluoxetine) for the treatment of relapse prevention of bulimia nervosa was supported by the one pivotal study HCIE. Study HCIE began with an 8 week open label portion, of which responders were then randomized into a placebo controlled 52 week relapse prevention study. The two primary efficacy variables identified were the time to relapse and the relapse rate.

The sponsor was able to demonstrate statistical significance for the efficacy variable of time to relapse ($p=0.016$ for a two sided test and $p=0.008$ using a one sided test). However, statistical significance was not demonstrated when comparing the relapse rate for the Prozac® and the placebo groups ($p=0.319$).

When considering the more important variable in affecting the course of illness, it would appear that time to relapse would be a more significant measure of efficacy than the absolute rate of relapse when comparing placebo and treatment groups. Because the time to relapse in the fluoxetine treatment group was

shown to be statistically significantly longer than the placebo group, there is evidence to support that fluoxetine is more effective than placebo in preventing relapse of symptoms of bulimia nervosa.

C. Safety

There were no deaths reported during this study. Adverse events which lead to withdrawal or were categorized as serious adverse events have been either previously reported in the labeling for Prozac (e.g. rash, seizure, hand tremor, nausea, hypertension), or a causal relationship is difficult to establish or is unlikely (e.g. suicide attempt, nervousness, anxiety, accidental injury, pelvic inflammatory disease, cervical carcinoma). Rhinitis was the only adverse event found to be statistically significantly observed with more frequency in the treatment group compared to placebo group, but this has been previously described in the labeling.

In conclusion, from the material submitted, there does not appear to be any unexpected events that have occurred during this study that have not been previously described in the labeling. At this time, there are no recommendations to amend the safety labeling for Prozac[®] (fluoxetine).

D. Dosing

All patients in the treatment group were administered 60 mg Prozac[®] (fluoxetine). This dose was chosen based on the acute trials in which efficacy for the treatment of bulimia was observed at a dose of 60 mg/day Prozac[®], but was not observed at a dose of 20 mg daily. It is unclear if a 40 mg Prozac[®] dosage would be effective in the treatment of bulimia nervosa.

E. Special Populations

The current labeling for Prozac[®] (fluoxetine) addresses pharmacokinetic differences in liver and renal disease, and the elderly population. There continues to be a need for testing of Prozac[®] (fluoxetine) for use in pregnancy. This becomes an issue with the population being treated for bulimia nervosa, as many of these patients are of childbearing potential.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

This NDA supplement proposes the use of Prozac® (fluoxetine), a selective serotonin uptake inhibitor, for treatment in the relapse prevention of bulimia. In the current labeling, the recommended dosage for the indication of bulimia is 60 mg/day, administered in the morning with optional titration up to that dose over several days. The current labeling establishes the safety and efficacy in 8-16 week trials for patients diagnosed with bulimia nervosa.

The proposed labeling changes would establish that efficacy and safety have been studied for (b) (4) a dose of 60 mg/day Prozac® (fluoxetine) for the treatment of bulimia nervosa.

B. State of Armamentarium for Indication (s)

At the current time, Prozac® (fluoxetine) is the only drug marketed for the indication of bulimia nervosa.

C. Important Milestones in Product Development

Prozac® (fluoxetine) was first approved for marketing in December 1987 as capsules and was later introduced as an oral solution (April, 1991), and tablets (March, 1999). The current labeling of Prozac® includes the indications of depression, obsessive compulsive disorder, and bulimia. The NDA supplement for bulimia was approved in November 1996 with supporting studies of 8-16 weeks duration.

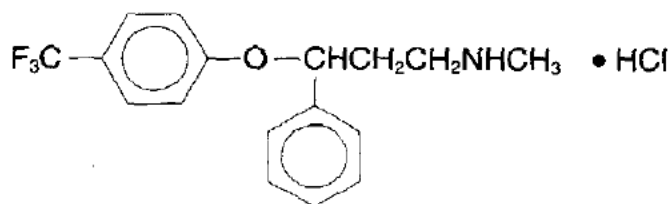
D. Other Relevant Information

Fluoxetine is also marketed under the trade name Sarafem® for the indication of premenstrual dysphoric syndrome.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

The chemical structure for fluoxetine hydrochloride (Prozac®) is:



Prozac® is manufactured as pulvules (10 mg, 20 and 40 mg), tablets (10 mg), and oral solution (20 mg/5 mL).

B. Animal Pharmacology and Toxicology

There were no new animal studies submitted with this NDA supplement.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Peak plasma concentrations of fluoxetine are observed after 6 to 8 hours. Food may delay its absorption, but does not appear to affect the systemic bioavailability of fluoxetine. Fluoxetine is metabolized in the liver to norfluoxetine and other unidentified metabolites. The primary route of elimination is hepatic with inactive metabolites excreted by the kidney. The elimination half-life for fluoxetine is 1 to 3 days after acute administration and 4 to 6 days after chronic administration. The active metabolite, norfluoxetine, has an elimination half-life of 4-16 days after acute and chronic administration.

B. Pharmacodynamics

Prozac[®] (fluoxetine hydrochloride) has been associated with the inhibition of CNS neuronal uptake of serotonin. Animal studies suggest that fluoxetine inhibits the reuptake of serotonin significantly more than reuptake of norepinephrine.

IV. Description of Clinical Data and Sources

The source of data in this review is the one clinical trial, **Protocol HCIE**, the 52 week placebo controlled relapse prevention study in patients with bulimia who were treatment responsive after eight weeks of open label treatment. Prozac[®] (fluoxetine hydrochloride) has previously been shown to be efficacious in the acute treatment of bulimia nervosa for which it is currently labeled.

V. Clinical Review Methods

A. How the Review was Conducted

There was only one study (Protocol HCIE) evaluated in this review for efficacy and safety of Prozac[®] for the treatment in preventing relapse of bulimia. Protocol HCIE began with an 8 week open label portion, of which responders were then randomized into a placebo controlled 52 week relapse prevention phase.

Individual case report forms were reviewed for the following patients: 010-1005, 002-213, 002-236, 003-308, 008-919, and 013-1305.

B. Overview of Materials Consulted in Review

The materials used in this review included the following:

Original NDA 18-936 (SE8-065) Submission: February 22, 2000

Response to information request: June 14, 2001

Statistical Review and Evaluation by Yeh-Fong Chen, Ph.D.

Clinical Inspection Summary by Ni A. Khin, M.D.: November 1, 2001

NDA #18-936, Supplement 4 Review for Bulimia Nervosa by Andrew Mosholder, M.D.: July 6, 1994

Review of Safety Update for Supplement 4 by Andrew Mosholder, M.D.: October 4, 1996

C. Overview of Methods Used to Evaluate Data Quality and Integrity

An inspection and audit of the data noted minor deficiencies of the informed consent process, and in areas of protocol deviations, drug accountability, data entry and record keeping. However, overall, the Division of Scientific Investigations recommended that the sponsor's data was acceptable based on an on-site investigation.

D. Evaluation of Financial Disclosure

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Acting Medical Director of the Prozac Product Team signed the Form 3454 testifying that, to her knowledge, there was no financial arrangement made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

VI. Integrated Review of Efficacy

A. Conclusions and Critical Differences from Sponsor's Proposed Label Claims

The sponsor identified two primary efficacy variables to assess in Protocol HCIE, the 52 week relapse prevention phase of the pivotal study. Statistical significance was demonstrated in the **time to relapse** when comparing the placebo and the fluoxetine treatment groups. No statistically significant difference was demonstrated in the **rate of relapse** between the fluoxetine and the placebo group. Of the two efficacy variables, it appears that the more important and sensitive measure of efficacy is the time to relapse; therefore, the data presented would support a claim of relapse prevention in the treatment of bulimia nervosa.

However, it should also be kept in mind that the 52 week trial was completed by only 13 (17%) of the fluoxetine group and 6 (8%) in the placebo group. Therefore, 131 (87.3 %) of the patients randomized had early withdrawals. (b) (4)

B. General Approach to Review of the Efficacy of the Drug

Protocol HCIE was the only study submitted for review for this NDA supplement to assess the effectiveness of fluoxetine in the long term treatment of relapse prevention in patients suffering with bulimia nervosa. For the purposes of efficacy, only the 52 week placebo controlled relapse prevention phase of Protocol HCIE are interpretable, as Period II is an acute open label portion, and Period I describes the wash out phase. The efficacy discussion will focus on the sponsor's two primary efficacy variables, namely, the time to relapse and the rate of relapse.

This review will refer to the statistical review of Yeh-Fong Chen, Ph.D., FDA statistician.

C. Detailed Review of Trial HCIE

Investigators/Location

Please refer to the Appendix A for details of the investigators and locations.

Study Plan

Objective(s)/Rationale

The primary objective of the study was to compare the safety and efficacy of fluoxetine 60 mg/day compared to placebo in preventing relapse over a 52 week period in patients diagnosed with bulimia nervosa, purging type, who responded to the 8 week open label acute therapy phase.

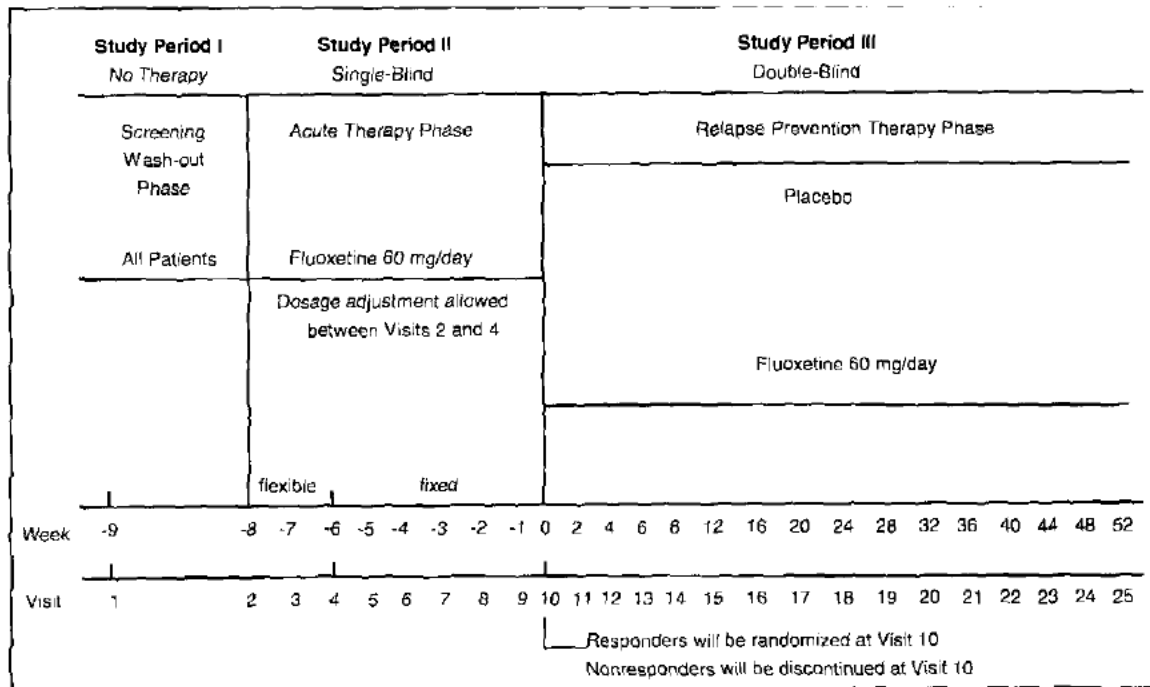
Population

Patients chosen for this study were physically healthy female or male outpatients ≥ 18 years old with a psychiatric diagnosis of bulimia nervosa, purging type according to DSM-IV. Excluded from the study were patients with comorbid schizophrenia, bipolar disorder, psychotic features, organic brain disease, and seizure disorder (seizure within the past year). Patients were not permitted to receive cognitive-behavioral therapy or any ongoing therapy during the study except for supportive psychotherapy. Other psychotropic medications were prohibited during the study, except for 1000 mg of chloral hydrate or up to 10 mg zolpidem tartrate daily, not to exceed 7 consecutive days.

Design

The following schematic from the sponsor's protocol summarizes the 3 periods of this study:

Figure 1: Sponsor's Schematic of Study HCIE



Study Period I was a screening and wash out phase. Screening included a history and physical, ECG and routine laboratory studies.

Study Period II was an 8 week, single blind acute phase with all patients receiving fluoxetine 60 mg/day. Vital signs and adverse events were monitored at the weekly visits. Dose adjustments were allowed between Visits 2-4. Patients who could not tolerate fluoxetine 60 mg/day were not permitted to proceed onto Study Period III. The dosing of fluoxetine 60 mg/day was chosen because this was the effective dose in reducing bulimic vomiting and binge eating in the acute trials.

Only **treatment responders** at the end of Study Period II were allowed to proceed to Study Period III. Treatment responders were defined as patients who had a decrease of at least 50 % in the frequency of

vomiting episodes during one of the 2 weeks prior to randomization (between Visits 8 and 9 or between Visits 9 and 10) compared to the baseline (Visit 2) frequency of vomiting.

Study Period III was a 52 week, double-blind, relapse prevention phase in which responders to fluoxetine 60 mg/day in Study Period II were randomly assigned to either fluoxetine 60 mg/day or placebo for 52 weeks. For the first 8 weeks of this period, patients were assessed every 2 weeks, and for the remainder of the study, assessments were to take place at 4 week intervals. Vital signs and adverse events were monitored at each visit. Please refer to Appendix B for the sponsor's schedule of events.

Analysis Plan

The primary focus of analysis for this study was data collected during Study Period III. The two primary efficacy variables were identified as the **time to relapse** and the **relapse rate**. The original protocol describes a comparison of the two estimated time-to-relapse distributions using a log-rank test (with a one-sided significance level of 0.05). To compare 12 month relapse rates between the fluoxetine and the placebo groups, the sponsor was to use the Cochran-Mantel-Haenszel tests. However, the FDA statistical review by Yeh-Fong Chen, Ph.D., suggested that, because the sponsor chose to have two primary efficacy variables, it would be more appropriate to use either a two-sided test of significant level of 0.05 or a one-sided test of significant level of 0.25. Also, it was suggested that an adjustment for the multiplicity should also be made.

Relapse was defined as patients who: 1) return to baseline (Visit 2) frequency of vomiting for one diary period (4-10 days), and 2) have a persistence of baseline frequency of vomiting for 2 consecutive diary periods. The investigator had the discretion to discontinue a patient after one diary period of relapse, but the patient must withdraw after two consecutive periods of relapse.

Time to relapse was defined as the number of days from the patient's randomization date to the date that the patient either met criteria for relapse or the date the patient discontinued due to relapse as decided by investigator discretion.

Secondary efficacy variables included the Clinical Global Impressions-Severity (CGI-S), Clinical Global Impressions-Improvement (CGI-I), Patient Global Impression (PGI), Eating Disorder Inventory (EDI), the 17-Item Hamilton Rating Scale for Depression (HAM_{D17}), and the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 265 patients screened, 233 patients entered Part II of the study in which they received the single-blind treatment with fluoxetine 60 mg daily. There were 150 (64.7 %) patients who were considered to be treatment responders during Part II and who were randomized to either treatment with fluoxetine (n=76) or placebo (n=74) for Part III of the study. The study was completed by 19 (12.7 %) patients; more specifically, 13 (17%) of the fluoxetine group and 6 (8%) in the placebo group completed the study. Therefore, 131 (87.3 %) of the patients randomized had early withdrawals.

Demographics /Group Comparability

The majority of patients participating in Part III, the placebo controlled portion of the study, were Caucasian females. Both treatment groups appeared to have comparable demographics. Tobacco and alcohol use for both groups was also comparable. The following table summarizes the demographics of patients randomized to Part III:

Table 1: Summary of Demographics for Part III of Protocol HCIE

	FLUOXETINE (N=76)	PLACEBO (N=74)
Female	74 (97.4%)	73 (98.6%)
Male	2 (2.6)	1 (1.4)
Afro-American	3 (3.9)	2 (2.7)
Caucasian	71 (93.4)	65 (87.8)
Hispanic	2 (2.6)	4 (5.4)
Asian	1 (1.4)	1 (0.7)
Other	0	2 (2.7)
Mean Age	29.5 ± 6.98	30.0 ± 9.25
Median Age	27.8	27.29

The sponsor also characterized the study population according to psychiatric history. The mean age of experiencing the first binge-eating episode was 18.2 years, and the first purge episode at a mean age of 19.0 years. Patients were actually diagnosed as having an eating disorder at the average age of 25 years old. Approximately 16 % of patients were hospitalized for an eating disorder and 27.3% were diagnosed with anorexia nervosa. There were no statistically significant differences between the two treatment groups regarding psychiatric history. The following table further summarizes differences in psychiatric history of the two treatment groups in Part III of this study:

Table 2 Summary of Psychiatric History of Eating Disorder

	FLUOXETINE (N=76)	PLACEBO (N=74)
Mean Age of 1 st binge	18.59 ± 4.54	17.88 ± 5.56
Mean Age of 1 st purge	18.61 ± 4.76	19.35 ± 6.06
Mean age 1 st diagnosed bulimic	25.25 ± 7.65	26.28 ± 9.3
Mean age 1 st diagnosed with eating disorder	24.83 ± 7.61	25.74 ± 9.63

Baseline values for Part III, the placebo controlled relapse prevention phase, was established to be the scores at the end of Part II (Visit 10). At Visit 10, the mean frequency of binge-eating and vomiting episodes was 3.4 and 4.3, respectively. The median CGI-S had a range from 1 (not ill) to 5 (markedly ill) indicating patients on average exhibited a mildly ill condition. The mean HAMD Total score was 5.3 with a range from 1 to 29 (higher score indicates greater depression). Both Dr. Chen and the sponsor concluded that there was no statistical difference between the treatment group and the placebo group at baseline with regard to demographics or the primary efficacy variables. The following table from Dr. Chen's review shows the severity of illness at baseline of the two treatment groups in Part III:

Table 3 Baseline values of treatment groups in Part III, placebo controlled relapse prevention phase.
(Table extracted from Dr. Chen's review)

Variable (Visit: 10)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value *
Binge Eating Episodes				
Mean (SD)	3.03 (4.83)	3.86 (5.08)	3.44 (4.96)	.975
Vomiting				

Variable (Visit: 10)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value *
Episodes Mean (SD)	4.05 (5.50)	4.46 (6.12)	4.25 (5.80)	.868
CGI-Severity Mean (SD)	2.89 (1.01)	2.92 (0.90)	2.91 (0.96)	.397
HAMD-17 Total Mean (SD)	4.62 (3.88)	6.08 (5.33)	5.34 (4.69)	.114
EDI Bulimia Mean (SD)	2.92 (3.56)	3.23 (4.23)	3.07 (3.90)	.967
EDI Body Dissatisfaction Mean (SD)	10.13 (7.46)	10.29 (8.30)	10.21 (7.86)	.360
EDI Interpersonal Distrust Mean (SD)	2.25 (2.68)	3.27 (3.59)	2.75 (3.19)	.141
EDI Ineffectiveness Mean (SD)	2.45 (2.83)	3.96 (4.78)	3.20 (3.97)	.242
EDI Interceptive Awareness Mean (SD)	3.41 (4.48)	3.77 (4.88)	3.58 (4.67)	.642
EDI Maturity Fears Mean (SD)	2.00 (2.42)	1.75 (2.77)	1.88 (2.59)	.349
EDI Perfectionism Mean (SD)	6.80 (4.58)	7.00 (4.79)	6.90 (4.67)	.811
EDI Drive for Thinness Mean (SD)	6.68 (5.47)	5.82 (5.59)	6.26 (5.53)	.026
Total EDI Mean (SD)	37.04 (22.04)	39.10 (27.19)	38.06 (24.67)	.487
YBC-EDS Preoccupation Total Mean (SD)	5.01 (2.35)	4.97 (2.83)	4.99 (2.59)	.150
Variable (Visit: 10)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value *
YBC-EDS Ritual Total Mean (SD)	4.36 (2.83)	4.39 (3.19)	4.37 (3.00)	.222
YBC-EDS				

Variable (Visit: 10)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value *
Total Score Mean (SD)	9.37 (4.76)	9.36 (5.37)	9.37 (5.05)	.141
Endpoint CGI Improvement			Mean End Scores	
1	28 (36.8)	27 (36.5)		
2	39 (51.3)	40 (54.1)		
3	9 (11.8)	7 (9.5)	1.74	
Endpoint PGI Improvement			Mean End Scores	
1	30 (39.5)	28 (37.8)		
2	36 (47.4)	36 (48.6)	1.75	
3	10 (13.2)	10 (13.5)		

* Means are analyzed using a Type III Sum of Squares Analysis of Variance (ANOVA).

Concomitant Medications

The most common concomitant medication identified was over-the-counter non-steroidal anti-inflammatories (ibuprofen and paracetamol). There was only one medication (acetylsalicylic acid) which had a statistically significantly different usage in the two treatment groups (fluoxetine: n=20 or 26.3%; placebo: n=9 or 12.2 %); otherwise, it did not appear that there were statistically significant difference in usage of medication between the treatment groups.

Efficacy Results

Only Part III, the placebo controlled relapse prevention phase of this study, is interpretable for the purposes of efficacy. Therefore, the discussion will be limited to the analysis of Part III. The primary efficacy variables were **time to relapse** and **relapse rate** based on the frequency of vomiting (see section of analysis plan above for definitions).

Applying the log-rank test to the Kaplan-Meier survival analysis, the fluoxetine group demonstrated a statistically significant increase in the **time to relapse** compared to the placebo treatment group (**p=0.008**). Please refer to Appendix C for the sponsor's survival curve of time to relapse. The sponsor provided a 1-year estimated rate of relapse for fluoxetine-treated patients to be 33% compared to the 51 % relapse rate in placebo-treated patients. As suggested by the findings using the Cox model (including therapy, sites, and therapy by site interactions), the lengthened time to relapse was consistent across study sites.

Dr. Chen, FDA statistical reviewer, also re-calculated the time to relapse taking into consideration that there were multiple primary efficacy variables, and that the sponsor may have incorrectly applied a one-sided significance level of 0.05, instead of applying a two-sided test at 0.05 or a one-sided test at 0.025. In her recalculations, Dr. Chen proposed that for time to relapse the p-value= **0.016**, which also demonstrates a statistically significant difference in time to relapse comparing the fluoxetine group with the placebo treated patients.

The Cochran-Mantel-Haenszel test was used to compare the relapse rates between the placebo treatment group and the fluoxetine treatment group. The **relapse rate** between the fluoxetine and the placebo group

was not found to be statistically significant (**p=0.319**). The sponsor conducted the Cox-proportional hazards model which indicated that the relapse rate did not depend on the baseline frequency of vomiting or binge-eating.

Secondary efficacy variables found to be statistically significantly different comparing the fluoxetine and the placebo group were as follows: binge-eating episodes (p=0.03), vomiting episodes (p=0.021), CGI-S (p=0.004), CGI-I (0.007), PGI-I (p=0.003), and the EDI (p=0.030). There was no statistically significant difference between the fluoxetine and the placebo group on the EDI subtotal scores and the HAM-D₁₇ (0.190). Please see Dr. Chen's statistical review for more detailed discussion of secondary efficacy variable findings.

Efficacy Conclusions

In the 52 week relapse prevention phase of the pivotal study, there was a statistically significant difference observed in the time to relapse when comparing the placebo and the fluoxetine treatment groups. The sponsor, using a one-sided significance level of 0.05, calculated p-value=0.008. Meanwhile, Dr. Chen, FDA statistician, suggested that it was more appropriate to use either a two-sided test with significance level of 0.05 or a one-sided test of significance level of 0.025 yielding p-value=0.016. Using either method, there was a statistically significant difference in time to relapse demonstrated. However, no statistically significant difference was demonstrated in the rate of relapse between the fluoxetine and the placebo group (p=0.319).

Although the sponsor was able to only demonstrate statistical significance in one of the two primary efficacy variables, it could be argued that the more clinically sensitive measure of relapse prevention is the time to relapse, rather than the relapse rate. Because the time to relapse in the fluoxetine treatment group was shown to be statistically significantly longer than the placebo group, there is evidence to support that fluoxetine is more effective than placebo in preventing relapse of symptoms of bulimia nervosa.

VII. Integrated Review of Safety

A. Description of Patient Exposure (i.e., number of patients at given duration, dose, demographic, distribution, country)

At Visit 1, 256 patients entered the original study; of these patients, 33 were either screen failures or decided not to participate. In this trial, 232 patients began single blind treatment with fluoxetine 60 mg qd. At Week 8, 150 patients were considered responders (i.e. a ≥ 50 % decrease from baseline in the frequency of their vomiting episodes during 1 of the preceding 2 weeks) and, thus, met criteria to enter the 52 week randomized placebo-controlled portion of the study. Of the 150 patients, 76 patients were randomized to the fluoxetine 60 mg daily treatment group and 74 patients were randomized to the placebo treatment group. Only 19 patients (12.7%) completed the study, and 131 patients (87.3%) discontinued early (63 receiving fluoxetine, 68 placebo). The study was completed by 19 (12.7 %) patients; more specifically, 13 (17%) of the fluoxetine group and 6 (8%) in the placebo group completed the study. Therefore, 131 (87.3 %) of the patients randomized had early withdrawals.

The 232 enrolled patients were exposed for an average of 52.4 days during acute phase. The 76 patients randomized to fluoxetine treatment during Part III (placebo controlled relapse prevention) had an average exposure of 172.8 additional days (225.2 days total) giving a total exposure of approximately **48 patient years**. Placebo treated patients were exposed to placebo for an average of 96.5 days during the relapse prevention phase.

The demographics for this submission were previously described above in the efficacy section (see Table 1 above).

B. Background and Methodology

Prozac® (fluoxetine) was first approved for marketing in December, 1987 and has been widely used since that time. The current labeling includes the indications of depression, obsessive compulsive disorder and bulimia nervosa. The NDA supplement for bulimia nervosa was approved in November 1996 with supporting studies of 8-16 weeks duration. The current submission has provided longer term safety data in a 52 week relapse prevention trial with participants who responded to treatment by the end of an open label 8 week phase.

C. Deaths/Other serious adverse events

There were no deaths in this NDA data base.

Other serious adverse events occurred in 15 patients taking the study drug during either the acute phase or the 52 week double-blind placebo controlled portion of the study. The following is the sponsor's summary table of serious adverse events:

Table 4 Summary of serious adverse events (sponsor's table)

Event Classification	FLX (N=82)	FLX/FLX (N=76)	FLX/PLC (N=74)	Total (N=232)
	n (%)	n (%)	n (%)	n (%)
PATIENTS WITH >= 1 EVENT	6 (7.3)	6 (7.9)	3 (4.1)	15 (6.5)
PATIENTS WITH NO EVENTS	76 (92.7)	70 (92.1)	71 (95.9)	217 (93.5)
UNINTENDED PREGNANCY	0	4 (5.3)	3 (4.1)	7 (3.0)
ABORTION	0	2 (2.6)	0	2 (0.9)
SUICIDE ATTEMPT	1 (1.2)	1 (1.3)	0	2 (0.9)
ACCIDENTAL INJURY	1 (1.2)	0	0	1 (0.4)
ACCIDENTAL OVERDOSE	0	1 (1.3)	0	1 (0.4)
ADDICTION	1 (1.2)	0	0	1 (0.4)
CERVIX CARCINOMA IN SITU	1 (1.2)	0	0	1 (0.4)
CONFUSION	1 (1.2)	0	0	1 (0.4)
EMOTIONAL LABILITY	1 (1.2)	0	0	1 (0.4)
HALLUCINATIONS	1 (1.2)	0	0	1 (0.4)
NERVOUSNESS	1 (1.2)	0	0	1 (0.4)
OVERDOSE	1 (1.2)	0	0	1 (0.4)
PERSONALITY DISORDER	1 (1.2)	0	0	1 (0.4)
PSYCHOSIS	1 (1.2)	0	0	1 (0.4)
THINKING ABNORMAL	1 (1.2)	0	0	1 (0.4)
VAGINAL HEMORRHAGE	0	1 (1.3)	0	1 (0.4)

All patient narratives of serious adverse events supplied by the sponsor are summarized in Table 6 below (under dropouts); the only exception is one 29 y.o. female patient listed as having an accidental overdose (#013-1307) who continued in the study.

D. Assessment of Dropouts

1. Overall pattern of dropouts

Of the 150 patients randomized in Part III of this study, 131 (87.3%) had an early withdrawal from the study. The most common reasons for withdrawal was due to lack of efficacy during both Parts II (26%) and III (pbo=29.7%; fluoxetine=17.1%). The following table summarizes the reasons for discontinuation in this study:

Table 5 Summary of Dropouts

	PART II (8 WEEKS)	PART III (52 WEEKS)	
	N=232	Fluoxetine (n=76)	Placebo (n=74)
Relapse/lack of efficacy	N=26 (11.2%)	17 (22.4%)	22 (29.7%)
Adverse Event	18 (7.8)	4 (5.3)	3 (4.1)
Lost to f/u	14 (6.0)	9 (11.8)	10 (13.5)
Patient Decision	15 (6.5)	18 (23.7)	20 (27.0)
Physician Decision	1 (0.4)	3 (3.9)	7 (9.5)
Protocol Variance	3 (1.3)	4 (5.3)	1 (1.4)
Non-compliance	5 (2.2)	8 (10.5)	5 (6.8)

2. Adverse events associated with dropouts

The following Table 6 below is a summary of dropouts based on the sponsor's patient narratives. There were no unexpected adverse events associated with dropouts described.

Table 6: Summary of all dropouts

Subject #	Age/Sex	Modal Dose (mg/d)	Duration (days)	Adverse Event
010-1007	23/F	60	43	Hand tremor
010-1005	28/F	60	170	Seizure
002-213	28/F	60	37	Nausea
002-236	29/F	60	4	Nausea
008-815	36/F	60	12	Nausea
001-101	49/F	60	27	Allergy to study drug
003-308	31/F	60	29	Urticaria
008-819	43/F	60	22	Maculopapular rash
002-229	28/F	60	9	Depression/suicidal thoughts
011-1119	23/F	60	60	Suicide Attempt
006-603	31/F	60	14	Suicide attempt
007-707	24/F	60	18	Psychotic reaction/mania?
002-209	26/F	60	26	Nervousness/Jittery
007-706	21/F	60	36	Nervousness/shakiness
005-500	37/F	60	7	Anxiety
013-1305	31/M	60	34	hypertension
016-1604	36/F	60	21	Thinking abnormal ("spaciness")
009-902	33/f	60	45	Addiction (alcohol)
011-1103	20/F	60	80	Pregnancy
010-1010	36/F	60	83	Pregnancy

Subject #	Age/Sex	Modal Dose (mg/d)	Duration (days)	Adverse Event
014-1405	20/F	60	58	Pregnancy
014-1406	26/F	60	69	Pregnancy
005-501	32/F	60	76	Pregnancy
005-508	24/F	60	??	Pregnancy
005-503	27/F	60	187	Pregnancy
014-1408	22/F	60	<19	Accidental injury/burn
008-802	27/F	60	??	Pelvic Inflammatory disease
009-900	32/F	60	0	Cervical carcinoma

E. Other safety findings

1. Adverse Events Incidence

It is difficult to interpret the findings from the acute phase of the study, as there was no placebo control group. The sponsor listed the most frequently reported treatment-emergent adverse event during the acute phase to be insomnia, nausea, headache, asthenia, rhinitis, nervousness, somnolence, and anorexia. The only event observed but not listed in the current labeling for Prozac submitted by the sponsor was vaginitis (n=3 or 1.3%); otherwise, no unexpected events occurred during that study.

For the placebo controlled portion of the study, the sponsor listed the most frequently reported treatment-emergent adverse event (occurring in $\geq 10\%$) in the fluoxetine group to be rhinitis, headache, depression, flu syndrome, insomnia, asthenia, anxiety, and accidental injury. Whereas, in the placebo group, the most frequently reported events were headache, depression, rhinitis, and asthenia. The sponsor identified rhinitis as the only event that occurred statistically significantly more frequently in the fluoxetine group than in the placebo group.

Please see Table 7 below for the common adverse events (i.e. observed in $\geq 5\%$ of the study drug group and occurring twice as often as in the placebo group) in the placebo controlled portion of the study.

Table 7 Common Adverse events occurring in $\geq 5\%$ of the fluoxetine group & twice the incidence in the placebo group (in the placebo-controlled portion of the study):

Event	Fluoxetine N=76	Placebo N=74
Pain	7 (9.2%)	2 (2.7)
Allergic reaction	4 (5.3)	1 (1.4)
Nausea	6 (7.9)	2 (2.7)
Tooth disorder	6 (7.9)	1 (1.4)
Vomiting	5 (6.6)	2 (2.7)
Somnolence	4 (5.3)	1 (1.4)
Dizziness	2 (2.6)	0
Rhinitis*	24 (31.6)	12 (16.2)
Pharyngitis	7 (9.2)	3 (4.1)
Bronchitis	4 (5.3)	2 (2.7)
Cough increased	4 (5.3)	2 (2.7)
Unintended pregnancy	5 (6.6)	2 (2.7)

* p-value=0.035 (sponsor used Fisher's Exact test)

2. Adverse events upon withdrawal of treatment

The sponsor did not provide data in this supplement assessing events occurring after withdrawal of treatment.

3. Laboratory Findings

Laboratory studies were conducted at the baseline of the acute phase, eight weeks later at the beginning of the placebo controlled portion of the study, and at the end of the study (at the end of 52 weeks or time of discontinuation). The following laboratory values were assessed: **Biochemistry:** AST, ALT, alkaline phosphorous, calcium, bilirubin, creatinine, blood urea nitrogen (BUN), electrolytes, uric acid, glucose, albumin, cholesterol, creatine kinase, amylase; **Hematology:** Hemoglobin, hematocrit, WBC, eosinophils, platelet count; **Urinalysis:** Glucose, protein, pH, ketones, bilirubin, urobilinogen, blood, nitrite.

The analysis and data presented by the sponsor focused on the laboratory values obtained during the placebo controlled study during which there were two scheduled assessments, once at the beginning of this study portion and once at the end.

It is noted that there were no patients reported in this NDA data base to have discontinued due to adverse events related to laboratory findings.

Comparing mean values, the sponsor identified the following laboratory values as showing statistically significant differences in the fluoxetine group compared to the placebo group: **magnesium**, ↓ 0.8 % (p=0.032); **urine pH**, ↓ 1% (p=0.029); **bicarbonate**, ↓ 0.04% (p=0.024), and **polyphils**, ↓ 2%, (p=0.052).

Trends in abnormal laboratory values revealed that low erythrocyte counts and abnormal urine red blood cell counts were found with more frequency in the fluoxetine group. Low erythrocyte counts were observed in four patients in the fluoxetine group (6.7%) compared to no patients in the placebo group. There were four patients in the fluoxetine group (7.3%) who had abnormal urine red blood cell counts compared with no patients in the placebo group. Otherwise, there were no statistically significant differences observed when comparing abnormal values in the two treatment groups.

The following table summarizes abnormal laboratory findings noted from the line listings of abnormal laboratories (submission of September 20, 2001):

Table 8: Select Abnormal Laboratory Findings

Patient ID #	Treatment group in pbo-controlled portion	Laboratory Test	Visit 1*	Visit 10**	Visit 25***
1-109	Placebo	Creatine phosphokinase NL: 19-265	123	668	511
		Bilirubin NL:3-22	27	14	26
12-1200	Placebo	Creatine phosphokinase	85	357	100

*Visit 1 is baseline prior to fluoxetine treatment;

**Visit 10 after the 8 week open label phase of fluoxetine

***Visit 25 is at the end of 52 week placebo controlled phase

It appears that both patients 1-109 and 12-1200 experienced an elevated creatine phosphokinase during the acute (8 weeks) treatment of fluoxetine; it is noted that this level began to normalize while they took placebo during the relapse prevention phase. There were no associated symptoms or other laboratory abnormalities reported for these two patients. Elevated creatine phosphokinase has been noted in the current labeling for Prozac.

There were no reported cases of jaundice or a combination of elevated ALT/AST and elevated bilirubin.

4. Vital Signs

Vital signs including sitting systolic and diastolic blood pressures, pulse, and body weight were collected at each visit (approximately every two weeks during the placebo controlled relapse prevent phase of the study). Baseline values were collected at the beginning of the acute phase treatment, and the change from baseline was determined at the end of the relapse prevention phase, or at early withdrawal. The mean and median values were are shown in the sponsor table below:

Table 9 Vital Signs: mean and median changes at the end of relapse prevention phase (from Sponsors ISS)

Therapy	n	Baseline		Change		Within group p-Value	Overall p-Value
		Mean $\pm$ SD	Median	Mean $\pm$ SD	Median		
Weight (kg)							
Flx/Flx	75	60.6 $\pm$ 11.8	59.4	1.80 $\pm$ 3.65	1.13	<.001	.495
Flx/Plc	72	61.2 $\pm$ 10.0	58.5	1.22 $\pm$ 2.29	0.91	<.001	
Sitting Diastolic Blood Pressure (mmHg)							
Flx/Flx	75	70.1 $\pm$ 9.76	70.0	1.04 $\pm$ 9.85	0.00	.419	.218
Flx/Plc	72	70.1 $\pm$ 9.92	70.0	0.14 $\pm$ 10.5	0.00	.948	
Sitting Systolic Blood Pressure (mmHg)							
Flx/Flx	75	111 $\pm$ 11.3	110	2.13 $\pm$ 13.0	2.00	.177	.511
Flx/Plc	72	111 $\pm$ 14.4	110	0.06 $\pm$ 14.0	0.00	.649	
Sitting Heart Rate (bpm)							
Flx/Flx	75	70.0 $\pm$ 10.6	68.0	0.96 $\pm$ 12.8	0.00	.741	.441
Flx/Plc	71	70.0 $\pm$ 10.3	68.0	0.14 $\pm$ 10.7	1.00	.648	

Abbreviations: Flx = fluoxetine; Plc = placebo; SD = standard deviation; bpm = beats per minute

As can be seen in the table above, there were statistically significant differences observed within each treatment group for weight change, but, when comparing the mean change from baseline, there was no statistically significant finding when comparing the fluoxetine and placebo groups. Changes in body weight, diastolic blood pressure, systolic blood pressure and sitting heart rate showed comparable changes (within the standard deviations) from baseline for both the fluoxetine and the placebo treatment groups; there were no statistically significant differences in changes from baseline for any of the vital signs.

The sponsor did not provide the full ranges of maximum and minimum values for vital signs, so a full review of outliers was not completed at this time.

5. Withdrawal reactions and abuse potential

The sponsor did not report or characterize any withdrawal reactions. The current submission did not provide data specifically focusing on observations of the first weeks of patients randomized to the placebo

group in the relapse prevention phase of the study. There were no abuse potential studies performed as part of this NDA supplement. Prozac[®] (fluoxetine), as currently labeled, is not a controlled substance.

6. Human Reproduction Data

Although there were several pregnancies occurring during this trial, there were no follow up reports on the progress of the pregnancy for those individuals.

F. Adequacy of Safety Testing

Although there is no evidence of cardiotoxicity in the acute studies of Prozac[®], it would have been helpful if the sponsor had monitored ECGs during this year long study. Because Prozac[®] is used to treat many patients for extended periods of time (years for some individuals), it would be of benefit to monitor for any ECG changes over a long duration.

G. Summarize Critical Safety Findings and Limitation of the Data

The sponsor is not proposing any changes to the safety labeling of Prozac[®](fluoxetine).

Of note in this safety data base, the Prozac[®] treatment group had statistically significant decreases in the following mean laboratory values compared to the placebo group: **magnesium**, ↓ 0.8 % (p=0.032); **urine pH**, ↓ 1% (p=0.029); **bicarbonate**, ↓ 0.04% (p=0.024), and **polyphils**, ↓ 2%, (p=0.052). However, although statistically significant, it is unclear if these mean changes are reflective of any clinical significance. Elevated creatine phosphokinase levels were observed in two patients, but this event has previously been described in labeling for Prozac.

Other trends in abnormal laboratory observations were low erythrocyte counts and abnormal urine red blood cell counts occurring with more frequency in the fluoxetine group. Low erythrocyte counts were observed in four patients in the fluoxetine group (6.7%) compared to no patients in the placebo group. There were four patients in the fluoxetine group (7.3%) who had abnormal urine red blood cell counts compared with no patients in the placebo group. Otherwise, there were no statistically significant differences observed when comparing abnormal values occurring in the two treatment groups.

There were no statistically significant findings in vital signs observed between the placebo and the treatment group; it is also noted that outliers for vital signs were unable to be located in this submission, so a full review of outliers was not completed at this time.

The only adverse event identified to be observed more frequently in the Prozac[®] group than in the placebo group is rhinitis, which has been previously described in the labeling for Prozac[®].

There were no deaths reported during this study. Adverse events which lead to withdrawal or were categorized as serious adverse events have been either previously reported in the labeling for Prozac (e.g. rash, seizure, hand tremor, nausea, hypertension), or a causal relationship is difficult to establish or unlikely (e.g. suicide attempt, nervousness, anxiety, accidental injury, pelvic inflammatory disease, cervical carcinoma).

In conclusion, from the material submitted, there does not appear to be unexpected events that have occurred during this study. At this time, there are no recommendations to amend the safety labeling for Prozac[®] (fluoxetine).

VIII. Dosing, Regimen, and Administration Issues

All patients in the treatment group were administered 60 mg Prozac® (fluoxetine). This dose was chosen based on the acute trials in which efficacy for the treatment of bulimia was observed at a dose of 60 mg/day Prozac®, but was not observed at a dose of 20 mg daily. It is unclear if a 40 mg Prozac® dosage would be effective in the treatment of bulimia.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The disease is thought to occur primarily in females. According to the DSM-IV, at least 90% of individuals with bulimia nervosa are female in clinic and population samples. The sample for this NDA supplement was comprised of 97% females and 3% men, which, as a sample, may only slightly under-represent the male population with bulimia.

B. Evaluation Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The age range of patients in this study was primarily adults in their early 20s to late 30s, an age group that might typically seek treatment for bulimia. There was no subgroup analysis for safety or efficacy conducted within this tested age group. The majority of patients in this supplement were female and Caucasian. The sponsor did not have sufficient exposure to characterize ethnic or gender variation, and, thus, did not perform any subgroup analyses.

C. Evaluation of Pediatric Program

Prozac® (fluoxetine) has been tested in children for the indications of depression and OCD, and a safety profile for use in the pediatric population is in the process of being reviewed; no pediatric labeling changes have been made as of the date of this review. Because bulimia is not frequently observed in children, and the symptoms are exhibited primarily in late adolescents, there does not appear to be a need for further testing in the pediatric population at this point in time.

D. Comments on Data Available or Needed in Other Population (Renal, Hepatic Compromised Patients, or Use in Pregnancy).

The current labeling for Prozac® (fluoxetine) addresses pharmacokinetic differences in liver and renal disease, and the elderly population. There continues to be a need for testing of Prozac® (fluoxetine) for use in pregnancy. This becomes an issue with the population being treated for bulimia nervosa, as many of these patients are of childbearing potential.

X. Conclusions and Recommendations

A. Conclusions

The sponsor was able to demonstrate statistical significance for the efficacy variable of time to relapse ($p=0.016$ for a two sided test and $p=0.008$ using a one sided test). However, statistical significance was not demonstrated when comparing the relapse rate for the Prozac and the placebo groups ($p=0.319$).

When considering the more important variable in affecting the course of illness, it would appear that time to relapse would be a more significant measure of efficacy than the absolute rate of relapse when comparing placebo and treatment groups. Because the time to relapse in the fluoxetine treatment group was

shown to be statistically significantly longer than the placebo group, there is evidence to support that fluoxetine is more effective than placebo in preventing relapse of symptoms of bulimia nervosa.

From a safety perspective, from the material submitted, there does not appear to be any unexpected events which have occurred during this study.

Therefore, this study lends support to the safety and efficacy of Prozac[®] in the treatment of relapse prevention for bulimia nervosa. It is recognized that this study is limited to observations for up to a year, and as a chronic illness, bulimia may require treatment for a much longer time period. It is also recognized that the study was completed by only 19 (12.7 %) patients; more specifically, 13 (17%) of the fluoxetine group and 6 (8%) in the placebo group completed the study.

B. Recommendations

Because this 52 week trial was completed by only 13 (17%) of the fluoxetine group and 6 (8%) in the placebo group, it is (b) (4)



At this time, there are no recommendations to amend the safety labeling for Prozac[®] (fluoxetine). However, it is noted that there were no ECGs done during this 52 week study, which would have been helpful to observe cardiac effects of this medication which may be prescribed for years at a time for chronic illnesses such as bulimia nervosa.

XI. Appendix

Appendix A

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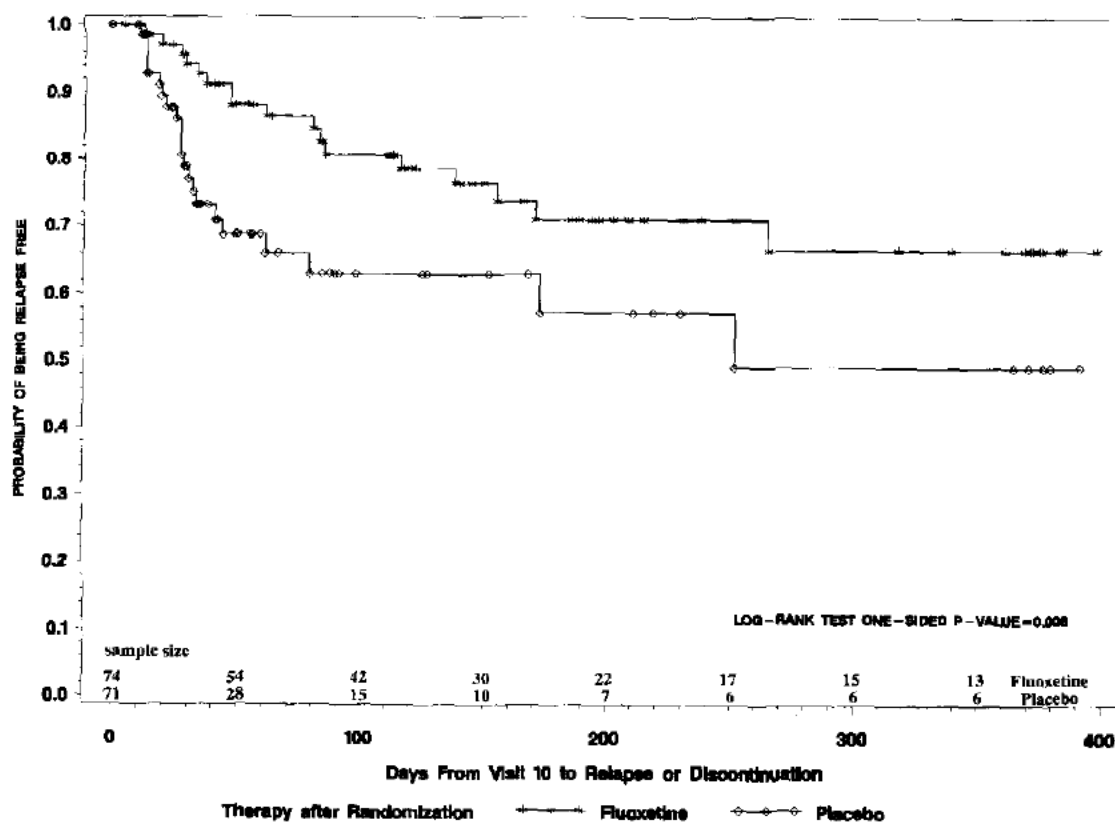
Appendix B

Schedule of Events: Protocol B1Y-MC-HCIE

Activity	Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14-24	25 (or later DC)
Informed consent document signed	Week	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	2	4	6	8 to 48	52
Patient number assigned		x														
Physical examination		x									x					x
ECG		x														
Medical history and psychiatric interview		x														
Consumptive habits		x														
Inclusion/exclusion criteria		x	x													
Vital signs and weight		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory analyses		x									x					x
Pregnancy test (if applicable)		x														
Presenting and preexisting conditions		x														
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary dispensed		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CGI-Severity			x								x		x		x	x
CGI-Improvement											x		x		x	x
PGI											x		x		x	x
HAMD ₁₇			x								x		x		x	x
EDI			x								x		x		x	x
YBC-EDS			x								x					x
Study Period II medication dispensed			x	x	x	x	x	x	x	x						
Patient randomization											x					
Study Period III medication dispensed											x	x	x	x	x	
Collection of compliance record				x	x	x	x	x	x	x	x	x	x	x	x	x
Patient summary																x

Appendix C

Sponsor's Survival Curve of Time to Relapse in the placebo controlled relapse prevention phase of Protocol HCIE



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

/s/

Roberta Glass
11/19/01 05:14:04 PM
MEDICAL OFFICER

Thomas Laughren
12/10/01 08:03:13 AM
MEDICAL OFFICER
I agree that these supplements are approvable; see memo
to file for more detailed comments.--TPL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

CHEMISTRY REVIEW(S)

NDA 18-936, SE8-065
NDA 20-101, SE8-027
NDA 20-974, SE8-001

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA #: 18-936
NDA #: 20-101
NDA #: 20-974

DATE REVIEWED: 6/19/02

REVIEW #: 1

REVIEWER: Donald N. Klein, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Efficacy	2/27/02	2/28/02	6/19/02

NAME AND ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:

Proprietary:	Prozac Pulvules, Prozac Oral Solution, and Prozac Tablets
Non proprietary/USAN:	Fluoxetine hydrochloride
Code Name/Number:	None
Chem. Type/Ther. Class:	Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION: Bulimia relapse prevention

DOSAGE FORM: pulvules; oral solution; and tablets.

STRENGTHS: 10mg; 20mg, and 40mg pulvules; oral solution: 20mg per 5 mL; 10mg tablets

ROUTE OF ADMINISTRATION: Oral

DISPENSED: ☒ RX ☐ OTC

SPECIAL PRODUCTS: ☐ Yes ☒ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

CA Name: Benzenepropanamine, N-methyl-γ-[4-(trifluormethyl)-phenoxy]-, hydrochloride

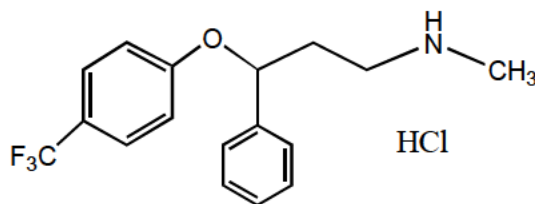
USAN Name: Fluoxetine Hydrochloride

Chemical Formula: C₁₇H₁₈NOF₃ . HCl

Molecular Weight: 345.79

CAS Registry Number: 59333-67-4

Laboratory code: None listed



N18-936, SE8-065
N20-101, SE8-027
N20-974, SE8-001

Eli Lilly, Prozac Pulvules, Tablets, Solution

2

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS:

1. NDA 20-101: Fluoxetine hydrochloride oral solution; Approved on 4/24/91.
2. NDA 20-974: Prozac Tablets, 10mg and 20mg; Approved 3/9/99.
3. NDA 18-936: Fluoxetine hydrochloride Prozac® Pulvules; Approved 12/29/87.

SUPPLEMENT PROVIDES FOR: To demonstrate the efficacy of fluoxetine hydrochloride over a greater period of time for the treatment of bulimia relapse prevention.

CONCLUSIONS: From the CMC standpoint, Approval is recommended.

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

/s/

Donald Klein
6/19/02 02:43:37 PM
CHEMIST

Thomas Oliver
6/19/02 05:14:34 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 18-936 /SE8-065
20-101/SE8-027
20-974/SE8-001
APPLICANT: Eli Lilly and Company
NAME OF DRUG: Prozac
INDICATION: Bulimia Nervosa
DOCUMENT REVIEWED: 2-22-01
MEDICAL OFFICER: Roberta Glass, M.D. (HFD-120)
STATISTICAL REVIEWER: Yeh-Fong Chen Ph.D. (HFD-710)

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I. Introduction and Summary of the Sponsor's Results

According to the sponsor, fluoxetine is currently approved for marketing in the United States for the treatment of depression, obsessive-compulsive disorder, and bulimia nervosa. At the time this trial was conducted, fluoxetine had not yet received marketing approval for bulimia nervosa. Evidence to support this study was provided from the following: fluoxetine has proven to be effective in reducing bulimic symptomatology in two 8-week double-blind trials and in one longer term, 16-week double-blind trial.

In the multicenter, placebo-controlled, double-blind trial of the Fluoxetine Bulimia Nervosa Collaborative Study Group, an 8-week study comparing fluoxetine 20 mg/day, 60 mg/day and placebo, fluoxetine 60 mg/day was shown to be most effective in reducing frequency of binge-eating and vomiting episodes, especially at endpoint. This study along with the two others referenced above, established the dose and efficacy of fluoxetine in the acute management of bulimia nervosa, but did not address relapse prevention or the necessary duration of treatment for responders to fluoxetine. The current study (B1Y-MC-HCIE), conducted in the U.S.A., was designed to address relapse prevention in fluoxetine-responsive bulimic patients.

According to the sponsor's study report, there were two primary endpoints, which were time to relapse and relapse rate, for the study. Continued fluoxetine treatment significantly increased the time to relapse compared with placebo treatment ($p=0.008$). But, the result shows no significant difference ($p=0.319$) between fluoxetine-treated and placebo-treated patients in the numbers of patients who relapsed in a 52-week period. With regard to the major secondary endpoints, mean change for binge-eating, vomiting, CGI-Severity, HAMD₁₇ Total, EDI Total, and YBC-EDS Total, all analyses showed fluoxetine was statistically significantly superior to placebo in preventing the re-emergence of symptoms, with the exception of the HAMD₁₇.

II. Summary of the Sponsor's Study

1. Name and Title of the Study

Study B1Y-MC-HCIE was a Multi-center, double-blind, randomized, parallel-group study comparing the efficacy of fluoxetine 60 mg/day and placebo on preventing relapse of bulimia nervosa symptomatology over a 52-week period.

2. Investigators and Centers

This multicenter study was conducted by 17 investigators, all psychiatrists or physicians specializing in psychiatry, at 16 study sites. Two of the 17 investigators share the same investigator number and the same group of patients.

3. Objectives

Primary Objectives:

- To compare the efficacy of fluoxetine 60 mg/day (FLX-60) and placebo (PLC) in preventing relapse over a 52-week period, as determined by time to relapse and

relapse rate, in patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) bulimia nervosa, purging type (vomiting), who responded to the 8-week single-blind acute therapy phase (Study Period II).

- To compare the long-term adverse events profile of fluoxetine 60 mg/day and placebo over a 52-week period, as determined by analysis of treatment-emergent adverse events, discontinuation rates, and laboratory test results in patients with DSM-IV bulimia nervosa, purging type (vomiting), who responded to therapy during Study Period II.

Secondary Objectives:

- To determine the response rate (percentage of patients who were treatment responders) at the end of Study Period II in patients with DSM-IV bulimia nervosa, purging type (vomiting).
- To determine the effect of fluoxetine on the results of the Yale-Brown-Cornell-Eating Disorder Scale (YBS-EDS).

4. Overall Study Design and Plan

This was a multi-center, double-blind, randomized, parallel, two-arm, 52-week study. The study compared the efficacy and safety of fluoxetine and placebo in approximately 150 patients with bulimia nervosa who responded to single-blind fluoxetine treatment during initial acute therapy.

A brief description of the three study periods is given below.

- Study Period I, No Therapy Screening Phase (Visits 1 and 2): Patients underwent psychological testing and physical screening. Patients who met the entry criteria returned in 1 to 2 weeks. Patients who continued to meet entry criteria at Visit 2 were assigned to single-blind fluoxetine treatment.
- Study Period II, Single-Blind, Acute Therapy Phase (Visits 2-10): At Visit 2, fluoxetine 60 mg/day was started. Dosage adjustment was allowed between Visit 2 and Visit 4 at the clinician's discretion in order to accommodate those patients who were initially sensitive to fluoxetine 60 mg/day.
- Study Period III, Double-Blind, Placebo-Controlled Relapse Prevention Phase (Visits 10-25): Responders from Study Period II were randomly assigned to fluoxetine 60 mg/day or placebo. Patients were seen at 2-week intervals for the first 8 weeks of double-blind therapy and then at 4-week intervals for the remainder of Study Period III. Patients who met relapse criteria at any point during Study Period III were discontinued from the study.

5. Efficacy Variables

The primary efficacy variable was the frequency of vomiting in patients with DSM-IV bulimia nervosa, purging type (vomiting). The primary outcome measure was the time to relapse and relapse rate based on the primary efficacy variable in patients who responded to 8 weeks of acute fluoxetine treatment. The following efficacy measures were collected at the schedule of events.

- a. **Frequency of binge and vomiting episodes:** Patients will record episodes of bingeing and vomiting on daily patient diaries.
- b. **Occurrence of laxative and diuretic use:** Patient will record whether or not they used laxatives or diuretics on daily patient diaries.
- c. **Clinical Global Impressions-Severity (CGI-Severity):** A clinical rating of the severity of the patient's bulimia nervosa. It is a 7-point scale where 1 = normal and 7 = extremely severe case of bulimia nervosa.
- d. **Clinical Global Impressions-Improvement (CGI-Improvement):** The CGI-Improvement is a clinical rating of the global change in condition and therapeutic effect of treatment relative to condition at baseline. It is a 7-point scale where 1 = very much improved and 7 = very much worse.
- e. **Patient Global Impression (PGI):** The PGI is a patient-rated perception of changes from the start of therapy. It is a 7-point scale where 1 = very much improved and 7 = very much worse.
- f. **Eating Disorder Inventory (EDI):** The EDI is a 64-item self-report measure that provides eight clinically derived sub-scales which reflect traits and behaviors of patients with eating disorders.
- g. **17-Item Hamilton Rating Scale for Depression (HAMD₁₇):** The HAMD₁₇ will be administered to assess coexistent depression, its change over the course of therapy, and the timing of such changes. It is a 17-item questionnaire completed by a trained observer. A trained observer may be a registered nurse, medical doctor, or study coordinator.
- h. **Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS):** The YBC-EDS is a clinician-rated assessment of symptom severity in patients with eating disorders. It is an 8-item scale assessing severity of preoccupations and rituals, with a set of six provisional items for assessing motivation for change.

5.1 Efficacy Criteria

To be designated a treatment responder at the end of Study Period II (Visit 10), patients fulfilled the following criterion:

- A decrease of at least 50% in the frequency of vomiting episodes during 1 of the 2 weeks prior to randomization (between Visits 8 and 9 or between Visits 9 and 10) compared with the baseline (Visit 2) frequency of vomiting

If a patient's baseline frequency of vomiting was 0 or 1, then 2 diary periods were allowed to elapse between Visits 1 and 2. In this case, the baseline frequency of vomiting was defined as the frequency recorded during the second diary period.

Patients were defined as experiencing relapse during Study Period III if they fulfilled the following criteria:

- A return to the baseline (Visit 2) frequency of vomiting for one diary period (4 to 10 days), and
- Persistence of the above criterion for 2 consecutive diary periods.

Time to relapse was defined as the number of days from the patient's randomization date to the date the patient met criteria for relapse or the date the patient was discontinued due to relapse-physician decision.

5.2 Efficacy Analyses

For Study Period II: Single-Blind Acute Therapy Phase

Only summary statistics (no inferential statistics) were produced for this study period. Specifically, change in the frequency of vomiting from baseline (Visit 2) to endpoint (LOCF) and response rates were computed.

For Study Period III: Double-Blind Placebo-Controlled Relapse Prevention Phase

An estimate of the distribution of time to relapse was computed for fluoxetine-treated and placebo-treated patients using the product-limit (Kaplan-Meier) method. All patients with at least one post randomization visit were included in these calculations. Patients who withdrew or completed the study without a relapse were considered to have censored time values.

The primary efficacy analysis for this study was a comparison of the two estimate time-to-relapse distributions using a log-rank test (with a one-sided significance level of 0.05). This analysis tested the null hypothesis of no difference in the time-to-relapse distribution between treatments. Furthermore, Cochran-Mantel-Haenszel tests were used to compare 12-month relapse rates between those fluoxetine-treated and placebo-treated patients. All patients either relapsing prior to 12 months or completing 12 months were included in the analysis.

A proportional hazards model was used as a secondary analysis to assess the relationship between time-to relapse and the baseline covariates (frequency of vomiting) and to assess the consistency of results across sites (using the score statistic). The score statistic assessed the significance of the addition of the treatment-by-site interaction to the proportional hazards model. If a statistically significance interaction ($p < 0.10$) was found, then further investigation of potential causes as well as analysis by site was performed. A

plot of the log-estimated time-to-relapse distribution and the time-dependent covariate may have been used to check the proportional hazard assumptions.

Change from randomization to endpoint (LOCF) was also computed for each patient for the frequency of vomiting episodes and for secondary efficacy measures. Summary statistics were computed by an analysis of variance (ANOVA) model with treatment, investigator and the treatment-by-investigator interaction as explanatory variables. Original scale data was fit to the ANOVA model, and transformed data may have been fit if deemed necessary.

III. The Sponsor's Efficacy Analyses and Conclusion

1. Study Patients

An overview of the disposition of the patient population by visit is provided in Figure 1.

Figure 1. Overview of Patient Disposition by Visit

Study Period I	Placebo Treatment	Entered (N=265)
Screening Wash-Out	Visit 1	
Study Period II	Fluoxetine (60 mg/day)	Fluoxetine Therapy
Single-Blind Fluoxetine	Visit 2-9	(N=232)
Acute Therapy		
Study Period III	Responders Randomized to Therapy (N=150)	
Double-Blind		
Relapse Prevention Therapy	Fluoxetine (N=76)	Placebo (N=74)
Visit 10	76	74
Visit 11	69	61
Visit 12	65	43
Visit 13	55	35
Visit 14	50	25
Visit 15	43	19
Visit 16	38	14
Visit 17	30	13
Visit 18	29	11
Visit 19	24	10
Visit 20	17	7
Visit 22*	17	6
Visit 23	16	6
Visit 24	15	6
Visit 25	13	6
Completed Study		

*There were no discontinuations at Visit 21.

Two hundred sixty-five patients entered this study at Visit 1. Thirty three of the 265 patients either failed inclusion/exclusion criteria at Visit 1 and were considered screen failures, or decided not to participate. Two hundred thirty-two patients began single-blind treatment with fluoxetine 60 mg daily at Visit 2.

A total of 150 patients (64.7%) were randomized to 1 of 2 treatment groups: fluoxetine 60 mg daily (76 patients) or placebo (74 patients). Of the 150 patients randomized, 19 (12.7%) completed the study and 131 (87.3%) discontinued early (63 receiving fluoxetine, 68 receiving placebo).

An overall summary of reasons for discontinuation in the acute phase is shown in Table 1. Twenty-six (11.2 %) patients discontinued due to lack of response, the most common reason for discontinuation in the acute phase.

An overall summary of reasons for discontinuation in the relapse prevention phase is shown in Table 2. Seventeen (22.4%) fluoxetine-treated and 22 (29.7%) placebo-treated patients discontinued due to relapse, the most common reason for study discontinuation. Four (5.3%) fluoxetine-treated and 3 (4.1%) placebo-treated patients discontinued due to adverse events. There were no statistically significant differences among the treatment groups for any individual reason for study discontinuation.

Table 1. Primary Reasons for Study Discontinuation for All Enrolled Patients in the Acute Phase

Primary Reason for Discontinuation	FLX-60 (N=82/232) n (%)
Adverse Event	18 (7.8)
Lost to Follow up or Patient Moved	14 (6.0)
Patient Decision	15 (6.5)
Physician Decision	1 (0.4)
Protocol Violation	3 (1.3)
Non-Responder	26 (11.2)
Non-Compliance	5 (2.2)

Table 2. Primary Reasons for Study Discontinuation for All Randomized Patients in the Relapse Prevention Phase

Primary Reason for Discontinuation	FLX60 (N=63/76) n (%)	PLC (N=68/74) n (%)	Total (N=131/150) n (%)	P-Value*
Adverse Event	4 (5.3)	3 (4.1)	7 (4.7)	.726
Lost to Follow up or Patient Moved	9 (11.8)	10 (13.5)	19 (12.7)	.758
Patient Decision	18 (23.7)	20 (27.0)	38 (25.3)	.638
Physician Decision	3 (3.9)	7 (9.5)	10 (6.7)	.176
Protocol Violation	4 (6.3)	1 (1.4)	5 (3.3)	.182
Relapse	17 (22.4)	22 (29.7)	39 (26.0)	.304
Noncompliance	8 (10.5)	5 (6.8)	13 (8.7)	.412

* Frequencies are analyzed using a Chi-Square test

2. The Sponsor's Efficacy Evaluation and Results

2.1 Demographic and Other Baseline Characteristics

2.1.1 Patient Baseline characteristics

Table 3 summarizes the demographic characteristics of the patients randomly assigned to fluoxetine or placebo treatment groups in the relapse prevention phase. One hundred forty-seven (98%) of the 150 patients randomized in this study were female. Patients were between the age of 18 and 58 years (mean age, 29.8 years). One hundred thirty six (90.7%) were Caucasian. There were no statistically significant differences in the demographic characteristics of fluoxetine- and placebo-treated patients. Demographic characteristics of all patients enrolled into the acute phase of the study are summarized in Table 3.1 in the Appendix.

Tobacco and alcohol consumption habits for all randomized patients are summarized in Table 4. Sixty-five (43.3%) randomized patients used alcohol and 28 (18.7%) randomized patients were smokers. Treatment groups were comparable at randomization with respect to demographic and habits. Tobacco and alcohol consumption habits for all patients enrolled in the acute phase of the study are summarized in Table 4.1 in the Appendix.

Table 3. Baseline Patient Characteristics for All Randomized Patients

Variable	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value
Sex: No. (%)				
Female	74 (97.4)	73 (98.6)	147 (98.0)	.576*
Male	2 (2.6)	1 (1.4)	3 (2.0)	
Origin: No. (%)				
African Descent	3 (3.9)	2 (2.7)	5 (3.3)	.392*
Caucasian	71 (93.4)	65 (87.8)	136 (90.7)	
Hispanic	2 (2.6)	4 (5.4)	6 (4.0)	
Other	0	2 (2.7)	2 (1.3)	
East/ SE Asian	0	1 (1.4)	1 (0.7)	
Age: yrs.				
Mean	29.51	30.04	29.77	.880**
Median	27.83	27.29	27.60	
Standard Dev.	6.98	9.25	8.16	
Minimum	18.74	18.40	18.40	
Maximum	47.47	58.30	58.30	

*Frequencies are analyzed using a Chi-Square test

** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA)

Table 4. Patient Habits for All Randomized Patients

Variable (Visit:1)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value
Currently A Drinker?				
No	43 (56.6)	42 (56.8)	85 (56.7)	.982*
Yes	33 (43.4)	32 (43.2)	65 (43.3)	
Currently A Smoker?				
No	60 (78.9)	62 (83.8)	122 (81.3)	.447*
Yes	16 (21.1)	12 (16.2)	28 (18.7)	

*Frequencies are analyzed using a Chi-Square test.

2.1.2 Psychiatric History

Baseline psychiatric histories for all randomized patients are summarized in Table 5. Patients were between the ages of 8 and 35 (mean age, 18.2 years) when they experienced their first binge-eating episode. Patients were between the ages of 10 and 35 (mean age, 19.0 years) when they experienced the first purge episode. However, patients were not diagnosed as bulimic or as having an eating disorder until 25.8 years of age or 25.3 years of age, respectively, on average (range, 12 to 58 years or 12 to 57 years, respectively). Approximately 16% of patients had been hospitalized for an eating disorder and 27.3% of patients had a history of anorexia nervosa. Patients started worrying about their weight and began their first diet between the ages of 6 and 35 years (mean age, approximately 14 years). Treatment groups were comparable at baseline with respect to their psychiatric histories. Psychiatric histories for all patients enrolled in the acute phase of the study are summarized in Table 5.1 in the Appendix.

Table 5. Psychiatric History for All Randomized Patients in Relapse Prevention Phase

Variable (Visit:1)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value*
Age: (yrs) First Binge Mean (SD)	18.59 (4.54)	17.88 (5.56)	18.24 (5.06)	.422
Age: (yrs) First Diagnosed Bulimic Mean (SD)	25.25 (7.65)	26.28 (9.30)	25.76 (8.49)	.583
Age: (yrs) First Diagnosed Eating Disorder Mean (SD)	24.83 (7.61)	25.74 (9.63)	25.28 (8.65)	.482
Age: (yrs) First Purge Mean (SD)	18.61 (4.76)	19.35 (6.06)	18.97 (5.44)	.858

Variable (Visit:1)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value*
Patient ever Hospitalized for Eating Disorder?				
Yes	13 (17.1)	11 (14.9)	24 (16.0)	.563
No	62 (81.6)	63 (85.1)	125 (83.3)	
Unknown	1 (1.3)	0	1 (0.7)	
History of Anorexia Nervosa?				
Yes	20 (26.3)	21 (28.4)	41 (27.3)	.777
No	56 (73.7)	53 (71.6)	109 (72.7)	
Age at Time of First Anorexia Nervosa Episodes Mean (SD)	19.75 (5.95)	17 (3.89)	18.34 (5.13)	.139
Number of Previous Episodes Mean (SD)	0.33 (0.60)	0.65 (2.46)	0.49 (1.78)	.564
Age: (yrs) First Worrying About Weight Mean (SD)	14.50 (3.64)	13.55 (5.17)	14.03 (4.47)	.216
Age: (yrs) First Diet Mean (SD)	14.50 (3.90)	15.05 (4.65)	14.77 (4.28)	.265

* Frequencies are analyzed using a Chi-Square test and Means are analyzed using Type III Sum of Squares of variance (ANOVA).

2.2 Baseline Variability

The severity of the illness was evaluated at Visit 10 through examination of both the primary and secondary efficacy measures. Table 6 summarizes these characteristics.

At Visit 10, the mean frequency of binge-eating and vomiting episodes was 3.4 and 4.3, respectively; both frequencies ranged from 0 to 34. The mean CGI-Severity score was 2.91 with a range from 1 (not ill) to 5 (markedly ill), indicating patients on average exhibited a mildly ill condition. The mean HAM-D₁₇ Total score was 5.3 with a range from 0 to 29, where a higher score indicates a greater degree of depression. The mean EDI-total score was 38.1 with a range from 2 to 134, where higher score indicates more severe eating disorder. The mean YBC-EDS total score was 9.4 with a range from 0 to 23, where a higher score indicates more severe eating disorder. Mean endpoint scores were 1.74 for CGI-Improvement and 1.75 for PGI scale scores ranged from 1 (very much better) to 3 (a little better) on both scales.

The means of these scores were analyzed using a type III sums of squares analysis of variance with a model including terms for investigator, treatment, and interaction. There were no significant differences between treatment groups at Visit 10 with the exception of drive for thinness, one of the EDI subtotal scores: fluoxetine-treated patients scored higher than placebo-treated patients ($p=0.026$). All of the scores utilized to assess severity of the illness decreased from Visit 2 to Visit 10 (see Tables 12 and 13 in the Appendix).

The between treatment group differences on the scores at randomization of both CGI-Improvement and PGI scales at Visit 10 were analyzed by proportional odds analyses. There were no significant differences between treatment groups.

Table 6. Severity of Illness at Visit 10 for All Randomized Patients in Relapse Prevention Phase

Variable (Visit: 10)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value *
Binge Eating Episodes Mean (SD)	3.03 (4.83)	3.86 (5.08)	3.44 (4.96)	.975
Vomiting Episodes Mean (SD)	4.05 (5.50)	4.46 (6.12)	4.25 (5.80)	.868
CGI-Severity Mean (SD)	2.89 (1.01)	2.92 (0.90)	2.91 (0.96)	.397
HAMD-17 Total Mean (SD)	4.62 (3.88)	6.08 (5.33)	5.34 (4.69)	.114
EDI Bulimia Mean (SD)	2.92 (3.56)	3.23 (4.23)	3.07 (3.90)	.967
EDI Body Dissatisfaction Mean (SD)	10.13 (7.46)	10.29 (8.30)	10.21 (7.86)	.360
EDI Interpersonal Distrust Mean (SD)	2.25 (2.68)	3.27 (3.59)	2.75 (3.19)	.141
EDI Ineffectiveness Mean (SD)	2.45 (2.83)	3.96 (4.78)	3.20 (3.97)	.242
EDI Interoceptive Awareness Mean (SD)	3.41 (4.48)	3.77 (4.88)	3.58 (4.67)	.642
EDI Maturity Fears Mean (SD)	2.00 (2.42)	1.75 (2.77)	1.88 (2.59)	.349

Variable (Visit: 10)	FLX-60/FLX-60 (N=76)	FLX-60/PLC (N=74)	Total (N=150)	P-Value *
EDI Perfectionism Mean (SD)	6.80 (4.58)	7.00 (4.79)	6.90 (4.67)	.811
EDI Drive for Thinness Mean (SD)	6.68 (5.47)	5.82 (5.59)	6.26 (5.53)	.026
Total EDI Mean (SD)	37.04 (22.04)	39.10 (27.19)	38.06 (24.67)	.487
YBC-EDS Preoccupation Total Mean (SD)	5.01 (2.35)	4.97 (2.83)	4.99 (2.59)	.150
YBC-EDS Ritual Total Mean (SD)	4.36 (2.83)	4.39 (3.19)	4.37 (3.00)	.222
YBC-EDS Total Score Mean (SD)	9.37 (4.76)	9.36 (5.37)	9.37 (5.05)	.141
Endpoint CGI Improvement			Mean End Scores	
			1.74	
Endpoint PGI Improvement			Mean End Scores	
			1.75	

* Means are analyzed using a Type III Sum of Squares Analysis of Variance (ANOVA).

2.3 Study Period III: Double-Blind Placebo-Controlled Relapse Prevention Phase

2.3.1 Primary Efficacy Analyses

Time to Relapse Analysis

A log-rank test was applied to the Kaplan-Meier survival function to compare time to relapse between fluoxetine-treated and placebo-treated patients.

Fluoxetine treatment significantly increase the time to relapse compared with placebo treatment (p=0.008). Figure 2 in the Appendix shows the survival plot for fluoxetine treated and placebo-treated patients. The 1-year estimated rate of relapse for fluoxetine-

treated patients was 33% (95% confidence interval, 19% to 48%) and the relapse rate for placebo-treated patients was 51% (95% confidence interval, 30% to 71%).

Relapse Rate Analysis

Cochran-Mantel-Haenszel test was used to compare 12-month relapse rates between fluoxetine-treated and placebo-treated patients, controlling for investigator. All patients either relapsing prior to 12 months or completing 12 months were included in the analysis. The result shows no significant difference ($p=0.319$) between fluoxetine-treated and placebo-treated patients in the numbers of patients who relapsed in a 52-week period, even though the chance of being relapse-free is consistently longer for the fluoxetine-treated patients than the placebo-treated patients across study period.

Relationship to Baseline Covariates Analysis

The Cox-proportional hazards models indicated that the relapse rate did not depend on the baseline frequency of vomiting ($p=0.424$) or binge-eating ($p=0.211$). The Cox model, which included therapy, sites, and therapy by site interactions, shows no significance on any interaction term or study site, suggesting that the superior time to relapse for fluoxetine-treated patients is consistent across study sites.

2.3.2 Secondary Efficacy Analyses

Summaries of mean change for binge-eating, vomiting, CGI-Severity, HAMD₁₇ Total, EDI Total, and YBC-EDS Total are shown in Table 7. All analyses showed fluoxetine was statistically significantly superior to placebo in preventing the re-emergence of symptoms, with the exception of the HAMD₁₇, which did show a trend toward statistical significance.

Table 7. Secondary Efficacy Endpoints for All Randomized Patients in Relapse Prevention Phase

Efficacy Variable	Fluoxetine			Placebo			P-Value*
	N	Baseline Mean±SD	Change Mean±SD	N	Baseline Mean±SD	Change Mean±SD	
Binge-eating	74	3.03±4.87	2.47±6.58	71	3.99±5.15	4.11±6.70	0.030
Vomiting	74	4.08±5.55	2.92±7.08	71	4.52±6.20	4.82±8.43	0.021
CGI-Severity	75	2.88±1.01	0.45±1.33	71	2.92±0.91	0.97±1.21	0.004
HAMD ₁₇ Total	75	4.60±3.90	2.03±5.66	71	6.03±5.43	3.23±6.60	0.190
EDI Total	71	37±22.2	7.79±25.5	69	40.2±27.4	17.41±24.5	0.030
YBC-EDS Total	63	8.94±4.50	2.92±7.91	60	9.55±5.07	7.38±6.80	0.002

*Analyzed by Type III Sum of Square from Analysis of Variance (ANOVA).

2.3.2.1 Binge-Eating Episodes

Both treatment groups demonstrated statistically significant increases in the mean number of binge-eating episodes from randomization to last visit. Fluoxetine-treated patients experienced a mean increase of 2.5 binge-eating episodes during double-blind treatment as compared with a mean increase of 4.1 binge-eating episodes in placebo-treated patients. The difference between the two treatment groups was statistically significant ($p=0.030$).

2.3.2.2 Vomiting Episodes

Fluoxetine-treated patients experienced a mean increase of 2.9 vomiting episodes during double-blind treatment as compared with a mean increase of 4.8 vomiting episodes in placebo-treated patients. The increase in vomiting episodes for fluoxetine-treated patients was statistically significantly smaller than that for placebo-treated patients ($p=0.021$). Both treatment groups demonstrated statistically significant increases in the mean number of vomiting episodes from randomization to last visit.

2.3.2.3 CGI-Severity

Both treatment groups demonstrated statistically significant increases in CGI-Severity scores from baseline to endpoint. Fluoxetine-treated patients experienced a mean increase of 0.45 points in the CGI-Severity score during double-blind treatment as compared with a mean increase of 0.97 points in placebo-treated patients. The difference between the two treatment groups was statistically significant ($p=0.004$), indicating that the placebo-treated patients had a greater increase in severity of bulimia at endpoint than the fluoxetine-treated patients.

2.3.2.4 CGI-Improvement

Endpoint score tabulation for each treatment group for the CGI-Improvement scale are shown in Table 8. Mean endpoint scores were 2.5 for fluoxetine-treated, and 3.1 for placebo-treated patients. The comparison of fluoxetine-treated versus placebo-treated patients was statistically significant ($p=0.007$). There was no strong evidence against the assumption of proportional odds ($p=0.618$).

Table 8. Endpoints of CGI-Improvement for All Randomized Patients in Relapse Prevention Phase

Variable	FLX-60 (N=75)	PLC (N=71)
Endpoint CGI Improvement		
1	22 (29.3 %)	10 (14.1%)
2	22 (29.3 %)	16 (22.5 %)
3	10 (13.3 %)	14 (19.7 %)
4	15 (20.0 %)	20 (28.2 %)
5	4 (5.3 %)	10 (14.1 %)
6	2 (2.7 %)	1 (1.4 %)

2.3.2.5 PGI-Improvement

Endpoint score tabulations for the PGI scale for each treatment group are shown in Table 9. Mean endpoint scores were 2.4 for fluoxetine-treated and 3.1 for placebo-treated patients. The comparison of fluoxetine-treated versus placebo-treated patients was statistically significant ($p=0.002$). However, there was evidence against the assumption of proportional odds ($p=0.003$). A Pearson Chi-square test was conducted, and the result shows that there is a significant difference between the two treatment groups ($p=0.003$). The fluoxetine-treated patients reported greater improvement at the end of the relapse prevention phase than did the placebo-treated patients.

Table 9. Endpoints of PGI for All Randomized Patients in Relapse Prevention Phase

Variable	FLX-60/FLX-60 (N=75)	FLX-60/PLC (N=71)
Endpoint PGI-Improvement		
1	24 (32 %)	12 (16.9 %)
2	23 (30.7 %)	13 (18.3 %)
3	11 (14.7 %)	17 (23.9 %)
4	10 (13.3 %)	14 (19.7 %)
5	2 (2.7 %)	13 (18.3 %)
6	5 (6.7 %)	2 (2.8 %)

2.3.2.6 Eating Disorders Inventory (EDI) scores

EDI Total

Both treatment groups demonstrated statistically significant increases in EDI scores from baseline to endpoint. Fluoxetine-treated patients experienced a mean increase of 7.8 points in the EDI score during double-blind treatment as compared with a mean increase of 17.4 points in placebo-treated patients. The difference between the two treatment groups was statistically significant ($p=0.030$).

EDI Subtotal

Summary of mean change for the EDI subtotal scores is shown in Table 10. There were no significant differences between fluoxetine-treated and placebo-treated patients on any of the EDI subtotal scores. However, patients treated with fluoxetine exhibited a numerically smaller mean increase in all subtotal scores compared with placebo-treated patients, except for Maturity Fears. Fluoxetine-treated patients experienced a mean increase of 0.23, whereas the placebo-treated patients experienced a mean increase of 0.21.

Table 10. EDI Subtotals for All Randomized Patients in Relapse Prevention Phase

Subtotal	Fluoxetine			Placebo			P-Value*
	N	Baseline Mean±SD	Change Mean±SD	N	Baseline Mean±SD	Change Mean±SD	
Drive for Thinness	75	6.53±5.35	2.11±6.19	70	6.03±5.61	4.23±5.82	0.129
Interceptive Awareness	75	3.32±4.45	1.25±5.51	69	3.88±4.98	3.04±5.33	0.284
Bulimia	75	2.81±3.46	1.79±5.29	70	3.33±4.30	4.20±5.59	0.142
Body Dissatisfaction	75	10±7.42	1.91±5.43	70	10.54±8.37	2.54±4.82	0.414
Ineffectiveness	74	2.47±2.84	1.24±4.14	70	4.06±4.85	2.17±4.78	0.566
Maturity Fears	74	2.03±2.43	0.23±2.68	70	1.79±2.81	0.21±1.85	0.499
Perfectionism	74	6.92±4.59	-0.28±3.2	70	6.96±4.74	0.37±2.75	0.183
Interpersonal Distrust	74	2.31±2.69	0.46±2.83	70	3.34±3.65	1.09±3.09	0.519

* Analyzed by Type III Sum of Square from an Analysis of Variance (ANOVA).

2.3.2.7 HAMD₁₇ Scores

Both treatment groups demonstrated statistically significant increases in HAMD₁₇ total scores from baseline to endpoint. Fluoxetine-treated patients experienced a mean increase of 2.03 points in the HAMD₁₇ total score during double-blind treatment as compared with a mean increase of 3.23 points in placebo-treated patients. The difference between the two treatment groups was not statistically significant (p=0.190).

2.3.2.8 YBC-EDS

YBC-EDS Total

Both treatment groups demonstrated statistically significant increases in YBC-EDS scores from baseline to endpoint. Fluoxetine-treated patients experienced a mean increase of 2.9 points in the YBC-EDS score during double-blind treatment as compared with a mean increase of 7.4 points in placebo-treated patients. The difference between the two treatment groups was statistically significant (p=0.002).

YBC-EDS Subtotals

Summary of the mean change in YBC-EDS Subtotal scores is shown in Table 11. Both treatment groups demonstrated statistically significant increases in YBC-EDS Preoccupation subtotal scores from baseline to endpoint. The difference between the two treatment groups was statistically significant (p=0.008).

Similarly, both treatment groups demonstrated statistically significant increases in YBC-EDS Ritual subtotal scores from baseline to endpoint. The difference between the two treatment group was statistically significant ($p=0.004$).

Table 11. YBC-EDS Subtotals for All Randomized Patients in Relapse Prevention Phase

Subtotal	Fluoxetine			Placebo			P-Value
	N	Baseline Mean $\pm$ SD	Change Mean $\pm$ SD	N	Baseline Mean $\pm$ SD	Change Mean $\pm$ SD	
Preoccupation	64	4.86 $\pm$ 2.24	1.53 $\pm$ 3.82	60	4.97 $\pm$ 2.56	3.63 $\pm$ 3.74	0.008
Ritual	63	4.14 $\pm$ 2.73	1.35 $\pm$ 4.51	60	4.58 $\pm$ 3.10	3.75 $\pm$ 3.79	0.004

2.3.3 Examination of Subgroups

No subgroup analysis of gender or origin were conducted because the large majority of patients were female (147 out of 150 randomized patients) and Caucasian (136 out of 150 randomized patients) (See Table 3).

2.4 Study Period II : Single-Blind Acute Therapy Phase

2.4.1 Response Rate

Of the 232 patients who received single-blind acute therapy, 151 (65%) patients met response criteria (a decrease in the frequency of vomiting episodes of $\geq 50\%$ compared with the baseline frequency). One hundred and forty nine responders were randomized. One responder (patient 0404) discontinued due to non-compliance and one responder (patient 0714) discontinued due to patient decision. One non-responder (patient 0215) was accidentally randomized as well.

2.4.2 Efficacy Measures

Summary of mean change for bingeing, vomiting, CGI-Severity, HAMD₁₇ Total, EDI, and YBC-EDS is shown in Table 12 in the Appendix. Fluoxetine-treated patients showed statistically significant decreases from baseline to randomization in all efficacy variables.

Summary of mean change for EDI Subtotal scores is shown in Table 13 in the Appendix. Fluoxetine-treated patients showed statistically significant decreases from baseline to randomization in all EDI Subtotal scores, which were considered clinically significant.

Summary of mean change for YBC-EDS Subtotal scores is shown in Table 14 in the Appendix. Fluoxetine-treated patients showed statistically significant decreases from baseline to randomization in both subtotal scores ($p<0.001$).

Summaries of endpoint scores during the acute phase for CGI-Improvement and PGI are shown in Table 15. Mean score at Visit 10 was 1.97 for CGI-Improvement and 1.93 for PGI indicating that patients are on average feeling “much better” at the end of the acute phase.

3. The Sponsor’s Efficacy Conclusion

Of the 232 patients enrolled in the single-blind acute phase of the study, 150 were randomized during the relapse prevention phase to 1 of 2 treatment groups: fluoxetine 60 mg/day (76 patients) or placebo (74 patients). The majority of the patients were women (98%) between the ages of 18 and 58 (mean age, 30 years). The treatment groups were comparable at baseline with respect to demographics and habits.

Approximately 32% of patients had a history of previous antidepressant drug therapy. Approximately 96.7% of patients took at least one concomitant medication during the relapse prevention phase of the study. There were no differences in the history of previous drug therapy at baseline or in the use of any single concomitant medications during the study.

At least 86% of the total patients were considered compliant at each visit. Treatment compliance was similar across treatment groups.

With respect to the primary efficacy variables, continued fluoxetine treatment significantly increased the time to relapse compared with placebo treatment ($p=0.008$). The survival plot for fluoxetine-treated and placebo-treated patients shows that the probability of relapse for placebo-treated patients is highest during the first few months after acute response, while the fluoxetine-treated patients have a superior and more gradually decreasing probability of remaining relapse free. The 1-year estimated rate of relapse for fluoxetine-treated patients was 33% (95% confidence interval, 19% to 48%). The relapse rate for placebo-treated patients was 51% (95% confidence interval, 30% to 71%).

Fluoxetine-treated patients experienced a statistically smaller mean increase for each of the secondary efficacy endpoints except HAMD₁₇ during the relapse prevention phase than placebo-treated patients. These endpoints included binge-eating episodes (2.47 versus 4.11, $p=0.030$), vomiting episodes (2.92 versus 4.82, $p=0.021$), CGI-Severity (0.45 versus 0.97, $p=0.004$), EDI Total (7.79 versus 17.41, $p=0.030$), and YBC-EDS Total (2.92 versus 7.38, $p=0.002$). There were no statistically significant differences between fluoxetine-treated and placebo-treated patients on any of the EDI subscores. Fluoxetine-treated patients experienced statistically smaller mean increases than placebo-treated patients on the YBC-EDS Preoccupation subtotal ($p=0.008$) and the YBC-EDS Ritual subtotal ($p=0.004$). Overall, fluoxetine-treated patients experienced less increase in symptoms than placebo-treated patients.

Of the 232 patients enrolled in the acute treatment phase, 151 (65%) responded to 8 week of treatment with fluoxetine 60 mg/day. During the acute treatment phase, patients had

clinically and statistically significant responses on all efficacy scales during 8 weeks of treatment with fluoxetine 60 mg/day.

Fluoxetine 60mg/day is efficacious for acute treatment of bulimia nervosa during 8 weeks of single-blind therapy. Continuation of treatment with 60 mg/day of fluoxetine for up to one year in bulimia nervosa patients who responded to fluoxetine 60 mg/day after 8 weeks of acute treatment was superior to placebo treatment in the prevention of relapse.

IV. This Reviewer's Findings and Comments

1. When this study was evaluated according to the sponsor's protocol, this reviewer was able to exactly duplicate the sponsor's statistical results for all the primary and secondary endpoints in both Study Period II and Study Period III. There was no any inconsistency found between the results of the sponsor and this reviewer.
2. For the primary endpoint, time to relapse, the sponsor proposed to test by one-sided significance level of .05, which was not correct. If there is only one primary endpoint in the study, either two-sided test of significance level of .05 or one-sided test of significance level of .025 should be performed. If there are more than one primary endpoint in the study then some kind of adjustment for the multiplicity should be made. So, instead of having p-value equal to 0.008 obtained by considering one-sided test, the p-value for time to relapse should be 0.016 before it was compared with the required significance level for adjusting any multiplicity.
3. It was not clearly addressed in the sponsor's original protocol if the primary endpoints of this study were time to relapse and relapse rate or was only the variable of time to relapse. There was nowhere mentioning 'the primary endpoint' in the protocol. In the section of 3.9.1.2. **Efficacy Criteria** of the protocol, the sponsor mentioned that 'The primary efficacy measure will be the frequency of vomiting episodes which will also be used to determine patient eligibility for Study Period III.' In Section 4.5.2 **Study Period III** under Section 4.5 **Efficacy Analysis** of the protocol, the sponsor addressed that

‘ The primary efficacy analysis for this study will be a comparison of the two estimated time-to-relapse distribution using a log-rank test (with a one-sided significance level of 0.05). This will test the null hypothesis of no difference in the time-to-relapse distribution between treatments. Furthermore, Cochran-Mantel-Haenzel tests will be used to compare 12-month relapse rates between fluoxetine-treated and placebo-treated patients. All patients either relapsing prior to 12 months or completing 12 months will be included in the analysis.

A proportional hazards model will be used as a secondary analysis to assess the relationship between time to relapse and the baseline covariates (frequency of vomiting) and to assess the consistency of results across sites (using the score statistic).’

What the role of the relapse rate was is not clear. It seemed to be one of the primary endpoints due to the word 'Furthermore' and not be included in the either secondary analysis or secondary efficacy measures. According to the sponsor's study report in this NDA submission, it was, however, clearly mentioned (on page 55 of Volume 38 of 72) that 'The primary efficacy variable was the frequency of vomiting in patients with DSM-IV bulimia nervosa, purging type (vomiting). The primary outcome measure was the **time to relapse** and **relapse rate** based on the primary efficacy variable in patients who responded to 8 weeks of acute fluoxetine treatment'. The sponsor also addressed in one of their primary objectives of this study that (in both study report and the original protocol) 'to compare the efficacy of fluoxetine 60 mg/day and placebo in preventing relapse over a 52-week period, as determined by **time to relapse** and **relapse rate**'. So this reviewer determined that both 'time to relapse' and 'relapse rate' were pre-specified as the primary endpoints for this study.

4. Since there were two primary endpoints in the study, i.e., time to relapse and relapse rate, the adjustment for probability of type I error, i.e., alpha, should be made for compensating the multiplicity. Now that p-value for the variable of time to relapse was .016 ($<.025$) and p-value for the variable of relapse rate was .319 ($>.025$), the conclusions stay the same after adjusting for the multiplicity by the Bonferroni procedure. The conclusion was that fluoxetine treatment significantly increase the time to relapse compared with placebo treatment but the result shows no significant difference between two treatment group patients in the number of patients who relapsed in a 52-week period.
5. Instead of being censored for patients who did not relapse and did not complete the study, this reviewer treated them as failures and re-ran the analysis. The p-value of log rank test showed 0.000208. So, the robustness of the sponsor's analysis for the primary endpoint, time to relapse, was verified.
6. Notice that the sponsor did not perform any subgroup analysis of gender or origin due to the large majority of female and Caucasian patients in the study.

Summary of this Reviewer's Findings and Comments

When this reviewer evaluated the sponsor's results according to their protocol, no inconsistency was found.

The sponsor used one-sided test with significance level of .05 to test the primary endpoint, time to relapse, which was not correct. They should use two-sided test with overall significance level of .05. So, the p-value for the primary endpoint, time to relapse was .016 not .008.

The sponsor did not clearly address in the protocol if the relapse rate was one of the primary endpoints. According to the sponsor's study report, however, time to relapse and relapse rate were clearly addressed as the primary endpoints. It was also consistent with one of the study's primary objectives. So, this reviewer determined some kind of

adjustment for the probability of type I error, i.e., alpha, should be made due to two primary endpoints.

Since the p-value for time to relapse was 0.016 (<0.025) and the p-value for relapse rate was 0.319 (>0.025), the conclusions were the same if we used the Bonferroni procedure for adjusting the multiplicity.

The robustness of the sponsor's test result for the variable of time to relapse was verified by reversing the censoring patients who discontinued study earlier.

Due to the large majority female and Caucasian patients, the sponsor did not perform any subgroup analysis.

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This review consists of 22 pages and 1 Appendix. MS Word: C:/yfchen/nda18936/HClE/data/review.doc

V. Appendix

Table 3.1 Baseline Patient Characteristics for All Enrolled Patients in Acute Phase

Variable	FLX-60 (N=232)
Sex: No. (%)	
Female	227 (97.8)
Male	5 (2.2)
Origin: No. (%)	
AFRICAN DESCENT	5 (2.2)
CAUCASIAN	205 (88.4)
EAST/SE ASIAN	3 (1.3)
HISPANIC	12 (5.2)
OTHER	7 (3.0)
Age: yrs.	
Mean	29.673
Median	27.602
Standard Dev.	8.434
Minimum	18.094
Maximum	67.113

Table 4.1 Patient habits for All Enrolled Patients in Acute Phase

Variable (Visit:1)	FLX-60 (N=232)
Currently A Drinker?	
No	129 (55.6%)
Yes	103 (44.4%)
Currently A Smoker?	
No	182 (78.4%)
Yes	50 (21.6%)

Table 5.1 Psychiatric History for All Enrolled Patients in Acute Phase

Variable (Visit: 1)	FLX-60 (N=232)
Age: (yrs) First Binge Mean (SD)	18.034 (4.684)
Age: (yrs) First Diagnosed Bulimic Mean (SD)	25.53 (8.451)
Age: (yrs) First Diagnosed Eating Disorder Mean (SD)	25.022 (8.612)

Variable (Visit: 1)	FLX-60 (N=232)
Age: (yrs) First Purge Mean (SD)	18.677 (4.956)
1 st Degree Relative with History? Yes No Unknown	54 (23%) 163 (70.3%) 15 (6.5%)
2 nd Degree Relative with History? Yes No Unknown	38 (16.4%) 165 (71.1%) 29 (12.5%)
1 st Degree Relative with Psychiatric History? Yes No Unknown	120 (51.7%) 105 (45.3%) 7 (3.0%)
2 nd Degree Relative with Psychiatric History Yes No Unknown	79 (34.1%) 130 (56.0%) 23 (9.9%)
Patient ever Hospitalized for Eating Disorder? Yes No Unknown	36 (15.5%) 195 (84.1%) 1 (0.4%)
History of Anorexia Nervosa? Yes No	63 (27.2%) 169 (72.8%)
Age: (yrs) at Time of First Episode Mean (SD)	18.095 (4.589)
Number of Previous Episodes Mean (SD)	0.513 (1.961)
Age: (yrs) First Worrying about Weight Mean (SD)	14.207 (4.251)
Age: (yrs) First Diet Mean (SD)	14.806 (4.156)
Distant Relatives History? Yes No Unknown	13 (5.6%) 175 (75.4%) 44 (19%)
Distant Relatives Psychiatric Disorder? Yes No Unknown	26 (11.2%) 153 (65.9%) 53 (22.8%)

Table 12. Secondary Efficacy Endpoints for All Enrolled Patients in the Acute Phase

Efficacy Variable	Fluoxetine			p-value
	N	Baseline Mean±SD	Change Mean±SD	
Bingeing	227	10.61±8.23	-6.40±6.45	<0.001
Vomiting	227	12.40±9.68	-7.04±6.90	<0.001
CGI-Severity	201	4.48±0.69	-1.25±1.06	<0.001
EDI Total	184	78.93±29.35	-35.38±28.35	<0.001
HAMD ₁₇ Total	201	10.80±6.32	-4.82±6.60	<0.001
YBC-EDS Total	200	18.94±4.61	-8.07±5.75	<0.001

Table 13. EDI Subtotal Scores for All Enrolled Patients in the Acute Phase

Efficacy Variable (Subtotal)	Fluoxetine			p-value
	N	Baseline Mean±SD	Change Mean±SD	
Drive for Thinness	197	13.65±5.46	-6.05±6.04	<0.001
Interceptive Awareness	198	10.17±6.41	-5.75±5.61	<0.001
Bulimia	199	11.36±4.79	-7.17±5.29	<0.001
Body Dissatisfaction	198	16.50±8.22	-5.47±6.26	<0.001
Ineffectiveness	195	8.29±6.10	-4.42±5.26	<0.001
Maturity Fears	193	4.12±4.50	-1.75±3.99	<0.001
Perfectionism	200	9.19±4.84	-1.78±3.21	<0.001
Interpersonal Distrust	198	5.21±4.10	-2.19±3.18	<0.001

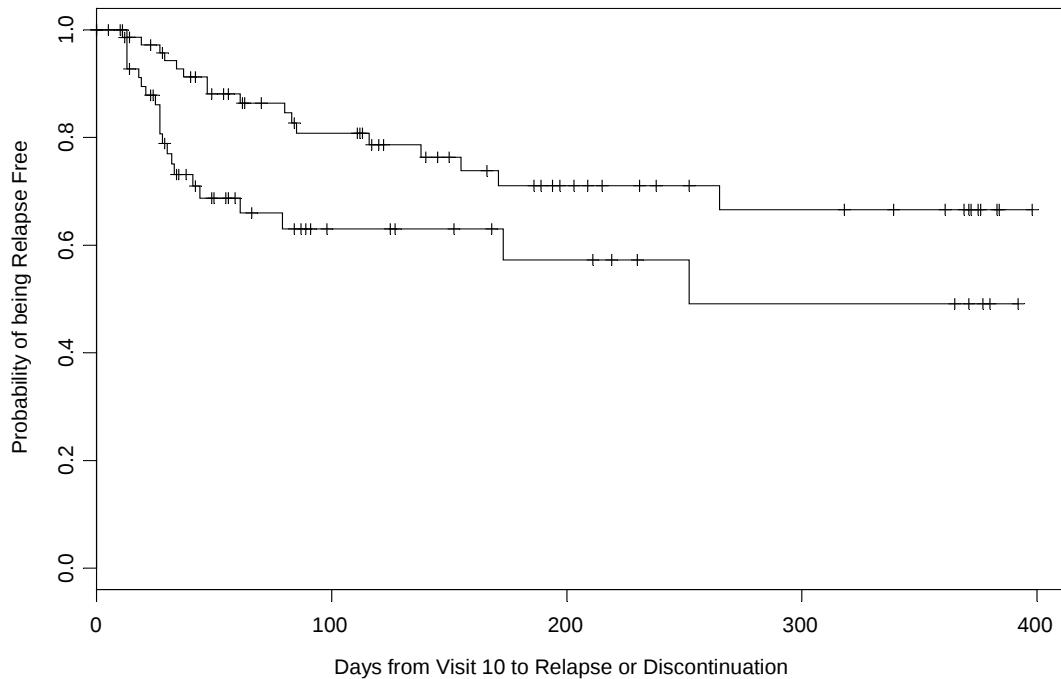
Table 14. YBC-EDS Subtotal Scores for All Enrolled Patients in the Acute Phase

Efficacy Variable (Subtotal)	Fluoxetine			p-value
	N	Baseline Mean±SD	Change Mean±SD	
Preoccupation	201	9.65±2.58	-3.89±3.05	<0.001
Ritual	200	9.29±2.56	-4.17±3.45	<0.001

Table 15. Endpoints of CGI-Improvement and PGI for All Enrolled Patients in the Acute Phase

Variable	FLX-60	Mean Score
Endpoint CGI Improvement (Visit: 10)		
1	55 (30.9 %)	1.97
2	83 (46.6 %)	
3	30 (16.9 %)	
4	10 (5.6 %)	
Endpoint PGI Improvement (Visit: 10)		
1	62 (34.8 %)	1.93
2	76 (42.7 %)	
3	33 (18.5 %)	
4	5 (2.8 %)	
5	2 (1.1 %)	

Figure 2. Survival Curve of Time to Relapse for All Randomized Patients in the Relapse Prevention Phase (Note: The top line is for fluoxetine treatment group and the down line is for placebo treatment group after randomization.)



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/s/

Yeh-Fong Chen
11/19/01 03:14:18 PM
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Kun Jin
11/19/01 03:31:29 PM
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George Chi
11/19/01 03:51:24 PM
BIOMETRICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

OTHER REVIEW(S)

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: November 1, 2001

TO: Paul David, R.Ph., Senior Regulatory Project Manager
Roberta Glass, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 18-936/S-065
NDA 20-201/S-027
NDA 20-974/S-001

APPLICANT: Eli-Lilly and Company

DRUG: Prozac (fluoxetine hydrochloride) Capsules, Solution and Tablets

CHEMICAL CLASSIFICATION: Type 6

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Bulimia Nervosa Relapse Prevention

CONSULTATION REQUEST DATE: July 18, 2001

ACTION GOAL DATE: December 23, 2001

I. BACKGROUND:

Fluoxetine is a selective serotonin reuptake inhibitor, which is currently marketed under the brand name of Prozac. Prozac is approved in the U.S. for use in the treatment of major depressive disorder, obsessive compulsive disorder and bulimia nervosa. In this NDA, the sponsor has requested the use of Prozac in bulimia nervosa relapse prevention. Inspection assignments were issued on August 2, 2001 for two domestic sites, Ferguson and Marx for Protocol B1Y-MC-HCIE. The inspection was for the purpose of validating data in support of

pending NDA 18-936/S-065, NDA 20-201/S-027 and NDA 20-974/S-001 for bulimia nervosa relapse prevention.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Ferguson	Murray	UT	8-2-2001	10-09-2001	VAI
Marx*	Princeton	NJ	9-10-2001*	10-30-2001	VAI

* The study was conducted in Encinitas, CA. This P.I. moved to Princeton, NJ.

A) Ferguson, M.D.

Forty-three subjects were screened and 40 subjects enrolled at this site. Twenty-seven subjects were randomized. Only 2 subjects completed the study. Twenty-five out of the 27 subjects discontinued. Reasons for discontinuation included relapse, poor compliance, and patients' decision. Signed and dated informed consents were present for all enrolled subjects.

An audit of 14 subjects was conducted for data verification. The inspection revealed failure to record concomitant medications for a few patients. Data appear acceptable.

B) Marx, M.D.

At this clinical site, 35 subjects were screened, 3 of these subjects failed to qualify and 32 patients enrolled. Twenty-five patients were randomized. Of the 25 subjects, only one individual completed the protocol and the remaining 24 were discontinued from the study. The reasons for discontinuation included lost to follow up, patients' decision and relapse.

An audit of 9 subjects was conducted. Protocol deviation was noted for 2 subjects in that they continued to participate in the study although they have missed at least 2 visits. Several minor deficiencies in data entry and drug accountability were also noted. Overall, data appear acceptable.

Signed and dated informed consents were present for all participants. The informed consent form, however, did not include foreseeable risks and/or discomfort such as anxiety, nervousness, drowsiness, diarrhea and lightheadedness.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Although minor deficiencies were noted during the informed consent process, and in the areas of protocol deviations, drug accountability, data entry and record keeping, the data from both sites appear acceptable for use in support of these pending NDA supplements.

[Note: The review and evaluation of the Marx audit was based on the FDA Investigator's Summary of Findings and preliminary EIR package without the exhibits. Should the EIR and exhibits from the Marx audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.]

There was no limitation to these inspections.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:

NDA 18-936

NDA 20-101

NDA 20-974

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/c/r/s

HFD-47/Khin

HFD-47/Hajarian

HFD-45/RF

rd:NK:11/01/01

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 18-936/S-065

NDA 20-101/S-027

NDA 20-974/S-001

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ITEM 13/14: PATENT INFORMATION

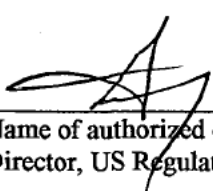
NDA 18-936

Prozac®

(fluoxetine hydrochloride)

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of fluoxetine, as indicated. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act and the subject of this supplemental application for which approval is being sought.

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)	Patent Owner's Name
US 4,314,081	February 2, 2001	Composition	Eli Lilly and Company
US 4,314,081*PED	August 2, 2001	Composition	Eli Lilly and Company
US 4,626,549	December 2, 2003	Method (Eating Disorders)	Eli Lilly and Company
US 4,626,549*PED	June 2, 2004	Method (Eating Disorders)	Eli Lilly and Company
US 4,971,998	November 20, 2007	Method (PMDD)	Interneuron
US 4,971,998*PED	May 20, 2008	Method (PMDD)	Interneuron
US 5,114,976	May 19, 2009	Method (Enhancing treatment of LLPDD)	Dr. Michael J. Norden
US 5,114,976*PED	November 19, 2009	Method (Enhancing treatment of LLPDD)	Dr. Michael J. Norden
US 5,744,501	May 19, 2009	Method (LLPDD)	Dr. Michael J. Norden
US 5,744,501*PED	November 19, 2009	Method (LLPDD)	Dr. Michael J. Norden
US 5,789,449	January 6, 2009	Method (Psychiatric Symptoms associated with PMS)	Dr. Michael J. Norden


Name of authorized official
Director, US Regulatory Affairs

6/14/01
Date

EXCLUSIVITY SUMMARY for NDA # 18-936/SE8-065, 20-101/SE8-027,
& 20-974/SE8-001

Trade Name Prozac (fluoxetine HCl) capsules, tablets, and
oral solution

Generic Name fluoxetine HCl

Applicant Name Lilly HFD- 120

Approval Date 7-29-02

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/

If yes, what type(SE1, SE2, etc.)? SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This supplement provides for clinical data providing

for the longer-term treatment of bulimia

d) Did the applicant request exclusivity?

YES / ☐ / NO / ☒ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ☒ / NO / ☐ /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / ☐ / NO / ☒ /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / ☐ / NO / ☒ /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	<u>18-936</u>	<u>Prozac capsules</u>
NDA #	<u>20-101</u>	<u>Prozac Solution</u>
NDA #	<u>20-974</u>	<u>Prozac tablets</u>

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved

product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that

could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # HCIE

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

— NDA # _____ Study # _____
— NDA # _____ Study # _____
— NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

— NDA # _____ Study # _____
— NDA # _____ Study # _____
— NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # HCIE

Investigation # __, Study # _____

Investigation # __, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 12,274 YES /X/ ! NO /___/ Explain: _____
!
!
!
!

Investigation #2 !
!
IND # YES /___/ ! NO /___/ Explain: _____
!
!
!
!

Investigation #3 !
!
IND # YES /___/ ! NO /___/ Explain: _____
!

!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	
_____	!	
_____	!	
_____	!	
_____	!	
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	
_____	!	
_____	!	
_____	!	
_____	!	

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain:

Signature of Preparer
Paul A. David, RPh
Title: Senior Regulatory Project Manager

Date

Signature of Office or Division Director
DNDP Division Director

Date

CC:
Archival NDA
HFD-120/Division File
HFD-120/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Russell Katz
8/8/02 07:31:22 AM

CERTIFICATION

NDA Application No.: 18-936

Drug Name: **Prozac[®] (fluoxetine hydrochloride)**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By:



Gregory T. Brophy, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: June 14, 2001

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see attached (Table 1)	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Christina Bodurow-Erwin, PhD	Acting Medical Director, Prozac Product Team
FIRM/ORGANIZATION	
Eli Lilly and Company	
SIGNATURE	DATE
Christina Bodurow Erwin	6/7/01

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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TO THE PUBLIC WITHOUT EXPRESS WRITTEN
CONSENT OF ELI LILLY AND COMPANY**

**Table 1: FDA FORM 3454 Attachment
Protocol B1Y-MC-HCIE**

Principal Investigators/Address	Sub-Investigators
Anne Becker, MD Harvard Eating Disorders Program Massachusetts General Hospital Parkman Street, WACC 725 Boston, MA 02114	(b) (6)
Barton J. Blinder, MD Newport Clinical Research 400 Newport Center Drive, Suite 706 Newport Beach, CA 92660	
Harry A. Brandt, MD Center for Eating Disorders, PA 7620 York Road Jordan Center, 4 th Floor Towson, MD 21204	
Lynn A. Cunningham, MD Vine Street Clinical Research 301 N. Sixth Street, Suite 330 Springfield, IL 62701	
James Ferguson, MD Pharmacology Research Corporation Commerce Park, Suite 350 448 East 6400 South Salt Lake City, UT 84107	
Tana Grady, MD Duke University Medical Center Department of Psychiatry DUMC 3837 Durham, NC 27710	
Harry Gwirtzman, MD Vanderbilt University Medical Center Division of Psychiatry 1500 21 st Avenue South Suite 2200 Nashville, TN 37212	
Katherine A. Halmi, MD New York Presbyterian Hospital- Cornell Medical Center 21 Bloomingdale Road White Plains, NY 10605	

Table 1: FDA FORM 3454 Attachment (continued)
Protocol B1Y-MC-HCIE

Principal Investigators/Address	Sub-Investigators
James Hudson, MD McLean Hospital 115 Mill Street Belmont, MA 02178	(b) (6)
Walter H. Kaye, MD Western Psychiatric Research Institute 3811 O'Hara Street Pittsburgh, PA 15213	
John Lauriello, MD Department of Psychiatry University of New Mexico Health Center, Room 470 2400 Tucker NE Albuquerque, NM 87131	
Russell D. Marx, MD 345 Saxony, Suite 201 Encinitas, CA 92024	
Pauline Powers, MD University of South Florida College of Medicine 3515 East Flatter Avenue Tampa, FL 33613	
Jeffrey Simon, MD Northbrooke Research Center 4600 west Schroeder Drive Brown Deer, WI 53223	
B. Timothy Walsh, MD New York State Psychiatric Institute Unit 98-Room 1132 722 West 168 th Street New York, NY 10032	
Kathryn Zerbe, MD Menninger Clinic 5800 SW Sixth Avenue Topeka, KS 66601	



NDA 18-936/S-065
NDA 20-101/S-027
NDA 20-974/S-001

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

We acknowledge receipt on February 28, 2002 of your February 27, 2002 resubmission to your supplemental new drug applications for Prozac (fluoxetine HCl) capsules (NDA 18-936), Solution (NDA 20-101), and Tablets (NDA 20-974).

This resubmission contains additional information regarding the proposed indication of (b) (4) of bulimia submitted in response to our December 20, 2001 action letter.

With this amendment, we have received a complete response to our December 20, 2001 action letter.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz
3/4/02 04:37:38 PM

DSI CONSULT: Request for Clinical Inspections

Date: July 18, 2001

To: Connie Lewin, GCPB Reviewer/HFD-47

From: Paul David, Senior Regulatory Project Manager, HFD-120

Subject: **Request for Clinical Inspections**
Eli Lilly and Company
Prozac (fluoxetine HCl) Capsules (NDA 18-936/S-065) Solution (NDA 20-101/SE8-027), and Tablets (NDA 20-974/SE8-001)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This Supplement provides for the following expansion of the patient population: a single, adequate and well controlled study for relapse prevention in bulimia.

Indication	Protocol #	Site (Name and Address)
Relapse prevention in bulimia	BIY-MC-HCIE	16 centers

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **11-1-01**. We intend to issue an action letter on this application by (action goal date) **12-23-01**.

All study centers are domestic (see attached list of investigators as well as our internal RTF meeting minutes dated 4-17-01).

Should you require any additional information, please contact Paul David.

Concurrence: (if necessary)

Russell Katz, MD, Division Director
Thomas Laughren, MD, Medical Team Leader
Roberta Glass, MD, Medical Reviewer

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>18-936/SE85-065; 20-101/S-027; NDA 20-974/S-001</u>	
Drug <u>Prozac (fluoxetine HCL) Capsules</u>	Applicant <u>Lilly</u>
RPM <u>Paul David</u>	Phone <u>x4-5530</u>
☒ 505(b)(1) ☐ 505(b)(2) Reference listed drug _____	
☐ Fast Track	☐ Rolling Review Review priority: ☒ S ☐ P
Pivotal IND(s) _____	
Application classifications: Chem Class _____ Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>12-23-01</u> Secondary <u>2-2-02</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: ☒ User Fee Paid
 ☐ User Fee Waiver (attach waiver notification letter)
 ☐ User Fee Exemption

- ◆ Action Letter..... ☐ AP ☒ AE ☐ NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling?	☐ Yes (include review) ☒ No
Immediate container and carton labels	N/A
Nomenclature review	N/A

- ◆ Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.

- Exception for review (Center Director's memo)..... N/A
- OC Clearance for approval..... N/A

◆ Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review)	☐ Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	_____
Copy of Applicant's commitments	_____
◆ Was Press Office notified of action (for approval action only)?.....	☐ Yes ☒ No
Copy of Press Release or Talk Paper.....	_____
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	_____
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	_____
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	X
Disclosable information – indicate where review is located	_____
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	none
Date of EOP2 Meeting _____	
Date of pre NDA Meeting _____	
Date of pre-AP Safety Conference _____	
◆ Advisory Committee Meeting	N/A
Date of Meeting	_____
Questions considered by the committee	_____
Minutes or 48-hour alert or pertinent section of transcript	_____
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	X
◆ Clinical review(s) and memoranda	X
◆ Safety Update review(s)	N/A
◆ Pediatric Information	
☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred Pediatric Page.....	X
☐ Pediatric Exclusivity requested? ☐ Denied ☒ Granted ☐ Not Applicable	

◆ Statistical review(s) and memoranda	<u>X</u>
◆ Biopharmaceutical review(s) and memoranda	<u>N/A</u>
◆ Abuse Liability review(s)	<u>N/A</u>
Recommendation for scheduling	<u> </u>
◆ Microbiology (efficacy) review(s) and memoranda	<u>N/A</u>
◆ DSI Audits	<u>X</u>
■ Clinical studies □ bioequivalence studies	<u> </u>

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ CMC review(s) and memoranda	<u>N/A</u>
◆ Statistics review(s) and memoranda regarding dissolution and/or stability	<u>N/A</u>
◆ DMF review(s)	<u>N/A</u>
◆ Environmental Assessment review/FONSI/Categorical exemption	<u>N/A</u>
◆ Micro (validation of sterilization) review(s) and memoranda	<u>N/A</u>
◆ Facilities Inspection (include EES report)	<u>N/A</u>
Date completed 	☐ Acceptable ☐ Not Acceptable
◆ Methods Validation	☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Pharm/Tox review(s) and memoranda	<u>N/A</u>
◆ Memo from DSI regarding GLP inspection (if any)	<u>N/A</u>
◆ Statistical review(s) of carcinogenicity studies	<u>N/A</u>
◆ CAC/ECAC report	<u>N/A</u>

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 17, 2001

TIME: 02:00 PM EDT

LOCATION: Conference Room E (4023)

APPLICATION: N18-936/SE8-065; 20-101/SE8-027; 20-947/SE8-001

TYPE OF MEETING: File/ Refuse-to-File

MEETING CHAIR: Russell G. Katz, M.D.

MEETING RECORDER: Merril Mille, R.Ph.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>HFD#</u>
1. Russell Katz, M.D.	Director	HFD-120
2. Thomas Laughren, M.D.	Clinical Team Leader	HFD-120
3. Roberta Glass, M.D.	Clinical Reviewer	HFD-120
4. Kun Jin, Ph.D.	Statistical Team Leader	HFD-713
5. Yeh-Fong Chen, Ph.D.	Statistical Reviewer	HFD-710
6. Constance Lewin, Ph.D.	DSI	HFD-45

BACKGROUND:

In an approval letter dated November 21, 1994, for use of Prozac in bulimia, the Agency requested an adequate and well-controlled relapse prevention trial in the maintenance of bulimia. The clinical study report for this trial was submitted as an efficacy supplement for the (b) (4) of relapse prevention in bulimia to 3 Prozac NDAs.

Submitted: February 22, 2001

Received: February 23, 2001

Filing date: April 24, 2001

Primary user fee due date: December 23, 2001.

MEETING OBJECTIVES: To determine if the efficacy supplements are acceptable for filing.

DISCUSSION POINTS (Bullet Format):

1. User Fee: The appropriate user fee was been paid on February 23, 2001.
(I.D. number (b) (4)/\$154,832)
2. Patent Information: (unknown)
3. Exclusivity Claim: (unknown)
4. Debarment Certification: Provided
5. Financial Disclosure: Missing.
6. Environmental Assessment: (Unknown) Request for categorical exclusion ?
7. Phase 4 Commitment: The clinical study report is intended to satisfy the post-approval commitment for the respective NDAs.
8. Clinical Efficacy Data: The supporting efficacy data is from a single Phase 4 study referred to as BIY-MC-HCIE. The primary outcome measure, according to the protocol, was a “win” on “time to relapse,” and the study appears on face to be positive on this outcome.
9. Clinical Safety Data: No issues.
10. Clinical Study Inspection: The Division recommends the inspection of this study by DSI.

DECISIONS (AGREEMENTS) REACHED:

- The application is satisfactory for filing.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

There was no assurance that Financial Disclosure information was provided in the submission.

ACTION ITEMS:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1. The application will be filed.		
2. We should ask the sponsor to correct the unreadable electronic files: Comments.XPT; Relapse.XPT; Summary.XPT	Project Manager	April 18, 2001
2. We should ask the sponsor to address the missing financial disclosure information.	Project manager	April 26, 2001

Minutes Preparer: _____
Merril J. Mille, R.Ph.

Chair Concurrence: _____
Thomas Laughren, M.D.
Psychiatry Team Leader

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

/s/

Merril Mille

4/24/01 11:24:43 AM

Thomas Laughren

4/24/01 11:27:04 AM



NDA 18-936/S-065
NDA 20-101/S-027
NDA 20-974/S-001

PRIOR APPROVAL SUPPLEMENT

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine HCl) capsules (NDA 18-936), Solution (NDA 20-101), and Tablets (NDA 20-974). The following information is pertinent to these supplements:

Review Priority Classification: Standard (S)

Date of Supplements: February 22, 2001

Date of Receipt: February 23, 2001

These supplemental applications provide for one adequate and well-controlled relapse prevention trial in the (b) (4) of bulimia.

We additionally note that this study responds to a Phase 4 commitment as requested in an Agency letter dated November 21, 1996.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 23, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 23, 2001 and the secondary user fee goal date will be February 23, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a

request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

NDA 18-936/S-065
NDA 20-101/S-027
NDA 20-974/S-001
Page 3

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz

3/1/01 03:53:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): HFD-710/BIOMETRICS			FROM: HFD-120/NEUROPHARMACOLOGY	
DATE 2-28-01	IND NO.	NDA NO. NDA 18-936/SE8-065 NDA 20-101/SE8-027 NDA 20-974/SE8-001	TYPE OF DOCUMENT Efficacy Supplement	DATE OF DOCUMENT 2-22-01
NAME OF DRUG Prozac (fluoxetine HCl) capsules (NDA 18-936), Solution (NDA 20-101), and Tablets (NDA 20-974)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Antidepressant/ OCD/Bulimia	DESIRED COMPLETION DATE UF DUE DATE 12/23/01
NAME OF FIRM: Lilly				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE--NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☐ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☒ OTHER (SPECIFY BELOW):			☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES			☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST	
COMMENTS/SPECIAL INSTRUCTIONS: Kun, Attached is the first volume, 1.1, of a 72 volume submission providing for a relapse prevention study in bulimia patients. The 60 Day Filing Date is 4/23/01, and the Primary UF Due Date is 12/23/01. The reviewing medical officer is Dr. Glass. Our 45 Day file/refuse to file meeting is Tuesday 4/17. Please e-mail me the reviewer assignment so that I can place the reviewer in RCM, and e-mail the DDR to provide the reviewer the trailer volumes (1.2-1.71). Thanks, Paul David, PM x 4-5530				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

/s/

Paul David

2/28/01 03:07:16 PM