

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75506

APPROVAL LETTER

AUG - 2 2001

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19943

Dear Sir:

This is in reference to your abbreviated new drug application dated November 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluoxetine Oral Solution USP, 20 mg (base)/5 mL.

Reference is also made to your amendment dated May 17, 2001 *and*
WV
9/7/01 June 29, 2001.

The listed drug product (RLD) referenced in your application, Prozac® Liquid of Eli Lilly and Company, is subject to a period of pediatric exclusivity which expires on August 2, 2001. In addition the listed drug product is subject to a period of patent protection which expires June 2, 2004, (U.S. Patent No. 4,626,549 [the '549 patent]). Your application contains a Paragraph IV Certification and a Method of Use Statement under Section 505(j)(2)(A)(vii)(IV) and Section 505(j)(2)(A)(viii) of the Act to the '549 patent. You informed us that Eli Lilly and Company initiated a patent infringement suit against you for your Paragraph IV Certification on the challenged claim in the United States District Court for the Southern District of Indiana (Eli Lilly and Company v. TEVA Pharmaceuticals USA, Civil Action No. IP 98-1435 C B/S). You have also notified us that you prevailed on one claim of the '549 patent in both the district court and in the court of appeals and a Method of Use Statement to another claim.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Fluoxetine Oral Solution USP, 20 mg

(base)/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Prozac® Liquid.

With respect to 180-day generic drug exclusivity, we note that TEVA Pharmaceuticals USA (TEVA) was the first to submit a substantially complete ANDA with a Paragraph IV Certification. Therefore, with this approval TEVA is eligible for 180-days of market exclusivity. Subsequent applications for this this drug product will be eligible for final approval not earlier than one hundred eighty days after:

- (1) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing, or
- (2) the date of a decision of a court (ii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier [Section 505(j) (B) (iv)].

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of this product, or the date of a decision of the court holding the relevant patent invalid, unenforceable or not infringed.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

^

/S/ -
/ Gary Buehler 8/2/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75506

DRAFT FINAL PRINTED LABELING

75-506
AP 8/2/01

NDC 0093-6108-12

FLUOXETINE
ORAL SOLUTION, USP
20 mg/5 mL*

Each 5 mL contains:
Fluoxetine Hydrochloride USP, equivalent to
20 mg Fluoxetine, alcohol 0.23%

Rx only



TEVA

Usual Dosage: See package literature.

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

Keep tightly closed.

Dispense in a light, light-resistant container, as defined
in the USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE
REACH OF CHILDREN.

L20306

Pg Ref B-2001

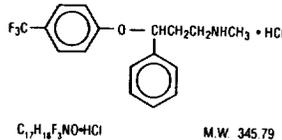
TEVA PHARMACEUTICALS USA
Sellersville, PA 19380

N
3
0093-6108-12
3
02 AUG -2 2001
3

marketed for the treatment of premenstrual dysphoric disorder (Sarafen™, fluoxetine hydrochloride). It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (+)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-β-hydroxy)propyl]amine hydrochloride, and has the following structural formula:

APPROVED

AUG - 2 2001



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

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, peppermint flavor, glycerin, purified water, and sucrose.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

The antidepressant and antiobsessive-compulsive 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 α₁-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently *in vitro* than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion:

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

The capsule, tablet 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 α₁-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 P4501D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-fluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the four active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-1D6) 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 P4501D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (see **Drug Interactions** under **PRECAUTIONS**).

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

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

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 at 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired

patients (see **Use in Patients With Concomitant Illness** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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

Clinical Trials:

Depression: The efficacy of fluoxetine for the treatment of patients with depression (≥18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Fluoxetine was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Fluoxetine was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subscore.

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

A study was conducted involving depressed outpatients who had responded (modified HAM-D-17 score of ≤ 7 during each of the last 3 weeks of open-label treatment and absence of major depression by DSM-III-R criteria) by the end of an initial 12-week open treatment phase on fluoxetine 20 mg/day. These patients (N=298) were randomized to continuation on double-blind fluoxetine 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 on a modified HAM-D-17 score of ≥ 14 for 3 weeks) was observed for patients taking fluoxetine compared to those on placebo.

Obsessive-Compulsive Disorder: The effectiveness of fluoxetine 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 fluoxetine doses of 20, 40, or 60 mg/day (or 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 fluoxetine 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 fluoxetine experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. While there was no indication of a dose response relationship for effectiveness in Study 1, a dose response relationship was observed in Study 2, with numerically better responses in the two higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined.

Outcome Classification	Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies			
	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.

INDICATIONS AND USAGE

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

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

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

The efficacy of fluoxetine 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 fluoxetine for extended periods should be reevaluated periodically (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

Obsessive-Compulsive Disorder: Fluoxetine 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 fluoxetine 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 fluoxetine 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 fluoxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Fluoxetine 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, fluoxetine 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

I20387



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 fluoxetine before starting an MAOI.

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

WARNINGS

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

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

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

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

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

Potential Interaction with Thioridazine—In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450H2D6 isozyme activity. Thus, this study suggests that drugs which inhibit P450H2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (see **PRECAUTIONS**).

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

PRECAUTIONS

General

Anxiety and Insomnia—In U.S. placebo-controlled clinical trials for depression, 12% to 16% of patients treated with fluoxetine and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

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

Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for fluoxetine in clinical trials collecting only a primary event associated with discontinuation) in U.S. placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia and nervousness (1% in depression) (see Table 2, below).

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients may be an undesirable result of treatment with fluoxetine.

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

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

Activation of Mania/Hypomania—In U.S. placebo-controlled clinical trials for depression, mania/hypomania was reported in 0.1% of patients treated with fluoxetine 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 U.S. placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with fluoxetine and no patients treated with placebo. In all U.S. fluoxetine clinical trials, 0.7% of 10,782 patients reported mania/hypomania.

Seizures—In U.S. placebo-controlled clinical trials for depression, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with fluoxetine and 0.2% of patients treated with placebo. No patients reported convulsions in U.S. placebo-controlled clinical trials for OCD. In all U.S. fluoxetine clinical trials, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed antidepressants. Fluoxetine 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 fluoxetine should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between OCD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD.

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 fluoxetine in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine 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 fluoxetine in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

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

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

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

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

Information For Patients—Physicians are advised to discuss the following issues with patients for whom they prescribe fluoxetine:

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

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

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

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

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

Laboratory Tests—There are no specific laboratory tests recommended.

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

Drugs Metabolized by P450H2D6—Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isozyme P450H2D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isozyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the four active enantiomers is comparable between poor and extensive metabolizers (see **Variability in Metabolism** under **CLINICAL PHARMACOLOGY**).

Fluoxetine, like other agents that are metabolized by P450H2D6, inhibits the activity of this isozyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450H2D6 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 P450H2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, vinblastine, and TCAs).

Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (see **CONTRAINDICATIONS** and **WARNINGS**).

Drugs Metabolized by Cytochrome P450H1A4—In an *in vivo* interaction study involving coadministration of fluoxetine with single doses of terfenadine (a cytochrome P450H1A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of P450H1A4 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 P450H1A4 activity is not likely to be of clinical significance.

CNS Active Drugs—The risk of using fluoxetine in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of fluoxetine and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see **Accumulation and Slow Elimination** under **CLINICAL PHARMACOLOGY**).

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

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

Benzodiazepines—The half-life of concurrently administered diazepam may be prolonged in some patients (see **Accumulation and Slow Elimination** under **CLINICAL PHARMACOLOGY**). 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 fluoxetine 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 TCA may need to be reduced and plasma TCA concentrations may need to be

discontinued (see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY, and Drugs Metabolized by P4501D6 under Drug Interactions).

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

Potential Effects of Coadministration 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., warfarin, digoxin) 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 anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered 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 fluoxetine.

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

Multiple doses of fluoxetine had been administered to 10,782 patients with various diagnoses in U.S. 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 non-drug factors to the side effect incidence rate in the population studied.

Incidence in U.S. 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 fluoxetine (incidence of at least 5% for fluoxetine and at least twice that for placebo within at least one of the indications) for the treatment of depression and OCD in U.S. controlled clinical trials.

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN U.S. DEPRESSION AND OCD PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event	Percentage of patients reporting event			P _t (N)
	Fluoxetine (N=1728)	Placebo (N=975)	Fluoxetine (N=266)	
Body as a Whole				
Asthenia	9	5	15	
Flu syndrome	3	4	10	
Cardiovascular System				
Vasodilatation	3	2	5	
Digestive System				
Nausea	21	9	26	
Anorexia	11	2	17	
Dry Mouth	10	7	12	
Dyspepsia	7	5	10	
Nervous System				
Insomnia	16	9	28	
Anxiety	12	7	14	
Nervousness	14	9	14	
Somnolence	13	6	17	
Tremor	10	3	9	
Libido decreased	3	—	11	
Abnormal dreams	1	1	5	
Respiratory System				
Pharyngitis	3	3	11	
Sinusitis	1	4	5	
Yawn	—	—	7	
Skin and Appendages				
Sweating	8	3	7	
Rash	4	3	6	
Urogenital System				
Impotency	2	—	—	
Abnormal ejaculation	—	—	7	

† Denominator used was for males only (N=690 fluoxetine depression; placebo depression; N=116 fluoxetine OCD; N=43 placebo OCD).

— Incidence less than 1%.

Associated with Discontinuation in U.S. Placebo-Controlled Clinical Trials (excl. data from extensions of trials)—Table 2 lists the adverse events associated with discontinuation of fluoxetine treatment (incidence at least twice that for p and at least 1% for fluoxetine in clinical trials collecting only a primary event related with discontinuation) in depression and OCD.

TABLE 2
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN U.S. DEPRESSION AND OCD PLACEBO-CONTROLLED CLINICAL TRIALS

DEPRESSION (N=392)	OCD (N=266)
Nervousness (1%)	Anxiety (2%)
—	Rash (1%)

Male and Female Sexual Dysfunction with SSRIs—Although changes in desire, sexual performance, and sexual satisfaction often occur as manifest of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their incidence. In patients enrolled in U.S. depression and OCD placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of the patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction including anorgasmia.

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

Priapism has been reported with all SSRIs.

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

Other Events Observed in All U.S. Clinical Trials—Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine U.S. clinical trials (10,782 patients) except (1) those listed in the body or foot of Table 1 above or elsewhere in labeling; (2) those for which the COSTART 1 were uninformative or misleading; (3) those events for which a causal relation to fluoxetine use was considered remote; and (4) events occurring in only one patient treated with fluoxetine and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definition: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1 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, hyperthermia, intentional injury, neuroleptic malignant syndrome photosensitivity reaction.

Cardiovascular System—Frequent: hemorrhage, hypertension; Infrequent: angor 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 vomit; Infrequent: aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulcer, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; Rare: biliary colic, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, iron deficiency, gastrointestinal hemorrhage, hematemesis, hemorrhage of colic hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, re hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, ton edema.

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

Hemic and Lymphatic System—Infrequent: anemia, ecchymosis; Rare: bicytopenia, hypochromic anemia, leukopenia, lymphedema, lymphocytopenia, purpura, thrombocytopenia, thrombocytopenia.

Metabolic and Nutritional—Frequent: weight gain; Infrequent: dehydration, general edema, gout, hypercholesterolemia, hyperkalemia, hypokalemia, peripheral edema.

Rare: alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System—**Inrequent:** 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; **Inrequent:** abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hyperesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder, psychosis, vertigo; **Rare:** abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delirious, dysarthria, dyslexia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

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

Skin and Appendages—**Inrequent:** 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; **Inrequent:** 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; **Inrequent:** abortion*[†], albuminuria, amenorrhea*[‡], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation*[‡], fibrocystic breast*[‡], hematuria, leukorrhea*[‡], menorrhagia*[‡], metrorrhagia*[‡], nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*[‡]; **Rare:** breast engorgement, glycosuria, hypomenorrhea*[‡], kidney pain, oliguria, priapism*[‡], uterine hemorrhage*[‡], uterine fibroids enlarged*[‡].

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

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

[‡] Adjusted for gender

Postintroduction Reports—Voluntary reports of adverse events temporally associated with fluoxetine that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Fluoxetine is not a controlled substance.

Physical and Psychological Dependence—Fluoxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the premarketing clinical experience with fluoxetine 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 fluoxetine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—Worldwide exposure to fluoxetine is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine, alone or with other drugs, reported from this population, there were 195 deaths. Among 633 adult patients who overdosed on fluoxetine alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdose, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdoses were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

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

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

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

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

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

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

Management of Overdose—Treatment should consist of those general measures employed in the management of overdose with any antidepressant.

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

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

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

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

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

DOSE AND ADMINISTRATION

Depression—

Initial Treatment—In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 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 *Geriatric Use* under **PRECAUTIONS**), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see *Liver Disease and Renal Disease* under **CLINICAL PHARMACOLOGY**, and *Use in Patients With Concomitant Illness* under **PRECAUTIONS**).

Maintenance/Continuation/Extended Treatment—It is generally agreed that acute episodes of 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 fluoxetine 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 fluoxetine 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 *Geriatric Use* under **PRECAUTIONS**), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see *Liver Disease and Renal Disease* under **CLINICAL PHARMACOLOGY**, and *Use in Patients With Concomitant Illness* under **PRECAUTIONS**).

Maintenance/Continuation Treatment—While there are no systematic studies that answer the question of how long to continue fluoxetine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of fluoxetine 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.

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 **PRECAUTIONS, 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 fluoxetine. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping fluoxetine before starting an MAOI (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

HOW SUPPLIED

Fluoxetine Oral Solution USP (contains fluoxetine hydrochloride, equivalent to 20 mg/5 mL of fluoxetine), a clear, colorless to pale yellow syrup with a mint odor, is available in bottles of 120 mL.

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

Protect from light.

Keep tightly closed.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

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 fenturamine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

*Sarafem™ is a trademark of Eli Lilly.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Printed in USA
Rev. E 3/2001

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75506

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

ANDA # 75-506

3. NAME AND ADDRESS OF APPLICANT

TEVA PHARMACEUTICALS USA
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

4. LEGAL BASIS FOR SUBMISSION

The listed drug is Prozac® Liquid, 20 mg/5mL of Eli Lilly & Co.

Teva Pharmaceuticals USA's certifies that to the best of its knowledge the patents held by Eli Lilly & Co. Expire on February 02, 2001 (US Patent# 4,314,081) and December 2, 2003 (US Patent#4,626,549).

Teva USA's opinion, there exist no listed exclusivities for the referenced drug product, Prozac, for NDA #20-101.

See notice of certification of infringement submitted February 8, 1999. See receipt of notice (patent amendment) submitted February 26, 1999. See patent amendment submitted April 26, 1999.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Fluoxetine Hydrochloride

8. SUPPLEMENT(s) PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

Submitted: November 20, 1998
New Corresp (Peppermint Flavor information): December 21, 1998
New Corresp : February 8, 1999
New Corresp (Patent amendment): February 26, 1999
New Corresp (Patent amendment): April 26, 1999
Amendment: September 7, 1999
Telephone amendment (labeling): December 28, 1999
Minor amendment: 5-12-2000
Telephone amendment: 7-6-2000
Facsimile labeling amendment: January 11, 2001
Labeling amendment: May 17, 2001
CMC Amendment: 6/29/01

FDA:

Refuse to file letter (peppermint Flavor): December 9, 1998
Acknowledgment: January 27, 1999
Major Deficiency letter: July 15, 1999

Labeling deficiency letter: July 28, 1999
Labeling deficiency letter: November 15, 1999
Minor deficiency letter: March 16, 2000
Telephone NA letter: 6-19-2000
Chemistry deficiency letter: December 13, 2000
Labeling Facsimile letter: January 19, 2001
Telephone conversation (labeling): March 15, 2001
Office letter: March 16, 2001
Telephone Conversation (CMC): 6/26/01

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

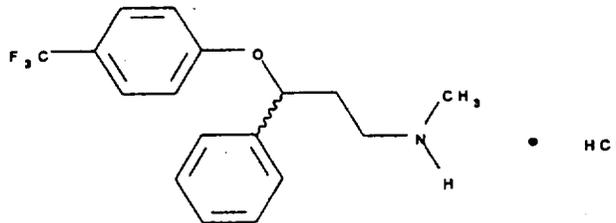
Oral Solution

14. POTENCY

20 mg/5 mL (base)

15. CHEMICAL NAME AND STRUCTURE

Fluoxetine Hydrochloride
 $C_{17}H_{18}F_3NO \cdot HCl$; M.W. = 345.79



(±)-N-Methyl-3-phenyl-3-[(α,α,α-trifluoro-p-toly)oxy]propylamine
monohydrochloride. CAS [59333-67-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

Q: Called firm by T. Ames on June 19, 2000 to request
certification that no Organic Volatile solvents are being

utilized (but specifically Benzene) in the production of the drug substance. Firm indicated that he would obtain and submit such a certification.

A: OK (see the certificate of 7-5-2000 amendment).

Q: 1. Regarding drug substance:

The Organic Volatile impurities for Fluoxetine Hydrochloride drug substance are not consistent with USP 24 <467> specifications. Please revise the OVI specifications and resubmit.

A: Called firm by T. Ames on June 19, 2000 to request certification that no Organic Volatile solvents are being utilized (but specifically Benzene) in the production of the drug substance. Firm indicated that he would obtain and submit such a certification.

Q: 2. Regarding method validation:

The following analyst's comments concerning the impurity testing, the system suitability testing should be addressed prior to approval:

The resolution for the impurity assay could not be obtained. The fluoxetine standard co-elutes with related compound A. There was no standard for the degradant 4-trifluoromethyl-phenol, therefore, it could not be determined if the system was suitable for detecting this degradant.

Although, your assay method requires the sum of all peak areas except those identified as a solvent front or placebo to be included in the calculations, there is no preparation of the placebo solution in the method. It is not possible to identify these peaks without the placebo or Relative Retention Times. The above comments apply to the impurities and degradation determination for the drug product. Please comment and resubmit the analytical methods for the drug product.

A: OK (MVD was acceptable by NE district Laboratories on 6-20-2000).

Amendment of 6/29/01: Revised DP specifications to meet current compendial specifications.

Status:

a. EER status: Satisfactory

EER was requested for TEVA Pharmaceuticals USA, Applied analytical Industries Inc.,

Acceptable on

10-22-1999.

b. Method Validation status: OK

Not requested for the drug substance (Compendial-USP drug).

The drug product is non-USP -- methods validation is requested on 7-6-99. Acceptable on 6-20-2000.

c. Bio-review status: Satisfactory
Satisfactory per A. Jackson reviewed on 2-16-99 and the waiver was granted.

d. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 5-31-2001.

e. DMF: Satisfactory

DMF was reviewed and found adequate by L. Tang on 7/12/2000.

f. Microbiology: N/A

9. Patents expire February 2, 2001 & December 2, 2003.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is considered as approvable based on the acceptable labeling. A TA letter will be issued.

19. REVIEWER:

DATE COMPLETED:

Sema Basaran, Ph.D.

6-5-2001; 7/2/01 (revised)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75506

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75506 SPONSOR :Teva Pharmaceuticals
DRUG & DOSAGE FORM : Fluoxetine HCL Oral Solution
STRENGTH (s) : 20 mg/5 mL
TYPE OF STUDY: Waiver
STUDY SITE: CLINICAL : N/A
 ANALYTICAL :N/A

STUDY SUMMARY : See Review

DISSOLUTION :N/A

PRIMARY REVIEWER :Andre Jackson BRANCH :I
INITIAL : ajf DATE : 2/16/99

Team Leader : Y.C. Huang BRANCH :I
INITIAL : yc DATE : 2/16/99

DIRECTOR:Dale P. Conner
DIVISION OF BIOEQUIVALENCE
INITIAL : DP DATE : 2/16/99

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL : _____ DATE : _____

Fluoxetine Hydrochloride
 20 mg/5 mL Oral Solution
 ANDA #75-506
 Reviewer: A.Jackson
 WP# 75506W.N98

Teva Pharmaceuticalls
 Sellersville, Pa.
 Submission Date:
 November 20, 1998

REVIEW OF A WAIVER REQUEST

I. BACKGROUND:

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL. The reference listed drug (RLD) is Lilly's Prozac Oral Solution, 20 mg/5 mL (NDA #20-101).

2. The drug is indicated for the treatment of depression.

II. FORMULATION COMPOSITION:

Comparative compositions of the test and the reference products are as follows:

Comparison of Formulation Amount/5mL
 (not for release under FOI)

	TEST	REFERENCE
Ingredient		
✓Fluoxetine	mg	20 mg
✓Flavor, Peppermint Natural ²	mg	mg
✓Glycerin, USP	mg ³	mg
✓Benzoic Acid, NF	mg	mg
✓Alcohol, USP	% ⁴	%
✓Sucrose	mg ⁵	mg
✓Purified Water, USP (Portion 1)	mg	
Purified Water, USP (Portion 2)	mg	
Purified Water, USP (Portion 3)	QS to final volume	
Water, purified		QS to final volume

1. Equivalent to 20 mg base.

2. This flavor is not listed in the IIG but the firm supplied information to OGD via an amendment on December 21, 1998 listing

the components of Flavor, Peppermint Natural which are in the IIG within an acceptable concentration range.

3. The amount is less than the reference but is within the % range listed in the IIG page 63.

4. The per cent is within the range (%) in the IIG page 3 for alcohol in oral solutions. The % per cent differs from that listed in vol. 1.1 pg. 103 in the ANDA 75-506. The reason may be the value used for density which was which may be different from that used by the firm.

5. The amount is % which is within the range of oral syrups in the IIG.

III. RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Teva Pharmaceuticals demonstrates that its Fluoxetine HCL oral solution 20mg/5 mL, falls under 21 CFR 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of in vivo bioavailability study be granted. The test product is deemed bioequivalent to Prozac® oral solution 20mg/5 mL manufactured by Eli Lilly.

Andre Jackson *JS*
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

Concur: (*JS*) Date: *2/16/99*
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-506 (original, duplicate), HFD-650 (Director),
HFD-652 (Huang, Jackson), Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-506

APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Fluoxetine oral solution 20mg/5mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

()

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 11 1998

FILE COPY

Fluoxetine Hydrochloride
20 mg/5 mL Oral Solution
ANDA #75-292
Reviewer: Z.Z. Wahba
File #75292w.d97

NU-PHARM Inc.
Ontario, Canada
Submission Date:
December 22, 1997
April 03, 1998

REVIEW OF A WAIVER REQUEST

I. BACKGROUND:

1. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL. The reference listed drug (RLD) is Lilly's Prozac[®] Oral Solution, 20 mg/5 mL (NDA #20-101).
2. The drug is indicated for the treatment of depression.

II. FORMULATION COMPOSITION:

Comparative compositions of the test and the reference products are as follows:

Comparison of Formulation
(not for release under FOI)

INGREDIENT	Test Product (amount/5 mL)	Ref. Product (amount/5 mL)
Fluoxetine HCl	^a 0.0224 g (22.4 mg)	EQ 20 mg
Alcohol, 95% USP	g	g
Artificial Freshmint Flavor (Code No. 26232)	mg)	mg
Benzoic Acid USP	g (mg)	mg
Glycerin USP 96%	g	g
Purified Water USP	kg ? or kg ?	QS
Sucrose NF	g	g

^a22.4 mg/5 mL as fluoxetine salt, equivalent to 20 mg/5 mL base.

III. DEFICIENCIES:

1. The firm's statement of composition for the Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL shows that the amount of water per 5 mL dose is 2.305 kg and 55.32 kg per 120 mL bottle (see vol. C1.1, page #104). In the firm's correspondence dated April 02, 1998, the firm stated that the amount of water per 5 mL dose is _____ kg and _____ kg per 120 mL bottle. The amount of water provided in the statement of composition cannot be correct for the 5 mL or 120 mL volume. Please submit a composition statement with the correct amounts.
2. Please provide the method of calculation (per weight and percentage) of the concentrations of all ingredients for the 5 mL dose, 120 mL unit bottle and ANDA batch.

IV. RECOMMENDATION

The information submitted by Nu-Pharm Inc. for its product, Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL has been found incomplete. The Division of Bioequivalence recommends that the waiver of an in vivo bioavailability should be denied. From the Bioequivalence point of view, the application is incomplete.

The firm should be informed of the above deficiencies and Recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED BDAVIT
FT INITIALED BDAVIT

/S/

6/8/98

Concur: _____

/S/

Date: 6/11/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-292

APPLICANT: NU-PHARM INC.

DRUG PRODUCT: Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your statement of composition for the Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL shows that the amount of water per 5 mL dose is kg and kg per 120 mL bottle (see vol. C1.1, page #104). In your correspondence dated April 02, 1998, the firm stated that the amount of water per 5 mL dose is kg and kg per 120 mL bottle. The amount of water provided in the statement of composition cannot be correct for the 5 mL or 120 mL volume. Please submit a composition statement with the correct amounts.
2. Please provide the method of calculation (per weight and percentage) of the concentration of all ingredients for the 5 mL dose, 120 mL unit bottle and ANDA batch.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75506

ADMINISTRATIVE DOCUMENTS

(this review supersedes the tentative approval summary dated 1/10/00)

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **75-506**

Date of Submission: **December 9 and December 28, 1999**

Applicant's Name: **Teva Pharmaceuticals USA**

Established Name: **Fluoxetine Hydrochloride Oral Solution, 20 mg (base)/5 mL**

Labeling Deficiencies:

INSERT

Please note that since you have filed a Paragraph 4 patent certification to the '549 patent you must include all the indications for this drug product (depression, bulimia, OCD) in the proposed insert labeling. The insert labeling must be the same as the reference listed drug, Lilly's Prozac®.

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - Tentative Approval Summary

Container Labels: 120 mL
Satisfactory in FPL as of September 7, 1999 submission.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Liquid

NDA Number: 20-101

NDA Drug Name: Prozac® Liquid (Fluoxetine Hydrochloride Oral Solution)

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 10/7/99 (S-024)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name			
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASEP guidelines)		X	
Does RID make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them? NOT USP			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? NO	x	X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. The model insert for this review is Prozac[®] Liquid, Lilly Research Laboratories, NDA 20-101/S-024 approved 10-7-99, revision date of 8-11-99.

2. Patent/Exclusivities:

Two patents are still in effect for the innovator. No. 4626549 for a method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) and method of treating animals suffering from an appetite disorder (use code U-154) expires December 2, 2003. The other patent, No. 4314081, is for the chemical entity itself, per Mary Ann Holovac at HFD-85, and expires February 2, 2001. The firm has filed under paragraph 4, claiming that patent No. 4626549 is invalid or will not be infringed. They have elected to leave out all bulimia and OCD information from the insert. **The firm is in court challenging U-84. According to Kim Dettelbach the firm can challenge one use code in court and make a statement that they are not claiming the other. This is what the firm will be doing. (This information taken from Teva's ANDA 75-452, their application for fluoxetine capsules.)** The latest development on this issue, after a meeting among P. Rickman, C. Hoppes, and A. Vezza on 9-21-00 - **TEVA can't do this because the use codes U-84 and U-154 are not identical to what is in the innovator's PI. As a result of this, TEVA will have to put all the OCD and bulimia information back in their proposed insert. This review instructs them to do that.**

3. The inactives are accurately listed in the DESCRIPTION section (p 101 v 1.2).

4. Teva Pharmaceuticals USA is the manufacturer (p 191 v 1.2).

5. The firm will market a 4 oz amber PET container and a 4 oz amber glass container, both with CRC lid (pp 265, 273, 280 v 1.2).

6. Alcohol calculations – The solution has mg of alcohol USP per mL (p 102 v 1.2). Their statement of the product containing 0.23% alcohol is accurate

$$\frac{.002 \text{ g} \times .955 \times 100\%}{0.814 \text{ g/mL}} = 0.23\%$$

7. Dispensing recommendations;

NDA – Dispense in a tight, light-resistant container.

ANDA - Dispense in a tight, light-resistant container.

USP – Preserve in tight, light-resistant containers (for Fluoxetine Capsules – as seen in Supp 7 of USP 23.)

8. Storage conditions:

NDA - Store at CRT

ANDA - Store at CRT

9. In PRECAUTIONS, General, Anxiety and Insomnia, the ≤ signs have been eliminated.

10. On September 22, 2000 Vezza, Hoppes and Rickman had a meeting regarding how to direct generic firms to revise fluoxetine labeling. The comments in this review are the results of that meeting.

Date of Review: 9-22-00

Date of Submission: 12-9-99 and 12-28-99

Primary Reviewer: Adolph Vezza

ISI for 9/25/00

Team Leader: ~~Charlie~~ Hoppes

Date:

ISI 9/25/00

cc:

ANDA: 75-506
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/9/22/00|V:\FIRMSNZ\TEVALTRS&REV\75506na4.l
Review

TENTATIVE APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH

*Updated
 by review
 of 9/22/00
 [Signature]*

ANDA Number: 75-506

Date of Submission: December 9 and December 28, 1999

Applicant's Name: Teva Pharmaceuticals USA

Established Name: Fluoxetine Hydrochloride Oral Solution, 20 mg (base)/5 mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No - Tentative Approval Summary

Container Labels: 120 mL
Satisfactory in FPL as of September 7, 1999 submission.

Professional Package Insert Labeling:
Satisfactory, in draft, as of December 28, 1999 submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prozac® Liquid

NDA Number: 20-101

NDA Drug Name: Prozac® Liquid (Fluoxetine Hydrochloride Oral Solution)

NDA Firm: Lilly Research Laboratories

Date of Approval of NDA Insert and supplement #: 10/7/99 (S-024)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: side-by-sides

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			

Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in PTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for PTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (PTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (PTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them? NOT USP			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? YES If so, was a food study done? NO	x	X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

- The model insert for this review is Prozac[®] Liquid, Lilly Research Laboratories, NDA 20-101/S-024 approved 10-7-99, revision date of 8-11-99.
- Patent/Exclusivities:

Two patents are still in effect for the innovator. No. 4626549 for a method of blocking the uptake of monoamines by brain neurons in animals (use code U-84) and method of treating animals suffering from an appetite disorder (use code U-154) expires December 2, 2003. The other patent, No. 4314081, is for the chemical entity itself, per Mary Ann Holovac at HFD-85, and expires February 2, 2001. The firm has filed under paragraph 4, claiming that patent No. 4626549 is invalid or will not be infringed. They have elected to leave out all bulimia and OCD information from the insert. The firm is in court challenging U-84. According to Kim Dettelbach the firm can challenge one use code in court and make a statement that they are not claiming the other. This is what the firm will be doing. (This information taken from Teva's ANDA 75-452, their application for fluoxetine capsules.)
- The inactives are accurately listed in the DESCRIPTION section (p 101 v 1.2).
- Teva Pharmaceuticals USA is the manufacturer (p 191 v 1.2).
- The firm will market a 4 oz amber PET container and a 4 oz amber glass container, both with CRC lid (pp 265, 273, 280 v 1.2).
- Alcohol calculations – The solution has mg of alcohol USP per mL (p 102 v 1.2). Their statement of the product containing 0.23% alcohol is accurate

$$\frac{.002 \text{ g} \times .955 \times 100\%}{0.814 \text{ g/mL}} = 0.23\%$$
- Dispensing recommendations;

NDA – Dispense in a tight, light-resistant container.
ANDA - Dispense in a tight, light-resistant container.
USP – Preserve in tight, light-resistant containers (for Fluoxetine Capsules – as seen in Supp 7 of USP 23.)
- Storage conditions:

NDA - Store at CRT
ANDA - Store at CRT
- In PRECAUTIONS, General, Anxiety and Insomnia, the ≤ signs have been eliminated.

Date of Review: 1-10-00

Date of Submission: 12-9-99 and 12-28-99

Primary Reviewer: Adolph Vezza

Date:

1/10/00

Team Leader: Charlie Hoppes

Date:

/S/

/S/

1/10/00

cc:

ANDA: 75-506
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/1/10/00|V:\FIRMSNZ\TEVA\TRS&REV\75506TAP.L
Review

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75506

CORRESPONDENCE

ANDA 75-506

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

|||||

DEC 9 1998

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated November 20, 1998, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

It appears that your proposed formulation contains an inactive ingredient, Natural Peppermint Flavor that has not been approved in a drug product for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. According to the regulation, there is reasonable basis to conclude that the inactive ingredient in your proposed product may raise safety questions because of the lack of information that you have provided regarding its use. The Office of Generic Drugs (OGD) will not file this application as an ANDA since new inactive ingredients must be the subject of a new drug application. Please provide additional information to support the safety of the use of this inactive ingredient in your proposed drug product. The information to demonstrate safety should include, but is not limited to, examples of approved drug products administered by the same route of administration which contain the same inactive ingredient within the same concentration range.

Please note that DMF authorization and composition alone is not sufficient data to prove safety. If you choose to provide the composition instead of pharmacology toxicology data, you must provide supporting data showing that **each** component and composition was used in an approved drug

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Carol Holquist
Project Manager
(301) 827-5862

Sincerely yours,

W
Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-506

Teva Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

JAN 27 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made our "Refuse to File" letter dated December 9, 1998, and your amendment dated December 21, 1998.

NAME OF DRUG: Fluoxetine Hydrochloride Oral Solution, 20 mg/5 mL

DATE OF APPLICATION: November 20, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 22, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under

section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

- 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement

agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

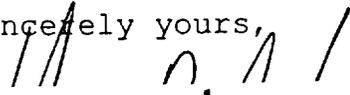
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,



Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-452 (capsules)
75-506 (oral solution)

21
T7 Amc

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

JUN 20 2000

Dear Madam:

We acknowledge your amendments dated April 28, 2000, for your Fluoxetine Hydrochloride Oral Solution (ANDA 75-506) and Fluoxetine Hydrochloride Capsules (75-452) applications. We note that you are not claiming the indication Obsessive Compulsive Disorder (OCD), and that you have deleted reference to that indication in your insert labeling.

The regulations for generic drug labeling, 21 CFR 314.94(a)(8)(iv), state in relevant part, that labeling proposed by the applicant, "... must be the same as the labeling approved for the reference listed drug except for ... omission of an indication or other aspect of labeling protected by patent or accorded exclusivity ...". Unless there is a patent or exclusivity that covers OCD, you must retain that indication in your labeling.

Our Office does not have expertise in the interpretation of patents. Since no patent listed in the Orange Book specifically claims OCD, we ask that you request clarification as to whether that indication is the subject of any patent.

We acknowledge your comments that you are challenging the validity and/or infringement of that part of the patent claiming a method of blocking the uptake of monoamines by brain neurons in animals but only insofar as it relates to the treatment of depression. However, we believe there should be clarification regarding patent 4,626,549, and that it should be specifically associated (or not associated) with the indications appearing in the labeling for the referenced listed drug.

To clarify whether OCD is specifically claimed by a patent, we refer you to 21 CFR 314.53(f) "Correction of patent information errors". Please follow the procedure outlined by that regulation to request clarification through HFD-90, Division of Data Management.

Please copy your applications with your letter to HFD-90. Please also provide a desk copy to Adolph Veza.

Sincerely yours,



6/19/00

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-545

74-685

75-452

75-506 ✓

75-872

MAR 16 2001

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Madam:

The Office of Generic Drugs (OGD) has reconsidered its position regarding the applicability of a listed patent to portions of the labeling of the reference listed drug, Prozac®, (fluoxetine hydrochloride) NDA 18-936, NDA 20-101 and NDA 20-974. This relates to U.S. patent number 4,626,549, which is listed in the Orange Book as covering two uses of fluoxetine hydrochloride. Use 84 is described by the NDA holder as "a method of blocking the uptake of monoamines by brain neurons in animals." Use 154 is described as "a method of treating animals suffering from an appetite disorder." Specifically, the Agency has concluded that applicants may remove statements related to "appetite disorders" from the proposed ANDA labeling. The Agency permits firms to omit from the labeling indications that are protected by patent and/or exclusivity pursuant to Section 505(j)(2)(A)(viii) of the Federal Food Drug and Cosmetic Act and 21 C.F.R. § 314.94(a)(8)(iv).

The labeling of the reference listed drug, Prozac®, includes the following indication: "*Bulimia Nervosa* --Prozac® is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa." We find that it is reasonable to consider bulimia an appetite disorder. One of the definitions in Dorland's Illustrated Medical Dictionary, 28th Edition, characterizes bulimia as an "abnormally increased appetite; hyperorexia".

Therefore, ANDA applicants may omit the statements related to "appetite disorders" from the labeling of their generic version of fluoxetine hydrochloride. The applicants are permitted to amend their paragraph IV (PIV) patent certification to the '549 patent to assert that the labeling does not infringe the patent or that the patent is invalid or unenforceable for some of the claims and also include a statement under Section 505(j)(2)(A)(viii) and 21 CFR § 314.94(a)(12)(iii) (a "section viii statement") that indicates that the method of use patent does not claim a use for which the ANDA applicants are seeking approval for other claims. In this case, because the '549 patent apparently contains a number of different claims described by the NDA holder as covering different uses, the section viii statement will essentially assert that the ANDA applicants are not seeking approval for one or more of the multiple uses claimed in the patent. In addition, the ANDA applicants are requested to specify the use(s) they are deleting from the labeling.

If you have any questions regarding this correspondence, please contact Cecelia Parise, R.Ph.,
Special Assistant for Regulatory Policy, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

/S/

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

C. P.
for
3/16/2001



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 3000
FAX: (215) 591 8600

June 29, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/A

ANDA #75-506
FLUOXETINE ORAL SOLUTION USP, 20 mg per 5 mL
TELEPHONE AMENDMENT - RESPONSE TO JUNE 26, 2001 TELEPHONE CONVERSATION

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA. The subject of this amendment is our response to a comment regarding updated specifications, specifically for chromatographic purity, set forth in a June 26, 2001 telephone conversation between Dr. Ubrani Venkataram from the Office of Generic Drugs (OGD) and Vincent Andolina of TEVA Pharmaceuticals USA. The response to this comment is addressed below.

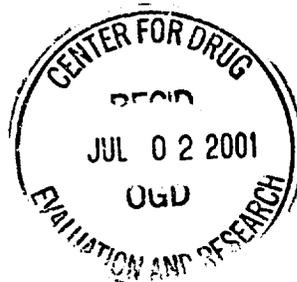
Please find enclosed, as requested, an updated Certificate of Analysis which incorporates the specifications as set forth in USP 24 Supplement 3.

It is TEVA Pharmaceuticals USA's opinion that the information provided herein represents a complete response to the deficiency presented in the June 26, 2001 telephone conversation. This information is submitted for your review and final approval of ANDA #75-506. Please note that we anticipate receipt of final approval of our ANDA upon the extended expiration of U.S. patent #4,626,549 for the reference listed drug, Prozac® (fluoxetine hydrochloride oral solution), on August 2, 2001. If there are any further questions, please do not hesitate to contact me at (215) 591-8642 or facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/jmd
Enclosures





labeling review
drafted 5/30/01
G. Vega

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 3000
FAX: (215) 591 8600

May 17, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773



ORIG AMENDMENT

LABELING AMENDMENT

N/AM

ANDA #75-506
FLUOXETINE ORAL SOLUTION USP, 20 mg (base)/5 mL
LABELING AMENDMENT- RESPONSE TO JANUARY 19, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment to the above referenced pending ANDA in response to the review letter dated January 19, 2001 from the Labeling Review Branch. For ease of review, please find attached a copy of this letter in **Attachment 1**. Also enclosed as **Attachment 2** is a copy of the FDA's March 16, 2001 letter. With regard to "appetite disorders", specifically bulimia, we are implementing the recommendations made within the March 16, 2001 letter from the Office of Generic Drugs which is deemed to supercede those of the Labeling Review Branch regarding this issue. We have adopted all other applicable recommendations from the Labeling Branch's January 19, 2001 and March 22, 2001 letters with the following exception: It is Teva Pharmaceuticals USA's format to not include the use of "Rx only" in the package insert. The March 22, 2001 letter is included as **Attachment 3**. Although the March 22, 2001 letter specifically refers to Fluoxetine Capsules USP, 10 mg, 20 mg, and 40 mg, it was deemed that recommendations proposed therein were applicable to the package insert and label for Fluoxetine Oral Solution USP, 20 mg (base)/5 mL.

Twelve final printed copies of package insert labeling as well as a comparison to our previous revision are included in **Attachment 4**. Twelve final printed copies of container labeling along with a comparison to the last submitted labeling is provided as **Attachment 5**.

It is Teva Pharmaceuticals USA's opinion that the information presented herein represents a complete response to the requests presented in the aforementioned review letter. This information is submitted for your continued reviewed and approval of this ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,



VA/jmd
Enclosure



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 3000
FAX: (215) 591 8600

January 11, 2001

NEW CORRESP

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

FACSIMILE AMENDMENT-
LABELING INFORMATION

*NAI by labeling
1/22/01 A. Vezza*

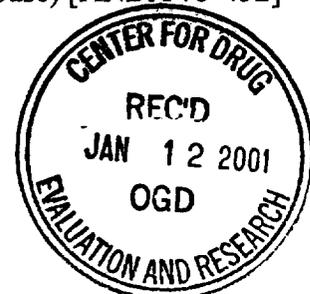
ANDA # 75-506
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, 20 mg (base)/5 mL
FACSIMILE AMENDMENT - RESPONSE TO REVIEW LETTER DATED DECEMBER 13, 2000

Dear Mr. Buehler:

We submit herewith a facsimile amendment to the above-referenced pending ANDA in response to a deficiency letter received from the Labeling Review Branch dated December 13, 2000. A copy of this letter is provided in **Attachment 1** for reference.

Please note that the December 13, 2000 deficiency letter requested inclusion of all indications for this drug product in TEVA's proposed insert labeling. However, we refer the reviewer to a document which TEVA submitted to the Agency on December 8, 2000 which discussed our proposed labeling and relevant information concerning Lilly's Paragraph IV Infringement Action against TEVA indicating why it is appropriate that depression and OCD are the only indications in TEVA's labeling at this time. Please note that this December 8, 2000 document was in reference to all three dosage forms, as provided in the following pending TEVA ANDA's:

- Fluoxetine Hydrochloride Oral Solution, 20 mg (base)/5 mL [ANDA 75-506]
- Fluoxetine Capsules USP, 10 mg (base), 20 mg (base) and 40 mg (base) [ANDA 75-452]
- Fluoxetine Tablets USP, 10 mg (base) [ANDA 75-872]



*ANDA # 75-506
Fluoxetine Hydrochloride Oral Solution, 20 mg (base)/5 mL
Facsimile Amendment- Response to 12/13/00 Deficiency Letter
January 11, 2001
Page 2*

A copy of TEVA's December 8, 2000 document is provided in **Attachment 2** for ease of reference.

The information provided herein in addition to that provided in our December 8, 2000 submission represents, in our opinion, a complete response to your letter of December 13, 2000 and is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,



VA/jbp
Enclosures



Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Deborah A. Jaskot, M.S., RAC
Executive Director, Regulatory Affairs

Phone: (215) 591 3000
FAX: (215) 591 8600

December 8, 2000 *

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

Handwritten signature
12/19/00
"NAJ"

ANDA 75-506 (Fluoxetine Hydrochloride Oral Solution, 20 mg (base)/5 ml)
ANDA 75-872 (Fluoxetine Tablets USP, 10 mg (base))
ANDA 75-452 (Fluoxetine Capsules USP, 10 mg (base), 20 mg (base), and 40 mg (base))

* Please note: This submission replaces the December 1, 2000 submission for the above referenced products.

Dear Mr. Buehler:

This is in response to the agency's correspondence dated September 25, 2000 regarding labeling comments for the above-referenced ANDAs. We also refer to the agency's correspondence dated July 29, 1999, September 2, 1999, November 15, 1999 (copies attached hereto), and the January 3, 2000 tentative approval of ANDA 75-452.

In its September 25 labeling comments, the agency appears to have reversed its earlier position that Teva may omit references to the Reference Listed Drug's ("RLD") indication for the treatment of bulimia nervosa from its generic fluoxetine labeling. As the agency stated:

Please note that since you have filed a Paragraph 4 patent certification to the '549 patent [U.S. Patent No. 4,626,549] you must include all the indications for this drug product (depression, bulimia, OCD) in the proposed insert labeling. The insert labeling must be the same as the reference listed drug, Lilly's Prozac®.



Teva disagrees that it must include the bulimia indication in its fluoxetine ANDAs. Teva's position is that it is entitled to omit bulimia from its labeling pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) because FDA and Lilly have consistently treated the bulimia indication as being covered by claims 1-3 of the '549 patent and Teva has not

challenged those claims in its Paragraph IV Notification to Lilly.¹ The fact that Teva has challenged other claims of the '549 patent including claim 7, which have recently been invalidated in litigation involving another generic applicant, does not affect Teva's right to omit the bulimia indication from its labeling.

Indeed, if FDA were to take the position that a patent that includes two or more distinct methods of use may only be subject to either a Paragraph IV Certification or a Use Statement, it would nullify the ability of generic applicants to use the Paragraph IV challenge procedure against invalid or non-infringed claims that are coupled with a valid claim under the same patent. Such a result would not only frustrate the purposes of the Hatch-Waxman Amendments, it would reward patent holders for invalid patent claims. In a closely analogous setting, the agency has stated explicitly that an ANDA applicant may "split" its certification to a single patent that contains distinct claims:

If, however, there are listed patents that present both a product and a method of use claim, the applicant may file a paragraph IV certification with respect to the product patent or product claim and a statement that the product that is the subject of the application does not involve a patented method of use with respect to the method of use patent or patent claim.²

Teva seeks nothing more than to apply this exact logic to the situation where a method of use patent contains more than one distinct use claim, reflected in more than one distinct indication in the corresponding product's label. If an applicant may submit one kind of certification or statement to a product claim in a patent and a different kind of certification or statement to a use claim in the same patent, an applicant certainly should be able to submit one kind of certification or statement to a use claim in a patent and a different kind of certification or use statement to a separate use claim or claims in the same patent.

Accordingly, to eliminate any possible confusion as to this issue, we submit herewith appropriate statements pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) with respect to claims 1-3 of the '549 patent. We seek the agency's prompt written acceptance of the accompanying "use statements" and the agency's concurrence that Teva may continue to omit bulimia from its fluoxetine labeling. If the agency is unwilling to provide a prompt favorable response, we request a face-to-face meeting with the agency and its legal counsel to discuss whether a cooperative resolution of this matter can be reached.

¹ Teva, however, does not concur that claims 1 – 3 validly cover the bulimia indication, but has chosen to exclude that indication from its labeling rather than challenge the corresponding claims, as is Teva's right under section 355(j)(2)(A)(viii).

² *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*, 59 Fed. Reg. 50,338, 50,347 (1994) (preamble to final rule).

A. The Act Permits ANDA Applicants To Omit Indications Covered By Method of Use Patents

The FDCA permits an applicant seeking approval of a generic drug to omit an approved indication for the Reference Listed Drug from its generic drug labeling if that use is protected by a patent or other exclusivity. Specifically, section 505(j)(2)(A)(viii) permits an ANDA sponsor to submit a “use statement” with respect to uses for which it does not seek approval:

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the [generic] drug applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

21 U.S.C. § 355(j)(2)(A)(viii).

The legislative history of section 355(j)(2)(A) clearly reflects Congress’ intent to allow ANDA applicants to seek approval for less than all of the approved indications of the RLD, and suggests that indications protected by patent could be omitted at the ANDA applicant’s discretion:

... The Committee has adopted the FDA’s policy of utilizing the term ‘same’ except that the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved as explained below.

First, an ANDA must include sufficient information to show that the conditions of use for which the applicant is seeking approval are the same as those that have been previously approved for the listed drug. The applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

* * *

Seventh, an ANDA must include a certification by the applicant regarding the status of certain patents applicable to the listed drug. ... With respect to all product patents which claim the listed drug and all use patents which claim an indication for the drug for which the applicant is seeking approval (hereafter described as a controlling use patent), the applicant must certify, in his opinion and to the best of his knowledge, as to one of four circumstances.

* * *

Eight, if there are indications which are claimed by any use patent and for which the applicant is not seeking approval, then an ANDA must state that the applicant is not seeking approval for those indications which are claimed by such use patent. For example, the listed drug may be approved for two indications. If the applicant is seeking approval only for indication No. 1, and not indication No. 2 because it is protected by a use patent, then the applicant must make the appropriate certification and a statement explaining that it is not seeking approval for indication No. 2.

Drug Price Competition and Patent Term Restoration Act of 1984, H.R. Rep. No. 98-857 (Part I), 21-22 (1984) (emphasis added).

B. FDA And Lilly Have Consistently Treated Bulimia As An Indication Covered By The '549 Patent

Lilly's Prozac is approved for three indications: depression, obsessive-compulsive disorder (OCD), and bulimia. Teva is only seeking approval of the depression and OCD indications for its generic fluoxetine products. Teva is not seeking approval of a bulimia indication, nor does Teva's proposed labeling anywhere refer to "treatment of animals suffering from an appetite disorder." Teva has notified Lilly of this in its Paragraph IV Notifications respecting the '549 patent. Claims 1-3 of that patent relate to a "method of treating animals suffering from an appetite disorder." As a result, Lilly's Paragraph IV Infringement Action against Teva does not assert infringement of claims 1-3 of the patent. Significantly, FDA has treated claims 1-3 as protecting the bulimia indication, and Lilly has acknowledged that omission of the bulimia indication from Teva's labeling will assure non-infringement of claims 1-3. Thus, for purposes of 21 U.S.C. § 355(j)(2)(A)(viii), Teva is entitled to omit this indication in seeking final approval of its fluoxetine ANDAs.

As the agency is aware, the bulimia indication for Prozac[®] was granted a three-year period of exclusivity based on claims 1-3 of the '549 patent. Specifically, after FDA approved a supplemental NDA for Prozac on November 21, 1996, the Orange Book listing for Prozac was amended to include Use Code U-154 ("method of treating animals suffering from an appetite disorder") as well as Exclusivity Code I-166 (treatment of bulimia). Although the I-166 exclusivity expired on November 21, 1999, the associated U-154 code remains in the Orange Book.

However, the '549 patent includes other unrelated claims that Teva has challenged on invalidity grounds and which Lilly has thus asserted against Teva. And, as FDA knows, the U.S. Court of Appeals for the Federal Circuit recently ruled that the key claim (claim 7, treatment of depression by the administration of fluoxetine) of the '549

patent is invalid. Eli Lilly v. Barr Laboratories. That decision is expected to become final by the expiration date of the earlier-expiring fluoxetine patent, No. 4,314,081 (the “ ’081 patent”), for which Teva has filed a Paragraph III Certification. Because Lilly has only asserted claims 6 and 7 against Teva, and because claim 6 will not stand once claim 7 is invalidated, as of the expiration date of the ’081 patent, claims 1-3 will be the only claims of the ’549 patent that Lilly would have any basis to assert against Teva,³ and then only in the event Teva is arbitrarily forced by FDA to seek approval of the bulimia indication.

It is also important to note that the agency has previously addressed the bulimia indication with respect to Teva’s fluoxetine ANDAs and concluded that Teva is entitled to omit the indication. Initially, on July 29, 1999, the agency initially requested that Teva retain the bulimia indication:

The “Orange Book” lists 2 use codes for U.S. Patent 4,626,549. Since you have made a Paragraph IV certification to the patent, which includes (U-154), the method of treating animals suffering from an appetite disorder, information regarding bulimia should be retained in the package insert. If your challenge is successful the information will be allowed. If on the other hand, your challenge is not upheld, you will be required to wait until the patent expires. In either case, the information regarding bulimia should be retained in the insert.

Labeling comments from Robert West to Deborah Jaskot, ANDA 75-452 (copy attached).

However, approximately one month later, on September 2, 1999, the agency recognized Teva’s right to exclude the bulimia indication and specifically instructed Teva to remove bulimia-related information from its proposed product labeling:

We acknowledge your comments regarding the bulimia indication from the Agency’s faxed labeling comments dated July 29, 1999. . . . Revise your insert labeling to be in accord with the attached mocked-up copy of the labeling of the reference listed drug, Prozac[®] (approved June 16, 1999; revised May 1999) minus bulimia information. Please note that the text and tables to be deleted have been circled.

Letter from Robert West to Deborah Jaskot re ANDAs 75-452 and 75-506 (copy attached). On November 15, 1999 FDA instructed Teva to remove additional bulimia-

³ Teva expects that Lilly’s patent infringement case will be dismissed against Teva once the Barr decision is final. We are not asking the agency to agree or disagree with that expectation, but only to recognize that upon such a dismissal there will be no litigation-based barrier to final approval of Teva’s ANDA.

related references from the precautions section of Teva's labeling. Letter from FDA to Teva dated November 15, 1999 (copy attached). Finally, after Teva completed all of FDA's requested deletions of bulimia-related information, Teva received tentative approval of ANDA 75-452 without inclusion of the bulimia indication.

Thus, there can be no dispute that FDA and Lilly have treated bulimia as being covered by claims 1-3 of the '549 patent, and it would be arbitrary and capricious for the agency to now reverse itself by not allowing Teva to omit that indication from its fluoxetine labeling under 21 U.S.C. § 355(j)(2)(A)(viii).⁴

In light of the foregoing, we were surprised and disappointed by the agency's apparent reversal with respect to the inclusion of the bulimia indication. Teva's litigation with Lilly over the '549 patent has always been predicated on Teva's right, as repeatedly confirmed by FDA, to omit bulimia from its fluoxetine labeling. The threatened reversal of FDA's position would have a substantial adverse impact on Teva's expectations and business planning and would force Teva, and most likely other fluoxetine ANDA holders, to consider legal recourse against the agency.

We trust that this response has clarified any questions the agency might have. Given the fact that this issue has arisen so late in the approval cycle (indeed post-approval with respect to ANDA 75-452), and so close to the expiration date of the unchallenged '081 patent, time is of the essence and we look forward to your prompt written concurrence with Teva's right to exclude bulimia from its fluoxetine labeling.


Deborah Jaskot
Executive Director Regulatory Affairs
Attachments

⁴ For FDA to treat the patent as a single method of use patent for purposes of defining the required indications in generic versions would indefensibly nullify the express statutory and regulatory provisions that permit generic applicants to omit protected indications from their product labeling. We urge the agency not to take such a position.



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

July 6, 2000

ORIG AMENDMENT
N/A.M.

TELEPHONE AMENDMENT

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #75-506
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION , 20 mg (base)/5 mL
TELEPHONE AMENDMENT - RESPONSE TO JUNE 19, 2000 TELEPHONE CONVERSATION

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA. The subject of this amendment is our response to a comment regarding organic volatile impurities set forth in a June 19, 2000 telephone conversation between Tim Ames from the Office of Generic Drugs (OGD) and Philip Erickson, Assoc. Director of Regulatory Affairs at Teva Pharmaceuticals USA. The response to this comment is addressed below.

We have provided certification from our raw material suppliers that listed in USP 24 section <467> are not used in the manufacturing process of fluoxetine hydrochloride. Furthermore the certifications identify the names and provide the limits for the solvents used in the of the manufacturing process.

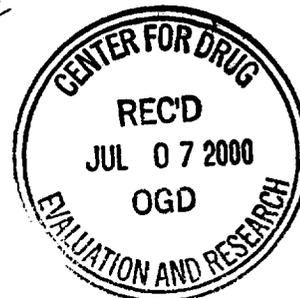
It is Teva Pharmaceutical USA's opinion that the information provided herein represents a complete response to all of the deficiencies presented in the June 19, 2000 telephone conversation. This information is submitted for your continued review and approval. If there are any further questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or facsimile at (215) 256-8105.

591-3000 x3142

Sincerely,

Deborah Jaskot

DAJ/brb
Enclosures





Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

May 12, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

NDA ORIG AMENDMENT
N/A

ANDA # 75-506
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, 20 mg (base)/5 mL
MINOR AMENDMENT - RESPONSE TO REVIEW LETTER DATED MARCH 16, 2000

Dear Mr. Buehler:

We submit herewith a Minor Amendment to the above referenced pending ANDA in response to your letter of March 16, 2000. A copy of the March 16, 2000 review letter is provided as Attachment 1. The deficiencies presented in the aforementioned letter are addressed in the order in which they were presented.

1. Per your request, we have updated the Organic Volatile Impurities Specifications in accord with USP 24 for the fluoxetine drug substance. Additionally, we have revised the assay limit from ' % to % per USP 24, Supplement 1. A copy of the revised raw material procedures manual is provided as Attachment 2.
2. We have addressed the method validation comments and forwarded them to the District Laboratory referenced in the review letter. A copy of our response to the District Laboratory is provided as Attachment 3.



Additionally, at this time, we wish to propose a manufacturing site change for our API manufacturer, Assia Chemical Industries Ltd., to the new TEVA Tech, Ltd. facility. Note that both of these companies/sites are part of our TEVA Group A.P.I. Division.

From:

Assia Chemical Industries Ltd.
(TEVA Group A.P.I. Division)
2 Denmark Street
P.O. Box 3190
Petah Tiqva 49517, Israel
CFN # 9610273

To:

TEVA Tech, Ltd.
(TEVA Group A.P.I. Division)
Ramat Hovav
P.O. Box 2049, Emek Sara
Beer Sheva 84874, Israel
CFN # 9613297

We have been notified by _____, the vendor of both companies, that they held a meeting with FDA personnel in July 1999 to discuss the implementation of this change. We are hereby submitting this manufacturing site change in accord with the agreement reached at that meeting. For your ease of review, a copy of the notification letter from _____ which includes the minutes from the July 1999 meeting, and an updated DMF authorization letter for DMF _____ are provided as Attachment 4.

The information provided herein represents, in our opinion, a complete response to your letter of March 16, 2000 and is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or by facsimile at (215) 256-8105.

Sincerely,



DAJ/mea
Enclosures



*Noted
A. Veza
1/16/01*

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

April 28, 2000

Gary Buehler, Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

NEW CORRESP

ANDA #75-506
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL
TELEPHONE AMENDMENT - RESPONSE TO MARCH 2, 2000 TELEPHONE CONVERSATION

Dear Mr. Buehler:

We submit herewith an amendment to the above referenced pending ANDA in accord with a telephone communication from Mr. Adolph Veza of your office on March 2, 2000. Mr. Veza inquired as to our reasons for not including the Obsessive Compulsive Disorder (OCD) indication in our proposed labeling. Our rationale follows:

Our ANDA contains a patent certification statement certifying to Section 505(j)(2)(A)(vii)(III) of the Federal Food, Drug, and Cosmetic Act as amended as to the 4,314,081 patent (Expiration Date: February 2, 2001) and to Section 505(j)(2)(A)(vii)(IV) of The Act as to the 4,626,549 patent (Expiration Date: December 2, 2003). The '549 patent covers two uses of the drug; (1) as a serotonin re-uptake inhibitor and (2) as an appetite suppressant. We are challenging the validity and/or infringement of that part of the patent claiming serotonin re-uptake inhibition but only insofar as it relates to the treatment of depression.

We previously notified Lilly that we will not use the bulimia indication on our product labeling. We asked Lilly's attorneys as to what their reaction is with regard to the bulimia indication since we were in the midst of litigation for this product. They responded that Lilly reserves the right to assert its patent against TEVA when and if the bulimia indication were to be incorporated into TEVA's labeling. It is therefore clear that Lilly will not agree in advance to refrain from litigation should any indication involving serotonin re-uptake inhibition (including OCD) other than depression treatment be included in TEVA's labeling.

2/2/01

We have presented to the Court in which the litigation is pending that TEVA is seeking approval from the FDA limited to the treatment of depression. Our ANDA is so limited.

In light of the foregoing, it is respectfully submitted that to reference any other indication would unnecessarily expose TEVA to a risk of litigation relating to an indication for which TEVA is not seeking approval from this agency.

It is also our understanding that the FDA has approved a similar limitation in the ANDA of Zenith Goldline (No. 75-245) at or about the beginning of November 1999.

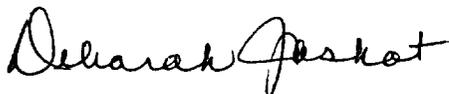
In accord with the Agency's submission guideline dated November 8, 1991, we draw your attention to the essentially identical amendment to the following application:

ANDA #75-452

FLUOXETINE CAPSULES USP, 10 mg and 20 mg

This information is submitted for your continued review and approval of ANDA 75-506. Should you have any further comments or questions, please do not hesitate to call me at (215) 256-8400 ext. 5249 or contact me via facsimile at (215) 256-8105.

Sincerely,



DAJ/mea
Enclosures



Labeling review
drafted 1/10/00
A. Vezza

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 721-9669

Toll Free: (888) TEVA USA
Phone: (215) 256-8400
FAX: (215) 256-7855

December 28, 1999

NDA ORIG AMENDMENT
N/AF

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ANDA #75-506
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL
TELEPHONE AMENDMENT - LABELING REVISION

Dear Mr. Sporn:

We submit herewith an amendment to above-referenced pending ANDA in accord with a telephone communication from Mr. Adolph Vezza of your office on December 17, 1999. Mr. Vezza instructed that we apply the comments from the letter faxed from your office on the same day for ANDA #75-452 (Fluoxetine Capsules USP, 10mg and 20mg) to this ANDA as well. Additionally, please find enclosed a side-by-side comparison of our proposed labeling with that which we last submitted. All differences are annotated. Please note that we have not included reference to NDC numbers in the How Supplied section as it is TEVA Pharmaceuticals USA's practice to keep inserts neutral so that they may be used in packaging with different distributor labels.

This information is submitted for your continued review and approval of ANDA 75-506. Should you have any further comments or questions, please do not hesitate to call me at (215) 256-8400 or contact me via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot PE

DAJ/mea
Enclosures





Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:

TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:

TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

December 9, 1999

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

AF
ANDA ORIG AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ANDA #75-506

FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL
LABELING AMENDMENT - RESPONSE TO REVIEW LETTER DATED NOVEMBER 15, 1999

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced pending ANDA in response to the letter from your office dated November 15, 1999. This amendment provides for revised package insert labeling. In accord with your request, all changes have been made. In addition, the following revisions have also been made: (1) Eliminated reference to the indication of treatment of Obsessive-Compulsive Disorder (OCD) in accord with a recent telephone discussion with Mr. Adolph Vezza of your office; (2) Changed from "US" to "U.S." throughout the insert based on revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections requested in the November 15, 1999 letter; and (3) Complied with a telephone request from Mr. Adolph Vezza of your office in which he instructed that we apply the comments from the September 2, 1999 facsimile we received for ANDA #75-452 (Fluoxetine Capsules USP, 10mg and 20mg) to this ANDA as well.

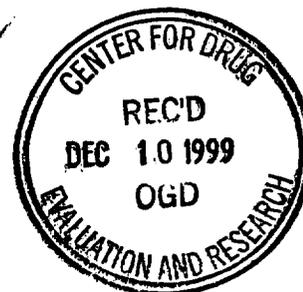
We submit herewith four draft copies of package insert labeling for your continued review and approval. Additionally, a comparison of our proposed labeling with that of our last submission is provided with all differences indicated.

If there are any further questions, please do not hesitate to contact me at (215)256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot

DAJ/mea
Enclosures





Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

September 7, 1999

*Labeling review
drafted 9/29/99
A. Veza*

FPL

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MAJOR AMENDMENT

ORIG AMENDMENT

Ac

ANDA # 75-506

FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL
MAJOR AMENDMENT - RESPONSE TO REVIEW LETTERS DATED 7/15/99 AND 7/28/99

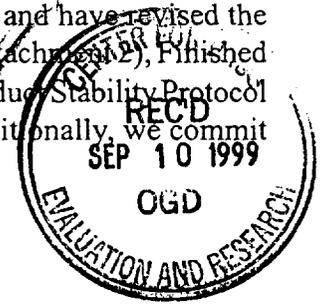
Dear Mr. Sporn:

We submit herewith a Major Amendment to the above referenced pending ANDA in response to your letter of July 15, 1999 and the additional labeling comments contained in the July 28, 1999 facsimile from Mr. Adolph Veza. The deficiencies presented in the aforementioned letters are addressed in the order in which they were presented.

I. Chemistry, Manufacturing and Controls

A. Deficiencies

1. Per your request, we have incorporated the drug substance grade, USP, in the components/ composition statement. See Attachment 1 for revised qualitative and quantitative components/ composition statements.
2. Upon comparison of our assay test contained in analytical method _____ for the drug substance Fluoxetine HCl USP and the assay method in USP 23, Supplement 8, we were unable to determine any differences between the two methods. Therefore, we have not provided comparative results as the methods are one in the same.
3. We note that our proposed product is a solution not a syrup and have revised the description accordingly. Revised Certificates of Analysis (Attachment 2), Finished Product Procedure Manual (Attachment 3), and Finished Product Stability Protocol (Attachment 4) incorporate this change in description. Additionally, we commit



that future stability reports will also incorporate this change in description.

4. We have added pH and Specific Gravity testing to the finished product release testing. A revised Finished Product Procedure Manual incorporating these additional tests is provided in Attachment 3.
5. In accord with your request, we have added an Assay for Fluoxetine, Assay for Benzoic Acid, and Specific Gravity testing on an in-process basis. We feel that these in-process tests provide adequate control of the manufacturing process. In support of this in-process testing we have provided a revised Production Batch Record which includes the sampling for the in-process testing as Attachment 5 and a Finished Product Procedure Manual incorporating these in-process tests is provided in Attachment 3.
6. On page 236 of the original ANDA, the theoretical yield is erroneously indicated as "1800 L (Weight of 2286 Kg)" on page 10 of the manufacturing directions for the pivotal batch. This calculation error had no effect on the identity, strength, quality, or purity of the drug product as the manufacturing directions indicate to q.s. to a target volume not weight. The weight is merely provided for informational purposes only. Note that the theoretical yield of 1800 L (Weight of 2296.8 Kg) was listed correctly for the proposed commercial manufacturing directions found on page 251 of the original ANDA.
7. In-process fill weight check sheets for the pivotal batch were inadvertently excluded from the original ANDA and have been provided in Attachment 6 per your request.
8. Contained in Attachment 7 is the requested USP <661> and <671> testing for the proposed container/closure configuration (4 oz round amber PET bottle with CRC).
9. We have revised the drug product description per your request. Revised Certificates of Analysis (Attachment 2), Finished Product Procedure Manual (Attachment 3), and Finished Product Stability Protocol (Attachment 4) incorporate this change in description. Additionally, we commit that future stability reports will also incorporate this change in description.
10. We have added pH and Specific Gravity testing to the finished product stability testing. A revised Finished Product Procedure Manual (Attachment 3) and Finished Product Stability Protocol (Attachment 4) incorporating these additional tests are provided herein.

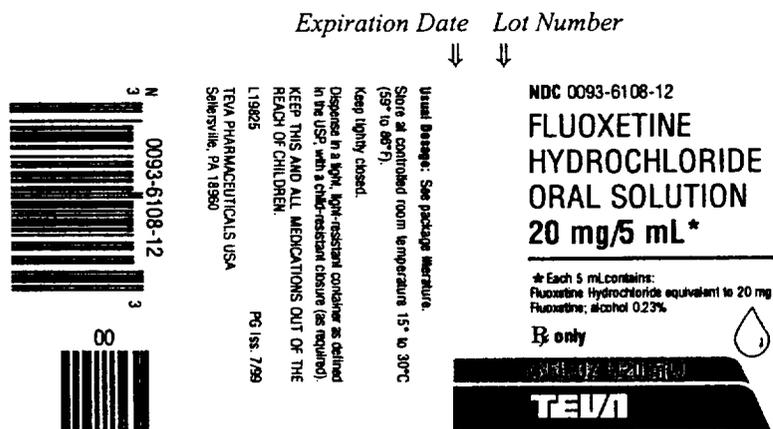
B. Notes and Acknowledgments

1. As stated previously, upon comparison of our assay test contained in analytical method for the drug substance Fluoxetine HCl USP and the assay method in USP 23, Supplement 8, we were unable to determine any differences between the two methods. However, we note and acknowledge that unmodified USP methods and procedures are official for this drug substance and that, in the event of a dispute, results obtained by USP 23 methods will be considered conclusive.
2. We note and acknowledge that methods validation will be performed on the drug product by a FDA laboratory.
3. We note that DMF# is under review.

II. Labeling

Final printed container label, product insert labeling and side-by-side comparisons which incorporate revisions requested are enclosed as Attachment 8.

With regard to comment 1.c., please note that the lot number and expiration date will appear as indicated below.



Regarding comment 2.b.ii., based on TEVA Pharmaceuticals USA format and recently approved labeling for other products, "Rx only" has not been included in our insert.

III. Bioequivalency

We note that the bioequivalency comments provided in this communication are preliminary and are subject to revision which may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

IV Additional Information

Additionally, at this time we propose the use of a 24 mm CRC using the _____ resin for the inner shell (X18416) as a replacement for the 24 mm CRC using the discontinued _____ resin for the inner shell (C18416) presented in the original ANDA. A portion of the pivotal batch, Lot #1054-023, presented in the original ANDA, has been recapped with the new closure and designated with the new Lot #1054-023A. The packaging and disbursement of this portion of the pivotal batch was disclosed on page 261 of the original ANDA.

In support of the inner shell cap resin change, we provide the following:

- Cap Diagram, Specifications, and DMF Authorization Letters (Attachment 9)
- USP <661> and <671> testing for the proposed container/closure configuration, 4 oz round amber PET bottle (C19589) with CRC. (Attachment 10)
- Finished Product Certificate of Analysis (Attachment 11)
- Stability Summary Reports (Attachment 12)

We note and acknowledge that changing to new a cap made from _____ resin is governed under 21 CFR 314.70, however, based on previous deficiency comments received when the bottle/cap resin had been or was soon to be discontinued and the replacement resin was not specified, we choose to include this information at this time.

The information provided herein represents, in our opinion, a complete response to your letter of July 15, 1999 and the July 28, 1999 facsimile from Mr. Adolph Vezza and is submitted towards the review and approval of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or by facsimile at (215) 256-8105.

Sincerely,



DAJ/mea
Enclosures



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

*NAS
Wmch
2/19/99*

February 8, 1999

NEW CORRESP

NC

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA# 75-506

FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL
NOTICE OF CERTIFICATION OF NON-INFRINGEMENT

Dear Mr. Sporn:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent No. 4,626,549 was provided to Eli Lilly & Company, as the holder of NDA 20-101, for Prozac® (Fluoxetine Hydrochloride Oral Solution) and owner of the patent, as well as Dista Products, the product manufacturer and distributor, in accord with 314.95(b). The notice dated February 2, 1999 contains the information as required under 314.95(c). A copy of the notice is provided herein.

This information is submitted for your review and approval. If there are any further questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

DAJ/mea
Enclosures

RECEIVED

FEB 10 1999

GENERIC DRUGS

*Madue
2-1-99*



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:

TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:

TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

February 26, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

*NAC
Teva is providing
Notice of Cert. Rec'd
via U.S. mail
H. Meeley
3/15/99*

PATENT AMENDMENT

NEW CORRESP.
NC

ANDA# 75-506

FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL
RECEIPT OF NOTICE UNDER SECTION 505(j)(2)(B)(I) AND 21 CFR 314.95

Dear Mr. Sporn:

In accord with 21 CFR 314.95 (e), TEVA Pharmaceuticals USA is hereby providing documentation of the receipt of all Notices of Certification for U.S. Patent No. 4,626,549. The last of the two notices sent to the affected patent owner, application holder, or authorized representative had been received by TEVA Pharmaceuticals USA on February 15, 1999. This date is evidenced by the attached copies of the return receipts. As evidenced on the return receipts, both Dista Products and Eli Lilly Company, in addition to the United States Postal Service, failed to fill in the date of delivery. Upon contacting the United States Postal Service concerning the missing information, they were unable to provide the date of delivery based on their records. Therefore, the United States Postal Service contacted Eli Lilly Company / Dista Products for the delivery date. On the facsimiles provided herein, a representative from Eli Lilly Company / Dista Products listed the date of delivery. Based on this information, in accord with 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is February 12, 1999, the first day after receipt of notice. The 45-day period will therefore end on March 28, 1999.

This information is submitted for your review and approval. If there are any further questions, please do not hesitate to contact me at (215) 256-8400 ext. 5249 or via facsimile at (215) 256-8105.

Sincerely,

Deborah Jaskot
DAJ/mea
Enclosures

RECEIVED

MAR 01 1999

GENERIC DRUGS

*Madura
3.2.99*



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

*→ TEVA claims they were not sued within the 45" window.
→ Lilly claims they included this application 75-506 in the lawsuit with 75-452. prior action. outcome relates to the first lawsuit and how it NAI at this point
6/19/99
N Greenberg*

April 26, 1999

NEW CORRESP

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

ANDA 75-506
FLUOXETINE HCl ORAL SOLUTION, equivalent to 20 mg Fluoxetine per 5 mL

Dear Mr. Sporn:

In a letter to the Office of Generic Drugs dated April 9, 1999, Eli Lilly and Company ("Lilly") requested that the approval of ANDA No. 75-506, filed by TEVA Pharmaceuticals USA, Inc. ("TEVA"), not be made effective until the expiration of the 30-month period provided by 21 U.S.C. § 355(j)(5)(B)(iii), subject to an appropriate ruling by the Court. However, Lilly's request is not in accordance with the applicable statutory requirements, and TEVA respectfully submits that this request should be denied.

As Lilly stated in its April 9 letter, Lilly received TEVA's Fluoxetine HCl Oral Solution ANDA filing notification on or about February 11, 1999. The 45-day window for Lilly to bring suit in order to trigger the 30-month delay period under 21 U.S.C. § 355(j)(5)(B)(iii) therefore expired on March 28, 1999. Lilly brought suit against TEVA on this ANDA on April 15, 1999. Lilly, therefore, failed to bring suit against TEVA within that 45-day window.

As Lilly states in its letter, on March 26, 1999, it filed a motion for leave to amend its complaint in a prior action filed against TEVA in October 1998, in respect to ANDA No. 75-452, in order to add a claim with regard to ANDA No. 75-506. On April 12, 1999, the Court in response to that motion granted Lilly leave to file its "Amended Complaint." (A copy of the Court's Order is attached; the relevant ruling is in paragraph 6 of the Order.) In so doing, the Court stated that the title of Lilly's new filing was not determinative of any issue of relation back to the date of Lilly's prior action filed in October 1998. At the time Lilly commenced that prior action, ANDA No. 75-506 was not yet filed.

RECEIVED

APR 27 1999

GENERIC DRUGS

*66-2799
NW
4-27-99*

Therefore, no claim of patent infringement with respect to ANDA No. 75-506 could have been brought at that time. Accordingly, and as a matter of law, Lilly's suit in response to ANDA No. 75-506 is a supplemental claim that cannot relate back to the filing date of its October 1998 complaint because the act upon which the claim is based—the filing of ANDA No. 75-506—had not yet occurred in October 1998. Rather, the filing date is the date that Lilly actually served its Amended Complaint incorporating a claim in response to the filing of ANDA No. 75-506 on April 15, 1999. As is apparent, April 15, 1999, is subsequent to the 45-day cut-off date of March 28, 1999. Because Lilly failed to bring suit in response to the filing of ANDA No. 75-506 within the 45-day period provided by law, TEVA respectfully requests that FDA deny Lilly's request for a 30-month stay on the effective approval of that ANDA.

Sincerely,



DAJ/emb
Enclosure



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:

TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Corresponding Address:

TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpsville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

December 21, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

*Labeling review
drafted 3/18/99
alizza*

NDA ORIG AMENDMENT
N/A/C

ANDA #75-506

FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg fluoxetine per 5 mL
RESPONSE TO REFUSAL TO FILE LETTER DATED 12/9/98

Dear Mr. Sporn:

We herewith submit an amendment to ANDA # 75-506, in response to your letter dated 12/9/98. The subject of this amendment addresses the decision to refuse to file this application based on 21 CFR 314.70 (a) (8) (ii), and safety concerns relating to Natural Peppermint Flavor manufactured by

Compositional information for Natural Peppermint Flavor is deemed proprietary by and is only accessible to individuals or firms that are authorized to access the applicable Drug Master File (DMF). Therefore, since will not relinquish confidential formulation information to TEVA Pharmaceuticals USA, TEVA must rely on the DMF authorization process to allow the FDA to review the data for the composition of Natural Peppermint Flavor and evaluate its safety.

Nonetheless, in response to the safety concerns, we are emphatically assured by that there is sufficient information contained in DMF to conclude this material is safe for use in formulating drug products for oral administration. In support of this statement, we have provided a DMF authorization for this material from In addition, based on the Agency's review of confidential composition information provided by on December 18, 1998, it has been determined that the ingredients have been previously approved in drug products for oral administration. Therefore, this application should be accepted for filing effective December 18, 1998.

RECEIVED

DEC 22 1998

GENERIC DRUGS

ANDA #75-506

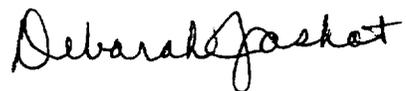
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg fluoxetine per 5 mL

RESPONSE TO REFUSAL TO FILE LETTER DATED 12/9/98

PAGE 2 OF 2

This information is submitted for your review and acceptance of ANDA # 75-506. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 256-8400 ext. 5249 or by facsimile at (215) 256-8105.

Sincerely,



DAJ/mea

Enclosures



Deborah A. Jaskot
Sr. Director, Regulatory Affairs

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
650 Cathill Road, Sellersville, PA 18960

Corresponding Address:
TEVA PHARMACEUTICALS USA
1510 Delp Drive, Kulpville, PA 19443

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 721 9669

Toll Free: (888) TEVA USA
Phone: (215) 256 8400
FAX: (215) 256 7855

RJF
C. Hufgust
11/20/98

November 20, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
FLUOXETINE HYDROCHLORIDE ORAL SOLUTION, equivalent to 20 mg fluoxetine per 5 mL

Dear Mr. Sporn:

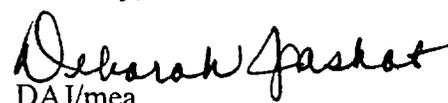
We submit herewith an abbreviated new drug application for the drug product Fluoxetine Hydrochloride Oral Solution, equivalent to 20 mg fluoxetine per 5 ml.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs April 1997 Guidance for Industry: Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application. These copies are presented in a total of 5 volumes; 2 for the archival copy and 3 for the review copy. The application contains a request for waiver of *in vivo* bioavailability study.

Two separately bound copies of the finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 256-8400 ext. 5249 or by facsimile at (215) 256-8105.

Sincerely,


DAJ/mea
Enclosures

RECEIVED

NOV 20 1998

GENERIC DRUGS