CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/S-036

APPROVAL LETTER

NDA 18-936/S-036
NDA 20-101/S-009

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Senior Director U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

MAR 25 1997

Dear Dr. Brophy:

Please refer to your October 24, 1994, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac (fluoxetine hydrochloride) pulvules (NDA 18-936) and solution (NDA 20-101).

Reference is also made to an Agency letter dated October 20, 1995, informing you that these supplemental applications were approvable.

We acknowledge receipt of your resubmission dated October 1, 1996, providing for a response to our October 20, 1995 Agency letter as well as your amendments dated January 21, and 28, 1997.

The User Fee goal date for these applications is April 2, 1997.

The above supplemental applications provide for revisions to the **Clinical Pharmacology**, **Indications and Usage**, **Precautions**, and **Dosage and Administration** sections.

We additionally refer to a telephone conversation dated March 19, 1997 between Mr. Dave Johnson, of your firm, and Mr. Paul David, of this Agency, providing for agreement to the labeling revisions transmitted via facsimile by your firm on March 20, 1997.

We have completed the review of these supplemental applications, including the submitted draft labeling, 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 enclosed marked-up draft labeling. Accordingly, these supplemental applications are approved effective on the date of this letter.

The labeling accompanying this letter should be used for marketing this drug product. This labeling is identical to the draft labeling agreed upon in your facsimile transmitted on March 20, 1997. For convenience, all labeling changes made since the approval of the last labeling supplement (18-936/S-004, Label Code - PV 2470 DPP) on November 21, 1996, appear as shaded text (redline font) in the attached labeling.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. These revisions are terms of the supplemental NDA approval. Marketing the product before making the agreed

upon revisions in the product's labeling may render the product misbranded and an unapproved new drug. Please submit 20 copies of the FPL as soon as it is available, in no case 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, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 18-936/S-036 and 20-101/S-009. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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, please contact Paul David, R.Ph., Project Manager, at (301) 594-5530.

Sincerely yours,

/S/ 3/25/97

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

ATTACHMENT

cc:
ORIG NDA 18-936/S-036
ORIG NDA 20-101/S-009
HFD-002/ORM (with labeling)
HFD-101/Office Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-120/DIV FILES 3/20/97 /S/ 3-21-97
HFD-120/PLeber/TLaughren/AMosholder/GBurkhart
HFD-120/GFitzgerald/BRosloff/EFisher 3/20/97 /S/ 3/20/97
HFD-120//PDavid /S/ 3.20.97 3/20/97
HFC-130/JAllen
HFD-713/TSahlroot/JChoudhury /S/ 3/21/97
HFD-860/RBaweja /S/ 3/20/97
03/13/97pd
Doc #DAVID\LTRPZS36.AP1
APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/S-036

APPROVED LABELING

ATTACHMENT 1

FINAL LABELING

Note: We have shaded (redline font) the parts of labeling that represent changes from currently approved Prozac labeling to facilitate supervisory overview.

PROZAC
FLUOXETINE HYDROCHLORIDE

DESCRIPTION

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

[Insert structural formula here]

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) or 20 mg (64.7 µmol) of fluoxetine. The Pulvules also contain F D & C Blue No. 1, gelatin, iron oxide, silicone, starch, titanium dioxide, and other inactive ingredients.

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.

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 a_1-adrenergic receptors has been hypothesized to be

associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant 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 and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Protein Binding

Over the concentration range from 200 to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and a_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 tricyclic antidepressants. 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 4 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 tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) 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 4-5 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.

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 two 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

Depression

The efficacy of Prozac for the treatment of patients with depression (≥ 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 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 depression. 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 < 7. 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 depression

by DSMIIIR 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 depression 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.

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 2 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

		Prozac		
Outcome Classification	Placebo	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 mg/day 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 3 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 3 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.

INDICATIONS AND USAGE

Depression

Prozac is indicated for the treatment of depression. The efficacy of Prozac was established in 5- and 6-week trials with depressed outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under Clinical Pharmacology).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied.

The efficacy of Prozac in maintaining an antidepressant response 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).

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 effectiveness of Prozac in long-term use, i.e., for more than 16 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).

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.

WARNINGS

Rash and Possibly Allergic Events

In US fluoxetine clinical trials, 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, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 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, 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, 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.

PRECAUTIONS

General

Anxiety and Insomnia

In US placebo-controlled clinical trials for depression, 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 obsessive-compulsive disorder, 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 in US placebo controlled fluoxetine clinical trials were anxiety (< 2%), insomnia (< 2%), and nervousness (< 1%) (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 depression, 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 depression, 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 antidepressants.

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, 0.7% of 10,782 patients reported mania/hypomania.

Seizures

In US placebo-controlled clinical trials for depression, 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, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide

The possibility of a suicide attempt is inherent in depression 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 depression and bulimia and depression, the same precautions observed when treating patients with depression 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

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 tricyclic antidepressants. Many drugs, such as most antidepressants, 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 4 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 tricyclic antidepressants).

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.

Benzodiazepines

The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology). Coadministration 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 Antidepressants

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 tricyclic antidepressant (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).

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/m^2 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 top 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 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/m^2 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/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 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/m^2 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

Evaluation of patients over the age of 60 who received Prozac 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs (see Age under Clinical Pharmacology).

Hyponatremia

Several 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 a placebo-controlled, double-blind trial, 10 of 313 fluoxetine patients and 6 of 320 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. 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 US 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 depression, OCD, and bulimia in US controlled clinical 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 depression, 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 DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event					
	Depression		**OCD**		**Bulimia**	
Body System/ Adverse Event	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)
Body as a Whole						
Asthenia	9	5	15	11	21	9
Flu syndrome	3	4	10	7	8	3
Cardiovascular System						
Vasodilatation	3	2	5	--	2	1
Digestive System						
Nausea	21	9	26	13	29	11
Anorexia	11	2	17	10	8	4
Dry mouth	10	7	12	3	9	6
Dyspepsia	7	5	10	4	10	6
Nervous System						
Insomnia	16	9	28	22	33	13
Anxiety	12	7	14	7	15	9

Nervousness	14	9	14	15	11	5
Somnolence	13	6	17	7	13	5
Tremor	10	3	9	1	13	1
Libido decreased	3	--	11	2	5	1
Abnormal Dreams	1	1	5	2	5	3
Respiratory System						
Pharyngitis	3	3	11	9	10	5
Sinusitis	1	4	5	2	6	4
Yawn	--	--	7	--	11	--
Skin and Appendages						
Sweating	8	3	7	--	8	3
Rash	4	3	6	3	4	4
Urogenital System						
Impotence†	2	--	--	--	7	--
Abnormal ejaculation†	--	--	7	--	7	--

†Denominator used was for males only (N=690 Prozac depression; N=410 placebo depression; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia).
--Incidence less than 1%.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS:
INCIDENCE IN US DEPRESSION, OCD, AND BULIMIA PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of patients reporting event	
	Depression, OCD, and Bulimia combined	
Body System/Adverse Event*	Prozac (N=2444)	Placebo (N=1331)
Body as a Whole		
Headache	21	20
Asthenia	12	6
Flu syndrome	5	4
Fever	2	1

Cardiovascular System		
Vasodilatation	3	1
Palpitation	2	1
Digestive System		
Nausea	23	10
Diarrhea	12	8
Anorexia	11	3
Dry Mouth	10	7
Dyspepsia	8	5
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	20	11
Anxiety	13	8
Nervousness	13	9
Somnolence	13	6
Dizziness	10	7
Tremor	10	3
Libido decreased	4	--
Respiratory System		
Pharyngitis	5	4
Yawn	3	--
Skin and Appendages		
Sweating	8	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	3	1
Urogenital System		

*Included are events reported by at least 2% of patients taking Prozac except the following events, which had an incidence on placebo ≥Prozac (depression, OCD, and bulimia combined): abdominal pain, abnormal dreams, accidental injury, back pain, chest pain, constipation, cough increased, depression (includes suicidal thoughts), dysmenorrhea, gastrointestinal disorder, infection, myalgia, pain, paresthesia, rhinitis, sinusitis, thinking abnormal.
--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) in depression, OCD, and bulimia.

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

Depression, OCD, and Bulimia combined	Depression	OCD	Bulimia
--	--	Anxiety (2%)	--
Insomnia (1%)	Insomnia (1%)	--	Insomnia (2%)
--	Nausea (1%)	--	--
Nervousness (1%)	Nervousness (1%)	--	--
--	--	Rash (3%)	--

Other Events Observed In All US Clinical Trials

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials (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 one 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 1 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: 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; 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, thrombcythemia, 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*.

†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, 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, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, 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, pancreatitis, pancytopenia, priapism, pulmonary embolism, QT prolongation, Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, 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

As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved 3 drugs yielding plasma concentrations as follows: fluoxetine,

1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the 2 deaths noted above, all other overdose cases recovered without residua.

Since introduction, reports of death attributed to overdosage of fluoxetine alone have been extremely rare.

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 6 dogs purposely overdosed with oral fluoxetine, 5 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

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for Prozac.

Due to the large volume of distribution of Prozac, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. A specific caution involves patients taking or recently having taken fluoxetine who might ingest by accident or intent, excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Other Antidepressants under Precautions).

The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR).

DOSAGE AND ADMINISTRATION

Depression

Initial Treatment

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 antidepressant response 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 no 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 antidepressants, the full antidepressant 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 Usage in the Elderly 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 depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical

to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of Prozac has shown that its antidepressant efficacy 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).

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 depression, 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 Usage in the Elderly 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 depression 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 Usage in the Elderly 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, bulimia is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 16 weeks has not been documented in controlled trials, some patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, patients should be periodically reassessed to determine the need for continued 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 coadministered or has been recently discontinued (see Other Antidepressants 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).

HOW SUPPLIED

Pulvules:
10 mg*, green and green (No. 3104)--(100s) NDC 0777-3104-02;
(20 FlexPak§ blister cards of 31) NDC 0777-3104-82
20 mg*, green and off-white (No. 3105)--(30s) NDC 0777-3105-30; (100s) NDC 0777-3105-02; (2000s) NDC 0777-3105-07; (ID†100) NDC 0777-3105-33; (20 FlexPak§ blister cards of 31) NDC 0777-3105-82

Liquid, Oral Solution: 20 mg*/5 mL, mint flavor (M-5120‡)--(120 mL) NDC 0777-5120-58
*Fluoxetine base equivalent.
†Identi-Dose® (unit dose medication, Dista).
‡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.

CAUTION--Federal (USA) law prohibits dispensing without prescription.

Literature revised [Insert date]
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/S-036

PHARMACOLOGY 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: January 18, 1995

FROM: Steven Sparenborg, Ph.D. SS
Pharmacology Reviewer

TO: Division File for: NDA 18-936 Prozac
NDA 19-839 Zoloft
NDA 20-031 Paxil
NDA 20-101 Prozac
NDA 20-187 Prozac

SUBJECT: Proposed changes for package insert labeling regarding Pregnancy Category and associated text.

Contents

cc: Tom Laughren, M.D.
Group Leader, Psychiatric Drug Products Group

Glenna G. Fitzgerald, Ph.D.
Supervisory Pharmacologist

APPEARS THIS WAY
ON ORIGINAL

INTRODUCTION

The drug products PROZAC, ZOLOFT and PAXIL are selective serotonin reuptake inhibitors (SSRI's) that have been approved for marketing in the recent past. Each of them carry the labeling of Pregnancy Category B. The SSRI LUVOX and the combined 5-HT and NE reuptake inhibitors EFFEXOR, SERZONE and ASENDIN have been labeled with Pregnancy Category C. The actual results from pre-clinical reproduction studies are very similar for all 7 drugs.

It is proposed that PROZAC, ZOLOFT and PAXIL be re-labeled to Pregnancy Category C and that labeling text be changed to report effects in rat pups. The justifications for making these changes are stated below. The text changes are proposed in the section headed as LABELING. The current labeling for LUVOX, EFFEXOR, SERZONE and ASENDIN are in Appendix A. No changes are proposed for these four drug products. They are included for comparison and to establish consistency in labeling among these seven drugs. A summary of the results for all pertinent reproduction studies is found in Appendix B.

The scope of this re-labeling proposal does not extend to tricyclic antidepressant drugs. The reproduction studies for those drugs, if performed, were not done with the same standards by which more recently approved drugs have been examined and may not have any Pregnancy Category in their labeling.

APPEARS THIS WAY
ON ORIGINAL

JUSTIFICATION

Labeling drugs in a consistent manner is necessary and desirable in a legal, a scientific, and a fair market sense.

LEGAL - 21 CFR 201.57 requires that any drug producing a toxic effect in the F_1 generation be labelled with pregnancy category C. The following text within quotation marks is taken from this section of the Code:

> Pregnancy category B is for drugs that "have failed to demonstrate a risk to the fetus...in animal reproduction studies...and there are no adequate and well-controlled studies in pregnant women".
>
> Pregnancy category C is for drugs that "have shown an adverse effect on the fetus...in animal reproduction studies...and there are no adequate and well-controlled studies in pregnant women, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks".

The labeling of LUVOX, EFFEXOR, SERZONE and ASENDIN was done with strict adherence to this code.

SCIENTIFIC -

Increased pup death within the first few days after birth is a common finding when serotonin reuptake inhibitors are given at high doses in reproduction studies. Researchers counted the number of pups found dead in either Days 0-4, Days 0-5 or Days 0-7 after birth (different sponsors chose different lengths of time). Within this early period, all of the drugs mentioned in the Introduction above were found to have significantly increased the number of dead pups beyond the number seen in control groups. The investigational new drugs _____ substantially inhibit serotonin uptake and they also increase pup mortality within this time period. Increased mortality in this period is not unique to serotonin reuptake inhibitors.

The effects of increased pup mortality, along with increased numbers of stillborn pups and reduced birth weights of pups, occur in the absence of significant maternal toxicity. This suggests that these effects are not readily attributable to an abnormal physiology in the dam brought about by high doses of the drug. Rather, the good health of the dams suggests that the drugs induce a developmental abnormality sufficient to kill some of the pups. It also suggests that effects on a human fetus might occur without any noticeable signs in the mother. Preclinical teratogenic effects have not been noted with any of these drugs.

Toxic Effects in Peri-Postnatal Studies

	Mortality	Stillbirths	Reduced Pup weight	Maternal Toxicity
SSRI's				
PROZAC	yes	yes	yes	no[a]
ZOLOFT	yes	yes	yes	yes[a, c]
PAXIL	yes	no	no	no
LUVOX	yes	yes	yes	yes[b]
5-HT & NE				
EFFEXOR	yes	yes	yes	no[a]
SERZONE	yes	no	yes	no[a]
ASENDIN	yes	yes	yes	?[d]

[a] Bodyweight gains in dams were reduced by about 5-15% relative to controls. Part of this difference could be attributed to lower pup weights, but mostly to reduced food intake at the start of dosing. Reduced weight gain need not be considered toxic to pups. A control group of dams that was pair-fed the same amount of food as a group treated with fluoxetine had reduced weight gain as did the treated group, but did not have reduced pup survival as did the treated group (see Vorhees, Acuff-Smith, Schilling, Fisher, Moran and Buelke-Sam, *Fund. App. Tox., 23*, 194-205.

[b] Fluvoxamine did not affect the bodyweights of the dams, but 3/46 treated dams had dystocia which led to the death of 2 of the dams and the loss of all three litters. 2 other treated dams had delayed parturition.

[c] Sertraline induced hyperactivity, nervousness or aggressiveness in some of the mid- and high-dose dams.

[d] Information about maternal toxicity was not available from the Division File for this drug. It is a tricyclic antidepressant approved in 1980.

The no-effect doses for pup mortality, expressed as multiples of the maximum recommended human dose based on body surface area, ranged from less than 0.2 to 1.3

MARKET EFFECT

The safety labeling of a drug product can be assumed to have an effect on the volume of prescriptions written for the drug. Doctors and patients may assume from current labeling that PROZAC, ZOLOFT and PAXIL are relatively more safe during pregnancy than LUVOX, EFFEXOR, SERZONE and ASENDIN. The data in reproduction studies do not suggest that one is more safe than another. Therefore, drugs labeled Category B may have an unfair market advantage over those labeled Category C.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

LABELING

Shaded areas of text are proposed additions to labeling. Comparative doses are based on a human weight of 60 kg. Doses based on body surface area were computed using conversion factors included in a CDER memo from Dr. J. De George, dated October, 1993.

PROZAC

Impairment of Fertility - Two fertility studies conducted in rats at doses of approximately indicated that fluoxetine had no adverse effects on fertility.

Pregnancy

Teratogenic Effects - Pregnancy Category ~~B~~ C:

Labor and Delivery

The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers

Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. No adverse effects on the infant were reported.

2 page(s) of revised draft labeling has been redacted from this portion of the review.

APPENDICES

A. LABELING FOR LUVOX, EFFEXOR, SERZONE and ASENDIN

LUVOX

Impairment of Fertility

In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy

Teratogenic Effects - Pregnancy Category C

In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis). While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of Luvox therapy to the mother.

EFFEXOR

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or up to 2 times on a mg/m^2 basis.

Pregnancy

Teratogenic Effects - Pregnancy Category C

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the maximum recommended human daily dose on a mg/kg basis, or 2.5 times (rat and 4 times (rabbit) the human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times (mg/kg) or 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of Effexor on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether venlafaxine hydrochloride or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Effexor is administered to a nursing woman.

Impairment of Fertility

A fertility study in rats showed a slight decrease in fertility at 200 mg/kg/day (approximately 3 times the maximum human daily dose on a mg/m^2 basis) but not at 100 mg/kg/day (approximately 1.5 times the maximum human daily dose on a mg/m^2 basis).

Pregnancy

Teratogenic Effects - Pregnancy Category C

Reproduction studies have been performed in pregnant rabbits and rats at daily doses up to 200 and 300 mg/kg, respectively (approximately 6 and 5 times, respectively, the maximum human daily dose on a mg/m^2 basis). No malformations were observed in the offspring as a result of nefazodone treatment. However, increased early pup mortality was seen in rats at a dose approximately 5 times the maximum human dose, and decreased pup weights were seen at this and lower doses, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. The no effect dose for rat pup mortality was 1.3 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Nefazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of SERZONE on labor and delivery in humans is unknown.

It is not known whether SERZONE or its metabolites are excreted in human milk, Because many drugs are excreted in human milk, caution should be exercised when SERZONE is administered to a nursing woman.

ASENDIN

Impairment of Fertility

Treatment of male rats with 5 to 10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.

PREGNANCY: Pregnancy Category C: Studies performed in mice, rats and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3 to 10 times the human dose. Decreased postnatal survival (between days 0 to 4) was demonstrated in the offspring of rats at 5 to 10 times the human dose. There are no adequate and well-controlled studies in pregnant women. ASENDIN a*moxipine* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women.

B. TOXICOLOGY SUMMARIES

PROZAC -

A segment III study was not performed with this drug, but pup delivery and rearing occurred in two Segment I studies. One study used gavage dosing of dams only at 2, 5, and 12 mg/kg from before mating through weaning. In the other, fluoxetine was put in the diet at concentrations of 0.002%, 0.005% or 0.0125% in the diet of males and females from before mating through weaning. The actual drug delivery to dams during gestation averaged 1.4, 3.5, and 8.6 mg/kg. Because of increased food consumption during lactation, dams received 2, 5.5, and 14 mg/kg, respectively, during the post-natal period.

The only evidence of maternal toxicity was reduced weight gain in the high-dose groups, which occurred before mating. These dams gained weight at a fast rate during lactation, so that their weights were about 95% of controls by the end of the study. The reduced weight gain was accompanied by similarly reduced food consumption before mating in the dietary study and throughout the treatment period in the gavage study.

Pup survival was reduced in the high-dose groups of both studies. By Day 7 pp, only 60-70% of live-born pups from treated dams were still alive, whereas 92-93% of control pups were alive. 7% of control pups were stillborn in the gavage study, but 14% of high-dose pups were stillborn. Fluoxetine did not affect the rate of stillbirths in the dietary study.

The bodyweights of pups born to high-dose dams were lower than controls (9-17% less) throughout all or most of the lactation period, but the difference did not increase over time.

ZOLOFT -

The sponsor performed two Segment I studies and two Segment III studies. A special study was performed which does not neatly fit into the Segments of standard reproduction studies. In this latter test, the dosing period was varied to isolate the critical period in which the drug caused pup deaths and low birth weights.

In the first Segment I study, doses of 10, 40 and 80 mg/kg were given to males and females. There was an effect of the drug on fertility. Females with plugs did not conceive, but it was not determined whether this was due to the male or the female. There was no problem with fertility in the second Segment I study. Doses of 10, 20 and 80 mg/kg were used in this study. Hyperactivity was noted in the MD and HD animals of the first study and nervousness was noted in the MD and HD animals of the second study. Body weight gain of the dams was only slightly affected in the first study (56% gain during gestation for controls, but only 49% for the HD dams). The 5% reduction noted in HD dams of the second study was attributed to their having fewer embryo's. Survival at Day 4 pp of the first study was 99.5%, 97.3%, 86% and 70% for the C, L, M and H groups, respectively. In the second study, survival rates at

Day 4 were 98.5%, 94.6%, 68.8% and 63.5%. Further reductions in survival after Day 4 were slight and not dose-related in either study. Pup weights for the HD group in the first study were about 10% less than controls on Day 1 and Day 4. Similarly, HD pup weights in the second study were 10% less than controls and the MD pups were 5% less than controls on Day 4. By Day 21 in both studies, surviving pups from treated dams did not weigh less than controls.

A standard Segment III was conducted using doses of 10, 20 and 80 mg/kg. Hyperactivity and aggressiveness were seen in some dams given 20 and 80 mg/kg. High-dose dams did not gain weight during the first three days of dosing, but resumed weight gain at a rate equal to the control group thereafter. The stillbirth rate was 0, 3, 8 and 16% for the C, L, M and H groups, respectively. Pup survival was drastically reduced by sertraline treatment. The survival rates on Day 4 of all liveborn pups were 99, 93, 75 and 47% . Pup weights of the mid- and high-dose groups were significantly reduced during the first four days, up to 83% of control weights, but gained rapidly thereafter so that they were equal to, or at most only 95% of controls by Day 21.

A Segment III cross-fostering study was performed using the dose of 80 mg/kg or vehicle. Dosing continued from Day 15 of gestation through Day 21 pp. The clinical signs and weight gain effects seen in this study were the same as those seen in the previous Segment III study. On Day 1 pp, the litters of half of the treated dams were exchanged with litters from control group dams and rearing continued through Day 21 pp. The survival rate of pups born to control group dams was 99%, whether raised by their own mothers or by foster mothers. The survival rates of pups born to treated dams were 42% and 45% for those raised by their birth mothers and by foster mothers, respectively. Pup body weights were affected as in the earlier Segment III study, showing a strong prenatal effect of the drug on birthweight. In this study, however, there was an effect of the drug during lactation, such that those pups reared by treated dams did not gain as much weight as those reared by control dams.

A final study revealed that the critical time period for sertraline to affect survival and birthweight was between gestation Day 15 and the end of gestation. Pups born to dams that received the drug between Day 0-5 or Day 0-10 or Day 0-15 did not have reduced survival or weight. The dose used in all groups was 80 mg/kg.

PAXIL -

Two Segment I and two Segment III studies were performed in which dams had the opportunity to give birth and raise pups through weaning age. Drug-related decreases in pup survival were found in each study.

Doses of 5, 15 and 50 mg/kg were used in the first Segment I study. Maternal toxicity was present at the mid- and high-dose groups as evidenced by drastically reduced weight gains, but the low dose did not affect weight gain in the dams. At the low-dose, only 3/12 dams had viable young after Day 9 pp. Survival in the higher dose groups was accordingly less than in the low-dose group. 13/14 control dams reared pups to weaning.

A second Segment I study used the dose of 1 mg/kg. There were no signs of maternal toxicity at this dose, but only 76.2% of treated pups survived until weaning. One of eleven treated dams suffered complete litter loss. All ten control dams raised some young to weaning age with a survival rate of 90.7% overall. Fetal weights were not lower than controls, but pup weights were not mentioned in a review of this study.

Doses of 1, 4, and 15 mg/kg were given to pregnant rats in a preliminary, modified, Segment III study. Dosing only took place on the last four days of gestation and the first four days of lactation. This study was only mentioned briefly in our review and the only results included were that the pup survival rates were 65 and 28% for the 4 and 15 mg/kg doses, respectively.

The final Segment III study also used a modified dosing regimen. The dose of 1 mg/kg was given to pregnant dams from Day 15 *post coitum* to Day 21 *post partum.* Doses of 3.3 and 10 mg/kg were given only on Days 5 to 24 *post partum.* These dosing regimens did not produce signs of maternal toxicity, but survival in the group treated with 1 mg/kg was significantly lower than in controls. The higher doses of 3.3 and 10 mg/kg did not affect survival. All four groups in this study had dams with reduced maternal mammary development, which apparently lowered survival in all groups in a non-drug-related manner. The survival rates on Day 25 were 83%, 71.4%, 93.5% and 88.2% for the C, L, M and H groups, respectively. The fact that the 3.3 and 10 mg/kg dose groups did not experience reduced survival strongly suggests that there is a critical period in which paroxetine exerts a lethal effect on the rat F_1 generation. That period lies within the range of 4 days before birth to 4 days after birth.

LUVOX -

Fluvoxamine was given to pregnant dams in a Segment I and a Segment III study at the doses of 5, 20 and 80 mg/kg. There was no sign of maternal toxicity in either study. Nevertheless, pup mortality increased in a dose-related and significant manner during the lactation period of the Segment III study, 4, 17, 17 and 25% for the C, L, M and H groups, respectively. Pup survival was slightly, but not significantly, reduced in the two higher dose groups of the Segment I study. Pup weights were not decreased by the drug.

A second Segment III study was performed with only one test-drug group, given 160 mg/kg of fluvoxamine per day, and a control group. Approximately half of the litters of each group were cross-fostered to dams of the opposite group on the day of birth. There still were no signs of maternal toxicity, except that two treated dams died of difficulties in delivery and another died of unknown causes. Two other treated dams lost their litters through dystocia. Aside from these four lost litters, 11/43 treated dams lost their litters during the first 4 days postpartum, one-third of which had been cross-fostered from control dams. All 48 control dams reared their own or a fostered litter.

Before the litters were cross-fostered, 16% more of the treated group pups were found to be non-viable than were the control group pups, most of which were stillborn. Considering all litters in which there were some survivors, the pup mortality rate in litters reared by treated dams was twice the rate of control-dam reared litters during Days 1-4 pp. Although birth weights were not affected by the drug, the body weights of pups born to and reared by treated dams were significantly lower than controls after weaning.

EFFEXOR -

The most severe fetal toxicity occurred in the rat Segment III study, in which doses of 10, 30, and 80 mg/kg were used. Weight gain in HD dams was interrupted during the first five days of dosing (20% less than controls). Food consumption was likewise interrupted, but weight gain and eating were not affected by drug-treatment during lactation. No other maternal toxicity was reported. There was a dose-dependent increase in the number of runts (28, 16, 42, 74 and 108 for C1, C2, LD, MD and HD, respectively). HD birth weights were 12-13% lower than controls and MD weights were lower by 8%. Weight gains during lactation were not lower in treated pups than in controls, groups, resulting in negligible weight differences at post-partum day 21.

Survival was drastically reduced for pups born to HD dams in the Segment III study. The effect was manifested at birth and during Days 0-5 post partum. 3.5% of control pups were stillborn, but 22% of HD pups were stillborn. 60% of those HD pups born alive died within the first 5 days, compared to only 10% of control pups. After that, survival rates were equal, but by Day 21 post-partum, all pups from 10 HD litters were dead. No other measures revealed any toxicity of the drug in the F_1 generation. Behavioral and sensory testing and developmental landmarks were normal for descendants of the drug-treated groups. The sponsor cited some evidence of maternal neglect and argued that it may have contributed to pup mortality, but the neglect may have been instigated by drug-induced pathology in the pups.

Similar toxicity might have been expected to occur in the Segment I study as well, but perhaps because of a lower dose (60 mg/kg vs. 80 mg/kg) it did not. Also, the metabolic reaction of the dams may have been different in the two studies. In the Segment I study, dosing had begun earlier and therefore may have allowed the dams to adjust metabolically and/or cognitively before having to care for pups.

SERZONE -

A Segment I study was conducted using doses of 50, 100 and 200 mg/kg given to male and female rats. There was no evidence of maternal toxicity, nor was the survival rate affected by any dose of the drug. Pup weights were slightly decreased in the HD group during Weeks 3-5.

Higher dose levels were used in a Segment III study (75, 150 and 300 mg/kg). Nefazodone produced a dose-related decrease in dam body weight, such that the final weight of the HD group was only 90% as much as the control group. Food consumption was also reduced in a dose-related manner. The HD group ate 25-40% less than controls in some weeks. The survival rates at Day 4 pp were 99, ?, 96 and 65% for the C, L, M and H groups, respectively. Pup weights at birth were 95 and 86% of controls for the M and H groups. There was no recovery of this decreased birth weight during lactation. On Day 21 pp, body weights were 90, 88 and 79% of controls for the L, M and H groups.

ASENDIN - The Pharmacologist's review of this drug was not available from which to write a summary.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/S-036

ADMINISTRATIVE DOCUMENTS

CONFERENCE CALL
NDA 18-936/S-036
NDA 20-101/S-009

Date: March 12, 1997; 3:00 - 3:40 PM
Location: Conference Room E; WOC2
Firm: Eli Lilly
Drug: Prozac (fluoxetine hydrochloride) Capsules (18-936) and solution (20-101)
Participants:
FDA:
Dr. Leber, Dr. Laughren, Dr.Mosholder, Dr. Burkhart, Dr. Fitzgerald, Dr. Fisher, Dr. Rosloff, Dr. Glass, and Mr. David

Lilly:

Judy Buelke-Sam, Toxicologist
Gary Tollefson, MD, Clinical Research Physician
Gary Goldstein, M.D., Clinical Research Physician
David Michaelson, M.D., Clinical Research Physician
Reed Tarwater, Ph.D., Regulatory Scientist
Greg Brophy, Ph.D., Director, Regulatory Affairs
Dave Johnson, Regulatory Scientist

Purpose
The Agency requested in an approvable letter for NDA supplements 18-936/S-036 & 20-101/S-009 dated October 1, 1995, that Lilly change their pregnancy category rating from a category B to a category C. Lilly contended that there was sufficient clinical data to refute the preclinical findings, and therefore, they requested to retain their category B classification.

Discussion
Both the Agency and Lilly agree that the preclinical findings demonstrate adverse events in newborn animals. However, the Agency does not believe that the clinical data submitted by Lilly, i.e., their fluoxetine patient registry and the Chambers, Pastuszak, and Nulman publications, constitute adequate and well controlled studies in pregnant women to demonstrate no risk to the fetus as defined in 21 CFR 201.57(f)(6).

Lilly's fluoxetine patient registry does not have the capacity to address the issue of neonatal risk primarily due to the fact that there was a 37% loss to follow- up in the registry. The other studies submitted by Lilly were too small to make any conjectures about neonatal risk. The addition of this information to the Prozac labeling would only falsely reassure prescribing physicians.

The Agency stated that the only way for Lilly to retain a category B rating would be to collect a large fluoxetine patient registry database with little to no patients lost to follow-up. Alternatively, they may conduct a large, well controlled clinical study.

Conclusions
The conversation concluded with Lilly agreeing to work with the Agency in formulating language for the pregnancy section of labeling. It was noted that labeling agreement has been reached between Lilly and

the Agency on all aspects of this supplement except for the revisions to the carcinogenicity, pregnancy, and labor and delivery sections of the labeling. The PDUFA due date for completion of these applications is April 2, 1997. Lilly stated that they would fax the Agency alternative labeling by COB March 14, 1997.

/S/

Paul A. David, R.Ph.
Project Manager

cc:
IND ORIG — /S/ 3-18-97
IND: DIV FILE
HFD-120/PLeber/TLaughren/AMosholder/GBurkhart
HFD-120/GFitzgerald/BRosolff/EFisher
HFD-120/PDavid
rd:03/14/97pd;
rev:03/14/97am;03/17/97gb
ft:03/18/97pd
DOC #DAVID\03-12-97.MM
MEETING MINUTES

3/7/97

MEMORANDUM

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

DATE: 3/05/97

FROM: Greg Burkhart M.D., M.S.
Safety Team Leader, Neuropharmacological Drug Products, HFD-120

TO: File: NDA 18-936 & NDA 20-201

SUBJECT: Review of Sponsor's Clinical Data Submitted in Response to the FDA Proposal to Change the Fluoxetine Pregnancy Category from B to C.

This memorandum reviews the clinical data cited by the sponsor in submissions dated October 1, 1996 and January 21, 1997. These data are purported to support the sponsor's position that fluoxetine should remain labeled as pregnancy category B.

Background

In the October 20, 1995 approvable letter, the FDA suggested that the pregnancy category of fluoxetine be changed from B to C. This change was proposed because animal reproductive studies observed increased stillbirth, increased neonatal mortality and decreased birth weight associated with maternal fluoxetine use. These findings were interpreted by the FDA as suggesting that maternal fluoxetine use could impair fetal growth and development.

According to 201.57, *"If animal studies have shown an adverse effect (other than a decrease in fertility), but adequate and well controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk in latter trimesters), the labeling shall state "Pregnancy Category B".* The October 1, 1996 and January 21, 1997 submissions are purported by the sponsor to contain clinical data from the sponsor's pregnancy registry and from three independent publications that, in their opinion, are adequate and well controlled and show no evidence of fetal risk from human maternal exposure in any trimester. The sponsor has concluded that these data in aggregate meet the burden of 201.57 and that fluoxetine should be labeled pregnancy category B.

Ambiguity in the semantics of 201.57 particularly under the subheading *"teratogenic risk"* makes the intent of the regulation difficult to interpret. First, it isn't clear whether this section,

which is presumably focused on teratogenic risk, also considers non-teratogenic fetal risks such as those resulting from either toxicity or that impair fetal growth and development. It seems to imply that a human late-pregnancy fetal risk that is non-teratogenic prohibits sufficient human evidence of no teratogenic risk from overriding positive animal reproductive findings at the point in 201.57 where it says, "*(and there is no evidence of risk in latter trimesters)* ".

An even more fundamental problem with 201.57 than vagueness about whether it is referring to teratogenic and/or non-teratogenic findings, is the epidemiologic meaning of "no evidence of risk" even assuming that the general context is that of teratogenic risk. This is directly relevant since 201.57 is stating that adequate and well controlled evidence of no human risk can override positive animal studies. Thus, the reviewer's interpretation of what "no evidence of risk" means can have a great impact on whether the evidence is sufficient. This problem is somewhat analogous to what interpretation can be given to active control trials that find no difference when there is no placebo group.

There are two epidemiologic concepts that are helpful to consider when defining what is meant by "no evidence of risk". For purposes of discussion, these are referred to below as *minimally detectable excess risk* and *outcome misclassification.* While they will be discussed somewhat separately, the principles underlying each overlap to a great extent.

Minimally detectable excess risk refers to what increase in risk above background must be detectable to argue that a set of clinical data shows "no evidence of risk". It is a function of not only the sample size but also the internal validity of the study(s) used to collect the data, this latter issue very much related to outcome misclassification. For example, experts would have little disagreement in concluding that a follow-up study of 10 pregnancies with a common first trimester exposure and normal birth outcomes is insufficient evidence of no fetal risk. In such a case, data validity would be largely irrelevant since the small sample size reduces the power to have observed anything anyway. Alternatively, 100,000 pregnancies in which both maternal exposure and fetal outcome have been grossly misclassified, may also provide insufficient evidence to conclude there is no fetal risk. In this case, not because of sample size, but because of the validity of the observations made.

If we go further and assume that validity is not an issue (or that it is a matter of review), then one can simply state what degree of excess risk the data is sufficiently powered to detect. If one is interested in detecting a 10 fold increase in a birth defect that occurs at a background of 1 per 1000 births, it would take about 1272 exposed and 1272 unexposed pregnancies to have sufficient power to have observed such an increased risk if one were present (with 80% power and a type 1 error of 0.05). If one is more restrictive by reducing the size of the increase that must be detectable then larger samples are required. To detect a 2 fold increase in risk with a background of 1 per 1000, 25, 471 would be required for each group. Of course these sample size estimates change depending on whether one assumes an equal sample size per group or whether one is using expected rates from historical or national data. Further, the examples are ignoring the issue of multiple comparisons that would be an issue since many outcomes would

be analyzed in such studies.

If the reviewer had to express the degree of increase that had to be detectable for there to be "no evidence of risk" and then evaluate whether the data resulted from adequate and well controlled studies, the reviewers task would be relatively straight forward, although there could be significant variability across reviewers. However, because 201.57 does not specify whether it is referring to individual birth defect outcome(s) or the overall birth defect risk, the reviewer must be cognizant of the effect of outcome misclassification on the minimal detectable excess risk. Historically, most analyzes of data collected on birth outcomes have compared the overall birth defect risk in the exposed group with that in an unexposed group or at least to that in historical data. Review of specific defects has usually focused on identifying "patterns of defects". Such an approach has probably resulted because few studies have had sufficient size to compare individual birth defect risks to expected risks.

Of course, if 201.57 is referring to an increase in the overall birth defect risk (background of approximately 3%) then the number of pregnancies followed would be smaller for a given minimal detectable excess risk greatly influencing the review. To detect a 10 fold increase in the overall birth defect risk, 36 pregnancies would be needed in each group while 814 would be needed in each group to detect a 2 fold increase in the overall birth defect risk. However, the apparent gain in study power resulting from using the overall birth defect risk ignores the potential outcome misclassification that could result. If a teratogen is associated with specific defects, then using the overall birth defect risk to evaluate its teratogenic risk from maternal drug exposure is analogous to using the all cancer rate to screen for selective carcinogens. Depending on the rarity of a specific cancer or birth defect group and "strength" of the carcinogen or teratogen, one could miss specific risks by focusing on the all cancer or overall birth defect risks.

In reality, there is so little data about human teratogens that it is difficult to speculate about how well overall birth defect risk functions as a surrogate for detecting teratogens. Most pharmacologic and non-pharmacologic exposures that are thought to be human teratogens because of human evidence of risk, have that evidence based mostly upon case series descriptions of rare birth anomalies. Such descriptions do not usually provide all birth defect risks.

Thus, 201.57 does not provide a clear direction as to what is meant by "no evidence of risk", presumably leaving it to regulatory interpretation. In fact, HFD-120 and other review divisions have included animal evidence of risk to growth and developmental in the "teratogenic section" using such data to select the appropriate pregnancy category. Usually in such a case, the teratogenic subsection heading is not included in the labeling.

Taking this approach, its my view that the human evidence necessary to override animal findings must address both teratogenic, and growth and development risks, particularly when the animal evidence is suggestive of potential risk in growth and development as in this case. Admittedly, the predictive validity of such animal findings is unknown. It is also my opinion that using the all

birth defect risk as the outcome of interest has little justification.

Thus, I defined "no evidence of risk" to be present if the clinical data resulted from adequate and well controlled clinical studies that were sufficiently powered to detect a relative increase of twice background for risk that occurs at about 1 per 1000 life births. I picked 1 per 1000 because severe life threatening risks of such magnitude have lead to post-marketing withdrawal of products or significant restrictions in their use. However, even risks approaching 1 per 10,000 users have been the basis for significant regulatory action so an more conservative position may be justifiable. Admittedly, these are arbitrary and value laden choices that can vary from product to product and reviewer to reviewer. Such an approach clearly places more burden on the data than just focusing on all birth defect risk. However, given that a "signal" of risk must already be present from animal reproductive studies to even be considering the question of whether there is "no evidence of risk" in human data, such a burden, in my opinion, is justified.

Review of Clinical Data

The sponsor has submitted a summary of the pregnancy experience from their registry that has included both retrospective and prospectively collected data. Some of these findings have appeared in publications (Goldstein) addressing fetal risk from first trimester fluoxetine exposure and fetal risk from late pregnancy exposure. In addition, the sponsor cites findings from three independently conducted published studies that included control groups to make comparisons; the Chambers, Pastuszak and Nulman publications. The Pastuszak and Nulman studies were mostly focused on first trimester use with limited 3rd trimester use while the Chambers study collected data on groups of users that included a 3rd trimester exposed group.

Sponsor's Fluoxetine Pregnancy Registry

The sponsor tracks both retrospectively and prospectively reported pregnancies that have been exposed to fluoxetine. Retrospective, in this case, refers to reports of pregnancy exposure that are made to the sponsor after an obstetrical procedure or birth outcome has occurred. Prospective refers to reports of pregnancy exposure that are made before such a procedure or birth. Because of concerns about biased reporting in retrospective registries, this review will mostly focus on the prospectively collected data.

Entry into the prospective registry can occur following reports of pregnancy exposure from either health professionals or patients. In either case, preliminary information is collected about the expectant mother during the initial report. This information includes a description of the extent of fluoxetine and concomitant medication use, and previous pregnancy history and outcomes. Interestingly, the name of the expectant mother is not collected, and there is no mention of whether each reported pregnancy is given an ID number for tracking purposes. This becomes an issue especially for health professional reporting since it is not clear how such reported pregnancies are tracked. No breakdown is given on the percentages of pregnancies reported by type of reporter.

Follow-up of the fluoxetine exposed pregnancies apparently does not occur until after the expected date of birth. The original reporter is contacted for information about fetal outcome. Again, it isn't clear how such follow-up is conducted.

Information about fetal outcome is taken directly from the narrative description provided by the reporter. Presumably, this means that, in come cases, health professionals are describing the outcome while in other cases, patients or other reporters provide the description. The focus of the follow-up was upon major anomalies with no information collected on neonatal complications or minor anomalies except in selective subsets of the data where neonatal outcome was the focus . Medical records were not collected and there was no formal control group.

As of April 9, 1996, 2071 pregnancies were prospectively reported to the registry. Of these 2071, 314 were still in utero, 155 had been therapeutically aborted, 38 did not have first trimester exposure, and 768 were loss to follow-up. In the submission, the sponsor described the birth outcomes for the remaining 796 live births with first trimester exposure (including 37 identified in clinical trials).

The significant degree of pregnancies that were lost to follow-up (768/2071=37%) raises the question of the overall validity of these data. If such censoring in follow-up was more likely with abnormal fetal outcome, then a substantial bias could result. According to the sponsor, most (not quantified in the submission) of the loss to follow-up resulted because the original reporter (I assume a health professional) could not remember the patient's name. If true, this observation would suggest that PID numbers were not used in follow-up. The sponsor's explanation for such a high degree of lost to follow-up, while logical, particularly if there was no use of patient identifiers for follow-up, doesn't alleviate the concern about bias. Any additional efforts to obtain follow-up on at least a sample of the 768 were not described in the submissions.

The explanation provided by the sponsor may not even be logical since the percentage of lost to follow-up was similar in the clinical trial population to that in spontaneous reported pregnancies suggesting that follow-up was poor even when patients were identified. (I assume they were clearly identified for clinical trial participation.) Of the 52 pregnancies occurring in clinical trials exposed to fluoxetine, 15 were lost to follow up (29%). Of the 17 placebo pregnancies, 9 were lost to follow-up (53%).

In the submission the sponsor summarized findings separately for the 759 prospectively reported pregnancies with first trimester exposure and the 37 identified in clinical trials. For the 759, the following outcomes were reported:

spontaneous abortion	101	(13.3%)
major malformations	23	(3.5%)
minor anomaly	1	
post-perinatal malformation	9	(1.4%)

According to the sponsor, no specific patterns of major anomalies were observed. These findings were consistent with the 426 retrospectively reported pregnancies, where there was no specific pattern of anomalies observed in 89 reported cases of abnormalities and additionally, there were no unusual findings for the 37 pregnancies occurring in fluoxetine clinical trials.

The sponsor also provided findings from an analysis of the 123 pregnancies with follow-up that had exposure in all three trimesters. (There were 23 others that had exposure in the 2nd and/or 3rd but not the first.) The documentation describing the follow-up for these 123 was not clear, but I think some of these pregnancies were included in the Goldstein publication that described fetal outcome for 112 pregnancies with 3rd trimester exposure to fluoxetine. It also appears that medical records were not used in this assessment, relying on narrative descriptions by the reported. Of the 123, 3 had major anomalies and 1 had post-perinatal anomaly. Of the remaining 119 there were 11 that had a neonatal complication (9.2%) with 7 (5.9%) admitted to the ICU. The Goldstein publication in 1994 reported on 112 that had exposure up to the time of delivery. Four had major birth defects and of the remaining 108, 15 were reported to have had a neonatal complication (13.9%).

While there was no control groups for any of these subset analyzes, the submissions argued that these rates were comparable to that observed by Chambers in national hospital discharge data. None of these analyzes considered birth weight. Of course, the same concern about bias introduced by limited follow-up that was raised about the full registry would also apply to these data since they relied on the same methods. No information was provided on the number of pregnancies in the registry that had 3rd trimester exposure and were lost to follow-up.

Pastuszak Publication

Pastuszak followed 128 pregnant women who were first exposed to fluoxetine in the first trimester for treatment of depression. Of these 128, six had exposure in the 3rd trimester. In two complicated matched pair analyzes, events after fluoxetine exposure were compared, first to 128 age-matched control exposures (acetaminophen, penicillin, dental xray) and then, in a 3 way comparison with 74 age-matched pregnant women with tricyclic antidepressant (TCA) exposure and 74 of the 128 pregnant women with control exposures. There was no clinical differences in weight gain, the percentage of premature births or neonatal complication rates. The all birth defect risk was comparable between groups. The only significant findings were increased risks for spontaneous abortion with fluoxetine and TCAs.

Nulman Publication

Nulman identified 80 pregnancies exposed to TCAs, 55 exposed to fluoxetine and 84 non-teratogenic exposed pregnancies. Apparently, all pregnancies were also identified in the first trimester. Of the 55 fluoxetine exposed pregnancies, 18 were exposed throughout pregnancy. Follow-up focused on neurobehavioral testing and birth weight. No differences were found

between groups.

Chambers Publication

I reviewed the Chambers article shortly after its publication in a memorandum dated October 11, 1996. A summary of this review follows.

Chambers et al prospectively defined fluoxetine and control pregnancy cohorts from women who made calls to the California Teratogen Information Service (CTIS) inquiring about fetal risk. Of about 1500 calls made to the CTIS inquiring about fluoxetine risk from 1989 through 1995, the authors estimate that 500 were made by pregnant women who were currently exposed to fluoxetine. From these 500, 228 were selected who agreed to participate in the study. For comparison, 254 pregnant controls were selected from those who called the CTIS over the same period inquiring about risks from acetaminophen, dental radiographs, or limited alcohol use.

The findings in the publication are based upon the following four comparisons made among members of the two study cohorts. (1) The risk for a major birth defect in live births with first trimester fluoxetine exposure was compared to that in live births in the control group. (2) The risks for several measures of neonatal outcome in live births with late fluoxetine (3rd trimester) exposure were compared to live births with early but not late fluoxetine exposure. (3) The extent of minor birth anomalies in live births with any pregnancy exposure to fluoxetine was compared to that in live births in the control group. (4) The risk of spontaneous abortion in pregnancies with 1st trimester exposure to fluoxetine was compared to that in control pregnancies.

While the risk for major birth defects and spontaneous abortions were reported to be no different with fluoxetine, significantly poorer neonatal outcomes were reported for live births with late fluoxetine exposure compared to outcomes in live births with early exposure. In addition, the extent of minor birth anomalies appeared to be greater with any fluoxetine use compared to live births in the control group. This latter finding is based upon Dr. Jones blinded examination of the children using a checklist that he purports to be predictive of occult major anomalies.

Based upon my read of the article and a short discussion with Dr. Jones, there were several differences between the compared groups that are worth noting. First, 82% of the women calling the CTIS who were included in the early fluoxetine group called during the 1st trimester compared to about 62% of women included in the late fluoxetine group. The women in the late exposed group were apparently, if I understood Dr. Jones correctly, more likely to be using additional psychiatric drugs and had a higher prevalence of reported smoking. While Dr. Jones, agrees that there are some differences between these two groups, he does not think that the difference in the risk for poor neonatal outcomes results from confounding by either indication (more severe depression) or by other exposures such as illicit drug use.

In a good review of the limitations of this study, the sponsor points out that neither the

identification of neonatal complications nor the decision to admit to an ICU were made blindly to maternal exposure. In addition, the finding of decreased birth weight was not clinically significant when controlling for maternal weight gain, a major determinant of birth weight. I also agree with the sponsor that the predictive validity of minor anomaly occurrence has not been defined, although the Chamber's study was the only one to have looked at such outcomes.

Discussion

While at first glance, there may appear to be substantial evidence suggesting no human fetal risk from maternal exposure to fluoxetine, on careful review the evidence is inadequate and insufficient resulting from poorly controlled studies. Thus, the human data is not sufficient, in my opinion, to override the reproductive animal study findings.

First, while the sponsor's registry data is relatively large when compared to other prescription drug registries, it still had limited power to detect individual birth defect risks. Assuming that 1 per 1000 life births was the background risk of interest, the registry data had 80% power to detect a relative increase of about 9 times this background. A second problem with the registry data was the substantial lost to follow-up. This latter issue could affect both analysis of overall birth defect risk and the subset analyzes of neonatal complications performed for pregnancies with 3rd trimester exposure or pregnancies exposed in all three trimesters. The sponsor may be able to address this limitation in follow-up by obtaining follow-up in a random sample. However, the lack of comparative data for the occurrence of neonatal complications would still limit the value of the subset analyzes.

All three publications were relatively small for analyzing major birth defect risk and only the Chamber's article had any significant late pregnancy exposure. Because of the difficulties with the comparability of the groups, Chamber's findings of increased rates of neonatal complications and minor anomalies with late fluoxetine exposure are difficult to interpret. More studies of the effects of late trimester exposure, not only of fluoxetine but the other SSRIs, are probably needed to address the issue of neonatal toxicity occurring after late pregnancy exposure.

Conclusion

Based upon my interpretation of the clinical data contained in the October 1, 1996 and January 21, 1997 submissions, the human pregnancy experience with fluoxetine is insufficient to override the animal findings. I would recommend pregnancy category C.

Because of the current limitations both in the registry data and in the findings from published studies, I would recommend against describing such findings in labeling. If findings from the available data are placed in labeling, a somewhat lengthy discussion of limitations would be necessary to provide balance.

If the sponsor can provide evidence that being lost to follow-up in the registry was unrelated to a birth defect occurrence, including registry data on major birth defect risk may be beneficial, although some caveats about limited study power may still be necessary.

Finally, the Chambers study findings raises the question about acute toxicity to the newborn from late pregnancy exposure. Since this concern could be extended to all SSRIs, some consideration could be given to using the FDA cooperative agreements to study the relationship between neonatal complications and maternal medication use, focusing on SSRIs.

/S/ 3-5-97

Greg Burkhart, M.D., M.S.
Safety Team Leader
Neuropharmacological Drug Products

cc:HFD-120\Burkhart\Mosholder

NDA 18-936
NDA 20-101

JAN 13 1994

Lilly Research Laboratories
Attention: M.W. Talbott, Ph.D.
Medical Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Talbott:

Please refer to your New Drug Applications submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac® (fluoxetine hydrochloride) capsules (NDA 18-936) and solution (NDA 20-101).

We have recently reviewed a case concerning the possible association between fluoxetine hydrochloride and colic in an infant. [Lester BM, Cucca J, Andreozzi L, Flanagan P, and Oh W. J Am Acad Child Adolesc Psychiatry, 1993, 32, 6:1253-1255.

This case report describes a six week old infant whose mother was receiving 20 mg/day of fluoxetine while breast feeding. The mother's milk contained 69 ng/ml fluoxetine and 90 ng/ml norfluoxetine. While nursing, the infant was colicky, but he improved significantly after switching to formula. When rechallenged with the mother's breast milk (fed from a bottle), he again developed symptoms of crying, sleep disturbance, vomiting and watery stools. On the second day of bottle feeding with breast milk, the infant's serum drug levels were 240 ng/ml of fluoxetine and 208 ng/ml of norfluoxetine.

The current package insert for Prozac® states under the subsection "Nursing Mothers" that in breast milk from one mother on fluoxetine, the combined fluoxetine/norfluoxetine level was 70.4 ng/ml. No adverse effects on the infant were noted, and no plasma drug levels were obtained from the child. The present case report is more significant because (1) relatively high drug concentrations were measured in the infant's blood and (2) breast feeding was associated with symptoms of colic.

Consequently we ask that you revise the "Nursing Mothers" subsection of the Prozac® package insert to include this case, and the labeling should state that breast feeding while on Prozac® is not recommended.

These changes should be instituted with the next printing (but not later than 3 months from the date of this letter) in order to furnish adequate labeling for effective use of this drug. Please submit these changes in final printed labeling under 21 CFR 314.70(c)(2), "Special Supplement - Changes Being Effected".

Should you have any questions concerning these NDAs, please contact Mr. Paul A. David, Regulatory Management Officer, at (301) 443-3504.

Sincerely yours,

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