CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

APPROVAL LETTER

ANDA 75-465

AUG 2 2001

Reddy-Cheminor Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
Attention: Paul V. Campanelli
66 South Maple Avenue
Ridgewood, New Jersey 07460

Dear Sir:

This is in reference to your abbreviated new drug application dated September 24, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluoxetine Capsules USP, 10 mg, 20 mg and 40 mg.

Reference is also made to the Tentative Approval letter issued on June 26, 2001 and to your amendments dated June 19, July 18 and 30, 2001.

The listed drug product referenced in your application is subject to a period of pediatric exclusivity which expires 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 action against you for your Paragragh IV Certification on the challenged claim in United States District Court for the Southern District of Indiana, Indianapolis Division (Eli Lilly and Company v. Cheminor Drugs, Ltd. and Reddy-Cheminor, Inc., Civil Action No. IP99-0024 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 made 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. However, because of the unique (split) 180-day generic drug exclusivity issues

associated with this drug product, the Agency is prohibited from approving all three strengths at this time. **Thus, only the 40 mg strength of the drug product is approved at this time. The 10 mg and 20 mg strengths shall remain tentatively approved** and will not receive final approval until the remaining 180 days of exclusivity has expired. The Division of Bioequivalence has determined your Fluoxetine Capsules USP, 40 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Prozac® Capsules, 40 mg of Eli Lilly and Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

With respect to 180-day generic drug exclusivity and its impact on the approvability of the various strengths presented in this application, we note that Dr. Reddy's Laboratories Limited (Dr. Reddy's) was the first to submit a substantially complete ANDA with a Paragraph IV Certification for the 40 mg strength only. Therefore, Dr. Reddy's is eligible for 180-days of market exclusivity for the 40 mg strength. Subsequent applications for the 40 mg strength will be eligible for final approval not earlier than one hundred and eighty days after:

(1) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

(2) the date of a decision of a court in action described in clause (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)].

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).

We are unable to grant final approval to the 10 mg and 20 mg strengths at this time because abbreviated applications for Fluoxetine Capsules USP, 10 mg and 20 mg, each containing a Paragraph IV Certification for these strengths were accepted for filing by OGD prior to the filing of your application.

Subsequent applicants for the 10 mg and 20 mg strengths may not be approved earlier than one hundred and eighty days after:

(1) the date the Secretary recieves notice from the applicant under the previous application of the first commercial marketing, or

(2) the date of a decision of a court in action described in clause (ii) holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier [Section 505(j)(5)(B)(iv)].

With respect to the "first commercial marketing" the Agency expects that you will begin commercial marketing of the 40 mg strength of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commence commercial marketing of the 40 mg strength.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application for the 40 mg strength require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application for the 40 mg strength 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 the 40 mg strength Fluoxetine Capsules USP.

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.

With respect to the continuation of the tentative approval status of the 10 mg and 20 mg strengths of this drug product, our decision is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

To provide for final approval of the 10 mg and 20 mg strengths, please submit a supplemental application as directed below. The Agency will provide written notice of the information needed to determine the earliest possible final approval date of your supplemental application for the 10 mg and 20 mg strengths under section 505(j)(5)(B)(iv) as soon as such information becomes available. The supplemental application, which must be submitted for prior approval between 60 and 90 days prior to the date you believe these strengths will be eligible for final approval, should include updated information such as final-printed labeling, and chemistry, manufacturing and controls data as appropriate. Alternatively, a prior approval supplement should be submitted to request final approval of these strengths and stating that no changes have been made to the application since the date of this letter. Because of the unique circumstances associated with exclusivity for this drug product, the office will entertain your request that the supplemental application be granted "expedited review" status.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the supplemental application will be made.

In addition to, or instead of the supplemental application requesting final approval of the additional strengths, the Agency may at any time prior to final approval, request that you submit an informational document containing the information stated above.

Failure to submit the supplemental application or informational document may result in rescission of the tentative approval determination, or delay in issuance of the final approval letter for the 10 mg and 20 mg strengths.

The 10 mg and 20 mg strengths of Fluoxetine Capsules USP may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of these unapproved strengths before the final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, the 10 mg and 20 mg strengths of the drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book").

Should you have any questions about the approval status of the various strengths of drug product presented in your application, or about the timing or content of the supplemental application to provide for final approval of the remaining strengths, please contact Ms. Bonnie McNeal, Project Manager, at (301) 827-5849.

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

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DRAFT FINAL PRINTED LABELING

FLUOXETINE Capsules, USP. 40 mg I 07/01 010743-01

010743-01 FLUOXETINE Capsules, USP 40 mg I 07/01

APPROVED

AUG - 2 2001

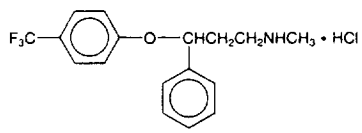
FLUOXETINE Capsules USP

Issued: July 2001

Rx Only

DESCRIPTION

Fluoxetine hydrochloride is an antidepressant for oral administration; it is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, 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-*p*-tolyl)oxy]propylamine hydrochloride and has the molecular formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. The structural formula is:



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

Each capsule contains fluoxetine hydrochloride equivalent to 40 mg (129.3 μmol) of fluoxetine and the following inactive ingredients: pregelatinized corn starch. The capsule shells and imprinting ink contain D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Red No. 40, gelatin, pharmaceutical glaze, silicon dioxide, sodium lauryl sulfate, synthetic black iron oxide, and titanium dioxide.

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

Absorption, Distribution, Metabolism, and Excretion:

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

The 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 α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* PRECAUTIONS).

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

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

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

Variability in Metabolism–A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450IID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the 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

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, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

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

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

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

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, 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 P450IID6 isozyme activity. Thus, this study suggests that drugs which inhibit P450IID6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

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

PRECAUTIONS

General

Anxiety and Insomnia–In 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-

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

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

Clinical Trials:

Depression–The efficacy of 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 subfactor.

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 HAMD-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 or a modified HAMD-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 (on a once a day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving 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 2 higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined.

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

		Fluoxetine		
Outcome Classification	Placebo	20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No Change	64%	41%	33%	29%
Minimally Improved	17%	23%	28%	24%
Much Improved	8%	28%	27%	28%
Very Much Improved	3%	8%	12%	19%

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

INDICATIONS AND USAGE

Depression–Fluoxetine 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 5 of the following 9 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 reevaluate 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 weeks (perhaps longer especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* Accumulation and Slow 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 P450IID6–Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in Metabolism *under* CLINICAL PHARMACOLOGY).

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

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

CNS Active Drugs–The risk of using 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 monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and Slow Elimination *under* CLINICAL PHARMACOLOGY *and* Drugs Metabolized by P450IID6 *under* Drug Interactions).

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

Potential Effects of 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, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* CLINICAL PHARMACOLOGY).

Warfarin–Altered 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 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295 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 ≥ 65 years of age and 93 patients ≥ 75 years of age. The efficacy in geriatric patients has been established (*see* Clinical Trials *under* CLINICAL PHARMACOLOGY). For pharmacokinetic information in geriatric patients, see Age under Clinical Pharmacology. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (*see* Hyponatremia *under* PRECAUTIONS).

Hyponatremia–Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when 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 ≥ 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 nondrug 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

	Percentage of patients reporting event			
	Depression		OCD	
Body System / Adverse Event	Fluoxetine (N=1728)	Placebo (N=975)	Fluoxetine (N=266)	Placebo (N=89)
Body as a Whole				
Asthenia	9	5	15	11
Flu syndrome	3	4	10	7
Cardiovascular System				
Vasodilatation	3	2	5	--
Digestive System				
Nausea	21	9	26	13
Anorexia	11	2	17	10
Dry mouth	10	7	12	3
Dyspepsia	7	5	10	4
Nervous System				
Insomnia	16	9	28	22
Anxiety	12	7	14	7
Nervousness	14	9	14	15
Somnolence	13	6	17	7
Tremor	10	3	9	1
Libido decreased	3	--	11	2
Abnormal dreams	1	1	5	2
Respiratory System				
Pharyngitis	3	3	11	9
Sinusitis	1	4	5	2
Yawn	--	--	7	--
Skin and Appendages				
Sweating	8	3	7	--
Rash	4	3	6	3
Urogenital System				
Impotence†	2	--	--	--
Abnormal ejaculation†	--	--	7	--

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 hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1,578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, 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 overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

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

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arhythmias), 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 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

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

Management of Overdose–Treatment should consist of those general measures employed in the management of overdosage with any 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 overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (*PDR*).

DOSAGE AND ADMINISTRATION

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 Capsules USP 40 mg* are white to off-white powder filled in size '0' hard gelatin capsules with opaque light blue cap and opaque white body, imprinted "FLUOXETINE" on cap and "R149" on body with 40 mg black ink and are supplied in bottles of 30, 100, 500.

NDC 49884-743-11 Bottles of 30

Abnormal ejaculation†	--	--	7	--

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

Associated with Discontinuation in U.S. Placebo-Controlled Clinical Trials (excluding data from extensions of trials)–Table 2 lists the adverse events associated with discontinuation of fluoxetine treatment (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 depression and OCD.

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

Depression (N=392)	OCD (N=266)
--	Anxiety (2%)
Nervousness (1%)	--
--	Rash (1%)

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

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

Priapism has been reported with all SSRIs.

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

Other Events Observed In All U.S. Clinical Trials–Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in U.S. clinical trials (10,782 patients) except (1) those listed in the body or footnotes of Table 1 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to fluoxetine use was considered remote; and (4) events occurring in only 1 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 definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 patients to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

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

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

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

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

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

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

+ Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
† Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
* Adjusted for gender.

Postintroduction Reports–Voluntary reports of adverse events temporally associated with 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

NDC 49884-743-11	Bottles of 30
NDC 49884-743-01	Bottles of 100
NDC 49884-743-05	Bottles of 500

* fluoxetine base equivalent (present as the hydrochloride)

PROTECT FROM LIGHT
Dispense in a tight, light-resistant container.
Store at controlled room temperature 15°- 30°C (59°- 86°F) (see USP).

Sarafem™ is a trademark of Eli Lilly.

ANIMAL TOXICOLOGY

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

Manufactured by:
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Manufactured for:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977 USA

Issued: July 2001

1501558

NDC 49884-743-05

FLUOXETINE
Capsules USP

40 mg

Rx Only

APPROVED

Dr. Reddy's

Each capsule contains:
Fluoxetine Hydrochloride, USP equivalent to 40 mg Fluoxetine.

Usual Dosage: See package insert for dosage and full prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Dispense in a tight, light-resistant container with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F) (see USP).
Keep tightly closed.

I0501

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Mfd. For: **Par Pharmaceutical, Inc.**
Spring Valley, NY 10977 USA

1501070

LOT

EXP

NDC 49884-743-01

FLUOXETINE
Capsules USP

40 mg

Rx Only

APPROVED

AUG - 2

Dr. Reddy's

Each capsule contains:
Fluoxetine Hydrochloride, USP equivalent to 40 mg Fluoxetine.

Usual Dosage: See package insert for dosage and full prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Dispense in a tight, light-resistant container with a child-resistant closure.

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

Keep tightly closed.

I0501

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Mfd. For: **Par Pharmaceutical, Inc.**
Spring Valley, NY 10977 USA

1501071

LOT

EXP

NDC 49884-743-11

FLUOXETINE
Capsules USP

40 mg

Rx Only

- 2 2001

Dr. Reddy's

Each capsule contains:
Fluoxetine Hydrochloride, USP equivalent to 40 mg Fluoxetine.

Usual Dosage: See package insert for dosage and full prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Dispense in a tight, light-resistant container with a child-resistant closure.

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

Keep tightly closed.

I0501

Mfd. By: **Dr. Reddy's Laboratories Limited**
Bachepalli - 502 325 INDIA

Mfd. For: **Par Pharmaceutical, Inc.**
Spring Valley, NY 10977 USA

1501072

LOT

EXP

75-456
AP
8/2/01

-1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

MEDICAL REVIEW

ANDA APPROVAL SUMMARY

ANDA: 75-465

DRUG PRODUCT: Fluoxetine Capsules USP, 10 mg, 20 mg, and 40 mg.

FIRM: Reddy-Cheminor, Inc.

DOSAGE FORM: Capsules

STRENGTHS: 10 mg, 20 mg, and 40 mg.

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The drug product will be manufactured, processed, controlled, packaged, and labeled at Cheminor Drugs Limited:

Cheminor Drugs Limited
Via IDA Bollaram
Bachepalli- 502 325
India
(OK on 8-1-99).

nufacturer-Active Ingredients:

The manufacturer of the drug substance, Fluoxetine Hydrochloride USP, is:

Dr. Reddy's Laboratories LTD.
Plot No. 137 &138,
Sri Venkateswara Co-operative Industrial Estate,
Bollaram, Narsapur Tq.
Medak Dt.
Andhra Pradesh, INDIA
DMF
(OK on 8-1-99).

Contract Laboratories:

None except analysis of container/closure system

This outside Laboratory will perform the container testing for the container/closure systems.

2. Dr. Reddy's Research Foundation

Bollaram Road, Miyapur
Hyderabad 500138
Andhra Pradesh, India

This outside Laboratory performed the Differential Scanning Colorimetry (Thermal Analysis) testing for the container/closure systems.

BIO STUDY:

Satisfactory per K Dhariwal reviewed on 11-8-2000 for 10 mg, 20 mg and 40 mg.

10 mg strength: in vitro dissolution testing
I. Executed batch #001A, USA
II. Executed batch #001B, Canada

20 mg strength: Bio-batch study and fasting and non-fasting conditions
I. Executed batch #001[Lot I], USA
II. Executed batch #001[Lot II], Canada

40 mg strength: in vitro dissolution testing under fasting
Executed batch ##E001

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Compendial drug substance and drug product.
This product is now the subject of a USP monograph so no FDA sample testing is required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration dating:

2 years expiration date with 1, 2 and 3 month accelerated stability data (40°C/75% R.H.) and 3 month room temperature stability data (25°C±2°C/60%±5%) on batch No.:001A for 30's and 100's (85 cc HDPE bottle) capsules package sizes for 10 mg, and on batch No.:001 (Lot-1) for 30's, 100's (85 cc HDPE bottle) and 1000's (950 cc) capsules package sizes for 20 mg, and on batch No.:E001 for 30's, 500's and unit dose blister (10's - only 3 months accelerated) capsules package sizes for 40 mg.

LABELING:

Satisfactory per A. Vezza reviewed on 6-8-2001 for TA letter only.

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

10 mg strength:
I. capsules (executed batch #001A, USA)
II. capsules (executed batch #001B, Canada)

20 mg strength:
I. capsules (executed batch #001[Lot I], USA)
II. capsules (executed batch #001[Lot II], Canada)

40 mg strength:
capsules (executed batch ##E001)

DMF was reviewed and found satisfactory by L. Tang on 2-24-2000.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

10 mg strength batch # batch #001A: cap batch size

20 mg strength batch #batch #001[Lot I](Bio-batch for fasting and non-fasting conditions): cap batch size

40 mg strength batch # ##E001 (in-vitro for fasting conditions): cap batch size

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch (blank batch):

10 mg strength capsules

20 mg strength Capsules

40 mg strength capsules

The proposed production batches have the same manufacturing process as the test batches or Bio-batches (see above). Scale-up meets OGD PPG 22-90.

CHEMIST: Lucia C. Tang DATE: 6-12-01

SUPERVISOR: Ubrani Venkataram DATE: 6-14-01

/S/ 6/20/2001.

75465AAP.P/Tang/6-12-01
v:\FIRMSAM\Cheminor\LTRS&REV\75465AAP.P.DOC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 75-465

3. NAME AND ADDRESS OF APPLICANT

Reddy-Cheminor, Inc.
U.S. Agent for Cheminor Drugs Ltd.
66 South Maple Avenue
Ridgewood, NJ 07450

4. LEGAL BASIS FOR ANDA SUBMISSION

Innovator Drug: Prozac
Innovator Company: EliLily
Patent Expiration Date: 11-11-99.
Two Patents are still in effect for the innovator:

4,626,549 has two use codes and expires 12-2-03- but this patent has gotten pediatric exclusivity and now expires 6-2-04.

4,234,081 is for the chemical entity itself and expires 2-2-01- this patent also got pediatric exclusivity and now expires 8-2-01.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Fluoxetine Hydrochloride Capsules, 10 mg, 20 mg and 40 mg

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

9. AMENDMENTS AND OTHER DATES:

Firm:

9-24-98: Original submission
9-14-99 Amendment for 1st NA letter
9-20-99: Amendment for additional strength (40 mg)
11-18-99: Patent amendment
12-10-99: Amendment
5-9-2000: Amendment

12-26-2000: Amendment
3-8-2001: Amendment
3-30-2001: Telephone Amendment
5-25-01: Labeling amendment
7-19-01: Labeling amendment
7-30-01 and 7-18-01 : Amendments
FDA:

11-19-98: Acknowledgment
6-15-99: 1st NA letter for 10 mg and 20 mg
3-20-2000: 2nd NA letter for 10 mg, 20 mg and 40 mg
11-16-2000: 3rd NA letter for 10 mg, 20 mg and 40 mg
3-08-2001: 4th NA letter
3-16-2001: Letter concerning labeling
3-29-2001: Telephone request

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF

13. DOSAGE FORM

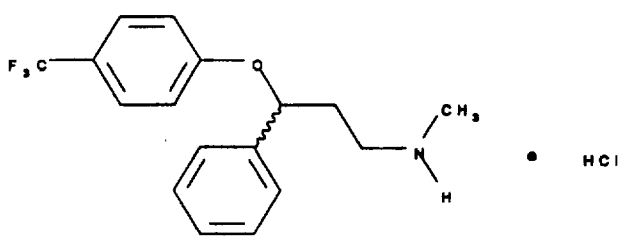
Capsule

14. POTENCY

10 mg, 20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Fluoxetine Hydrochloride
Formula: $C_{17}H_{18}F_3NO.HCl$; Molecular weight: 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

July 18, 2001 Labeling amendment was reviewed and found acceptable per A. Vezza on 7-x-2001.

Status:

a. EER status: Acceptable

EER was requested for Cheminor and Doctor Reddys Laboratories by Tim Ames on December 3, 1998 and found acceptable August 1, 1999.

b. Method Validation status: Adequate

Not required since both drug substance and finished product are official USP items.

c. Bio-review status: Satisfactory for 10 mg and 20 mg

Satisfactory per K Dhariwal reviewed on 12-8-98 for 10 mg and 20 mg.

d. Bio-review status: Satisfactory for 40 mg

Satisfactory per K Dhariwal reviewed on 11-8-2000.

e. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 7-30-2001.

f. DMF : Satisfactory

DMF has been reviewed and found satisfactory by L. Tang on 4-12-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval, 10 mg and 20 mg for 2nd TA, 40 mg for full Approval.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 7-28-2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 17 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-465 APPLICANT: Reddy-Cheminor, Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules
10 mg, 20 mg, 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. Your waiver request for fluoxetine hydrochloride 40 mg capsule is denied for the following reasons:

1. The Office of Generic Drugs generally does not grant upward waivers.
2. As confirmed by you, the innovator's 20 mg and 40 mg capsules are not proportionally formulated and do not have similar dissolution profiles.
3. Innovator's labeling states that fluoxetine's metabolism is not proportional to dose.
4. The Agency has no conclusive data to show proportional fluoxetine bioavailability between 20 mg and 40 mg capsules.

You are, therefore, requested to conduct a fasting study on your fluoxetine hydrochloride 40 mg capsules. However, you do not need to conduct a non-fasting study on the 40 mg capsules.

Sincerely yours,

/S/

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

Fluoxetine Hydrochloride
10 mg, 20 mg and 40 mg Capsules
ANDA #75-465
Reviewer: Kuldeep R. Dhariwal
File name: 75465SDW.300

Reddy-Cheminor, Inc.
66 South Maple Avenue
Ridgewood, NJ 07450
Submission Date:
March 30, 2000

Review of an Amendment

September 24, 1998: Fasting and non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
December 10, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsule granted.
September 20, 1999: Waiver request for an additional strength, 40 mg.
November 16, 1999: The following deficiencies were communicated to the firm: If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.
March 30, 2000: Response to November 16, 1999 deficiencies.

Firm's response:

1. **Capsule fill weight data:** The average fill weights were found to be 227 mg and 267 mg per capsule for 20 mg and 40 mg innovator products respectively. Thus, from the composition standpoint, 20 mg and 40 mg innovator capsules are not weight proportional. The fill weights for Cheminor products are 220 mg and 440 mg for 20 mg and 40 mg capsules respectively.

   Reviewer's comments: Firm's data confirm that the innovator strengths (20 mg and 40 mg) are not proportional. The test 20 mg and 40 mg capsules are weight proportional.

2. **IR spectrum:** IR spectra of 20 mg and 40 mg innovator capsules are similar indicating that the two strengths of innovator product contain same ingredients.

   Reviewer's comments: The infra-red spectra suggest only the qualitative similarity in chemical composition of the two strengths.

3. **Dissolution:** Cheminor conducted comparative dissolution studies on 2x20 mg, 1x40 mg Prozac® capsules and 1x40 mg Cheminor capsules. All three products dissolved greater than % in 20 minutes. The 40 mg innovator product and the 40 mg Cheminor product exhibit very similar dissolution profiles. The Prozac® 20 mg capsules show higher dissolution at 10 minutes time-point compared to both, Prozac® 40 mg and Cheminor 40 mg capsules. has calculated that following a 40 mg dose, the predicted Tmax is about 6.5 hours with a half-life of 38 hours. Hence, minor differences in dissolution profiles before the 20 minute time interval are unlikely to affect bioavailability.

   Reviewer's comments: The dissolution data given in Table 1 support the previous data. The F_2 comparison showed that dissolution profile of innovator 40 mg capsule is different from innovator 20 mg capsule (F_2=43.75) (review dated November 16, 1999; file name: 75465SDW.999).

4. **Biostudies:** Cheminor's fasting and food effect bioequivalence studies were conducted using 2x20 mg doses of the test and reference products. Therefore, a 40 mg dose of fluoxetine was tested *in vivo*. The products are immediate-release capsules and the only excipient for both the test and reference products is starch. The starch is used as a filler and the fact that the innovator 20 mg and 40 mg products are not weight proportional should not cause a difference *in vivo* between administration of a 2x20 mg dose or 1x40 mg dose.

   It should be noted that Cheminor conducted the biostudies for the 20 mg product prior to the approval and availability of the 40 mg innovator product. Cheminor's exhibit batch of the 40 mg capsules was manufactured and tested prior to the availability of the innovator 40 mg product.

   Reviewer's comments: A biostudy conducted using 2x20 mg capsule (40 mg dose) is not considered the same as a biostudy conducted using 1x40 mg capsule.

5. **Inference from reference listed drug:** The 40 mg product is listed in the Orange Book as the reference listed drug, the 10 mg and 20 mg products are not. This would indicate a level of similarity between the 10 mg, 20 mg, and 40 mg innovator products, such that biostudy waivers may be granted within the product line.

Reviewer's comments: The firm conducted biostudies on 20 mg strength and is requesting an upward waiver for 40 mg strength, which is usually not granted. The reservation in granting upward waiver in this case is due to the following reasons:

a) The reference 20 and 40 mg capsules are not proportionally formulated like the test 20 and 40 mg capsules.
b) The F_2 test between 20 and 40 mg reference capsules fails.
c) The labeling of the reference listed drug states that fluoxetine's metabolism is not proportional to dose.
d) The Agency has no conclusive data to show proportional fluoxetine bioavailability between 20 mg and 40 mg capsules.

6. **Chronology of events leading to Cheminor's biowaiver request:**
   - August 26, 1999: Innovator lists and advertises Prozac capsules, 40 mg on Lilly website.
   - September 3, 1999: Innovator launches Prozac capsules, 40 mg. The Orange Book cumulative supplement 7 (July 99) lists 20 mg Prozac capsule as RLD.
   - September 20, 1999: Cheminor amends ANDA 75-465 to request inclusion of 40 mg strength. At the time of this amendment, there is no RLD for Prozac 40 mg capsule.
   - October 18, 1999: The Orange Book cumulative supplement 8 (August 99) lists Prozac 40 mg capsule as RLD. This supplement, available to industry in October 1999, indicates the product was approved on June 15, 1999.

We acknowledge that the innovator 20 mg and 40 mg capsules are not weight proportional, however we believe that based on the data provided, a biowaiver for Cheminor's fluoxetine hydrochloride 40 mg capsule is supported. We respectfully request that the Agency reconsider the request for a waiver of *in vivo* bioavailability/bioequivalence study requirements for Cheminor's fluoxetine hydrochloride capsules, USP 40 mg.

Reviewer's comments:

1. The Cheminor's product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional. Therefore, the firm will be requested to conduct a fasting study on its fluoxetine hydrochloride 40 mg capsule.
2. The non-fasting study on 40 mg strength is not necessary. The firm has conducted a non-fasting study on 20 mg capsule (dose 2x20 mg) for the approval of 20 mg strength.

Recommendations:

The waiver of *in vivo* bioequivalence study requirements for fluoxetine hydrochloride 40 mg capsule manufactured by Cheminor is denied. The firm is requested to conduct a fasting study on 40 mg capsule. The non-fasting study on 40 mg capsule is not necessary.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 5/4/2000

Concur: /S/ Date 5/8/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride Capsules
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: March 30, 2000
File Name: 75465SDW.300

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes (USP 24)
Reference Drug: Prozac®
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Prozac capsule (Reference) Lot # 2 ND49M Strength(mg) 40			Prozac capsule (Reference) Lot # 1AD33A Strength(mg) 20 (2x20)		
	Mean %	Range	%CV	Mean %	Range	%CV
5	19		34.2	24		32.9
10	54		27.8	87		7.1
15	81		20.1	95		1.7
20	94		6.4	96		1.4
30	97		2.5	96		1.4
45	97		3.5	97		1.3

Sampling Times (Minutes)	Test Product Lot # E001 Strength(mg) 40			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
5	13		33.8			
10	58		20.9			
15	87		9.9			
20	95		2.3			
30	95		1.6			
45	96		1.5			

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 10 and 20 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:
>
> Not less than %(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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,

/S/

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

Fluoxetine Hydrochloride
10 mg and 20 mg Capsules
ANDA #75465
Reviewer: Kuldeep R. Dhariwal
Filename: 75465SDW.998

Cheminor Drugs Limited
7-1-27 Ameerpet
Hyderabad 500 016
India
Submission Date:
September 24, 1998

Review of Fasting and Non-fasting Bioequivalence Studies, Dissolution Data and Waiver Request

The firm has submitted single dose bioequivalence studies under fasting and non-fasting conditions and dissolution data comparing its fluoxetine hydrochloride 20 mg capsules with Dista Pharmaceutical's (Lilly) Prozac® 20 mg capsules. The firm has also requested for waiver of *in vivo* bioequivalence study requirements for its 10 mg capsules. To support the request, the firm has submitted comparative dissolution profiles on 10 mg capsules of its product and reference listed drug Prozac®.

Introduction:

Fluoxetine hydrochloride is an antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemic mixture (50/50) of R and S enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity.

Following a single oral dose of 40 mg, peak plasma concentrations (15-55 ng/mL) are observed between 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be taken with or without food. It is extensively metabolized in liver to norfluoxetine and a number of unidentified metabolites. The only identified active metabolite, norfluoxetine is formed by demethylation of fluoxetine. The elimination half life of fluoxetine is about 1 to 3 days and that of norfluoxetine is 4 to 16 days.

Fluoxetine is indicated for the treatment of depression. The initial recommended dose is 20 mg/day administered in the morning. 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.

The reference listed drug is Prozac® (Dista Pharmaceuticals-Lilly) and is available as 10 and 20 mg capsules (pulvules) and as 20 mg/5 mL liquid oral solution.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #:	971712
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Period I November 8, 1997 Period II January 31, 1998
Analysis Dates:	March 2 to April 8, 1998
Study Design:	Randomized, two-way crossover design with a wash-out period of 12 weeks
Randomization Scheme:	AB: 2,4,7,8,9,11,13,14,15,17,19,21,25, 26,28,32,34,36 BA: 1,3,5,6,10,12,16,18,20,22,23,24, 27,29,30,31,33,35

Treatments:

A= Fluoxetine Hydrochloride, 2x20 mg capsules; Cheminor Drugs; Batch #001; Batch size: capsules; Manufacture Date: September 1, 1997; Assay: %; Uniformity of dosage units: %

B= Prozac®, 2x20 mg capsules; Dista Pharmaceuticals; Batch #1AD33A; Expiry Date: March 2000; Assay: %; Uniformity of dosage units: %

Formulation of Test Product: Table 1

Subjects: 36 male subjects were enrolled according to the criteria specified in the protocol

Housing:	From the evening before dosing until after the 36 hour blood draw
Dosing:	After 10 hour fast, with 240 ml water
Sample Collection:	Blood samples (10 mL) were collected at predose (0 h) and at following times after dosing:1,2,3,4,5,6,7,8,10,12,16, 24,36,48,60,72,84,96,120,144,168,336, 504 and 672 hours.

B. Study Results:

1. Clinical:

Drop-outs:	Subject #23 and 33 withdrew after period I. Subject #28 elected to withdraw after 36 hour blood draw in period II for medical reasons. Subject #28 vomited three times after dosing in period II (reference drug) and was later diagnosed with Crohn's disease. Thus, 33 subjects completed the study. Samples from first 30 subjects were analyzed.
Adverse Events:	Some subjects experienced nausea, headache, lightheaded etc. The events were comparable on test and reference drugs. Subject #30 had loose stools after 2 h of dosing in period II (test drug) and subject #28 had vomiting (see above).
Protocol Deviations:	There were a few sampling time deviations. The pharmacokinetic parameters were calculated using actual sampling times.

2. Analytical:

Method:
Internal Standard:
Linearity:

Regression:

Accuracy:

Precision:

Reassays: Following samples were reassayed for reasons shown against them:

	Fluoxetine	Norfluoxetine
Poor chromatography	12	14
Lost in processing	7	7
Anomalous sample value	3	2
H/L std missing	0	9

The firm has provided following pre-study method validation results:

Linearity:

Accuracy:

Precision:

Recovery:

Stability:

3. Pharmacokinetics/Statistics:

FLUOXETINE:

Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	97.02-103.53%
	$LAUC_{0-inf}$	97.56-103.83%
	LC_{max}	99.62-106.00%
Test/Reference Ratio:	AUC_{0-t}	1.01 (0.82-1.19)
	AUC_{0-inf}	1.01 (0.83-1.19)
	C_{max}	1.03 (0.82-1.26)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.89-0.98)
	Reference	0.96 (0.92-0.98)

NORFLUOXETINE:

Mean Plasma Concentrations:	Table 3 and Figure 2
Pharmacokinetic Parameters:	Table 3

90% Confidence Intervals:	$LAUC_{0-t}$	100.76-106.35%
	$LAUC_{0-inf}$	101.25-105.92%
	LC_{max}	99.87-109.19%
Test/Reference Ratio:	AUC_{0-t}	1.04 (0.86-1.36)
	AUC_{0-inf}	1.04 (0.92-1.27)
	C_{max}	1.06 (0.82-1.90)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.79-0.99)
	Reference	0.95 (0.77-0.98)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits.
   Fluoxetine: There was no statistically significant period, sequence or treatment effect for any of these parameters.
   Norfluoxetine: There was significant period and treatment effect for $LAUC_{0-t}$ and $LAUC_{0-inf}$. In addition, significant sequence effect was observed for LC_{max}. The significant sequence effect is acceptable because it is a single dose study including healthy subjects and is based on an acceptable study protocol, contains an acceptable validated assay methodology and the study data are acceptable.
4. The fasting study is acceptable.

Bioavailability of Fluoxetine HCl Capsules, 20 mg Under Non-Fasting Conditions:

A. Study Information:

Protocol #:	971713
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Period I November 1, 1997
	Period II January 24, 1998
	Period III April 18, 1998
Analysis Dates:	May 19 to June 4, 1998

Study Design: Randomized, three-way crossover design with a wash-out period of 12 weeks

Randomization Scheme:
ABC: 2,3,13,22
BCA: 1,5,15,20
ACB: 4,7,11
CBA: 6,10,16,21
CAB: 8,12,14
BAC: 9,17,18,19

Treatments:

A= Fluoxetine Hydrochloride, 2x20 mg capsules; Cheminor Drugs; Batch #001; administered after a 10 hour fast

B= Fluoxetine Hydrochloride, 2x20 mg capsules; Cheminor Drugs; Batch #001; administered after a standard breakfast

C= Prozac®, 2x20 mg capsules; Dista Pharmaceuticals; Batch #1AD33A; administered after a standard breakfast

Lot numbers of drug products administered in this study are the same as those for the fasting study.

Subjects: 22 male subjects were enrolled according to inclusion/exclusion criteria specified in the protocol

Dosing: Treatments B and C: Subjects were given OGD approved standardized breakfast 30 minutes before dosing after a fast lasting at least 9.5 hours. The dose was given with 240 mL of water.
Treatment A: Subjects were given a single oral dose of the assigned formulation with 240 mL of water after a 10 hour fast.

Sample Collection: Blood samples were collected at predose (0 h) and at following times after dosing: 1,2.5,4,5,6,7,8,9,11,16,24, 36,48,60,72,84,96,120,144,168,336,504 and 672 hours.

Housing: From the evening before dosing until after the 36 hour blood draw

B. Study Results:

1. Clinical:

Drop-outs: Subject #11 and 18 withdrew after period I and II respectively. Thus, 20 subjects completed the study. Samples from first 18 subjects were analyzed.

Adverse Events: Some subjects experienced headache, sore throat, coughing etc. The events were comparable on test and reference drugs.

Protocol Deviations: There were a few sampling time deviations. The pharmacokinetic parameters were calculated using actual sampling times.

2. Analytical:

Method:
Internal Standard:
Accuracy:

Precision:

Reassays:

3. Pharmacokinetics/Statistics:

FLUOXETINE:
Mean Plasma Concentrations: Table 4, Figure 3
Pharmacokinetic Parameters: Table 5

AUC_{0-t}/AUC_{0-inf} Ratios:	Test	Fasting	0.95	(0.87-0.98)
	Test	Non-fasting	0.96	(0.92-0.98)
	Ref.	Non-fasting	0.95	(0.88-0.98)
Test non-fasting/Ref. non-fasting:		AUC_{0-t}	1.08	(0.83-1.34)
		AUC_{0-inf}	1.06	(0.85-1.28)
		C_{max}	1.07	(0.86-1.36)

NORFLUOXETINE:

Mean Plasma Concentrations:	Table 6, Figure 4		
Pharmacokinetic Parameters:	Table 7		
AUC_{0-t}/AUC_{0-inf} Ratios:	Test Fasting	0.94	(0.77-0.99)
	Test Non-fasting	0.93	(0.74-0.98)
	Ref. Non-fasting	0.94	(0.78-0.98)
Test non-fasting/Ref. non-fasting:	AUC_{0-t}	1.04	(0.86-1.26)
	AUC_{0-inf}	1.06	(0.84-1.32)
	C_{max}	1.06	(0.81-1.95)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. Ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting are within acceptable limits. The non-fasting study is acceptable.

In Vitro Dissolution Testing:

The dissolution testing was done using FDA method: 900 mL water, apparatus II (paddles) at 50 rpm. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence study. The test and reference products dissolve more than % in 30 minutes (Table 8).

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 10 mg capsules. The comparative quantitative compositions of 10 and 20 mg capsules are shown in Table 1. The 10 mg capsules are proportionally similar in their active and inactive ingredients to 20 mg capsules. The amount of pregelatinized starch is adjusted to account for the difference in the amount of active ingredient between the two strengths.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Cheminor Drugs on its fluoxetine hydrochloride

capsules, 20 mg, lot #001, comparing it to the reference product Prozac® capsules 20 mg, lot #1AD33A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that Cheminor's fluoxetine hydrochloride 20 mg capsule is bioequivalent to the reference product, Prozac® 20 mg capsule manufactured by Dista (Lilly).

2. The bioequivalence study conducted under fed conditions by Cheminor Drugs on its fluoxetine hydrochloride capsules 20 mg, lot #001, comparing it to the reference product Prozac® capsules 20 mg, lot #1AD33A manufactured by Dista (Lilly) has been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Cheminor's fluoxetine hydrochloride 20 mg capsules is similar to that of the reference product Prozac® 20 mg capsule manufactured by Dista (Lilly).

3. The dissolution testing conducted by Cheminor on its fluoxetine hydrochloride 10 mg and 20 mg capsules is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing its 20 mg capsule of the test product with 20 mg capsule of the reference product Prozac® manufactured by Dista. The formulation for the 10 mg strength of the test product is proportionally similar to the 20 mg strength of the test product which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 10 mg capsules of the test product is granted. The 10 mg capsule of the test product is therefore deemed bioequivalent to the 10 mg capsule of Prozac® manufactured by Dista (Lilly).

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL water at 37°C using apparatus II (paddles) at 50 rpm. The test products should meet the following specifications:

> Not less than % of the labeled amount of fluoxetine in the dosage form is dissolved in 30 minutes.

5. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR ____ /S/ Date 12/8/1998

Concur: /S/ Date 12/10/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Table 1

Comparative Quantitative Composition of Fluoxetine Capsules

Ingredients	Strength			
	10 mg		20 mg	
	mg/capsule	%	mg/capsule	%
Fluoxetine Hydrochloride	11.18*	5.00	22.36**	10.00
Pregelatinized starch				
Total				

* equivalent to 10 mg fluoxetine
** equivalent to 20 mg fluoxetine

Hard Gelatin Capsule Components:
Empty gelatin capsule contains: FD&C Blue #1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate

Table 2

MEAN PLASMA FLUOXETINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.25	1.07	1.21	1.04	1.03
2	7.55	3.63	7.01	3.85	1.08
3	13.98	4.62	12.95	5.38	1.08
4	20.09	5.57	17.25	4.57	1.16
5	22.60	5.25	21.42	4.92	1.05
6	24.37	5.45	24.25	5.92	1.00
7	23.43	5.04	23.25	6.12	1.01
8	23.62	5.50	22.84	5.44	1.03
10	21.45	5.15	21.17	4.99	1.01
12	20.45	4.72	20.24	5.00	1.01
16	18.03	4.45	17.62	4.95	1.02
24	14.45	4.38	14.72	4.47	0.98
36	11.06	4.14	11.21	4.17	0.99
48	8.52	3.61	9.19	4.10	0.93
60	6.71	3.56	6.67	3.52	1.01
72	5.75	3.43	5.59	3.29	1.03
84	4.46	3.12	4.50	3.19	0.99
96	3.73	2.76	3.80	3.12	0.98
120	2.50	2.53	2.44	2.39	1.03
144	1.68	2.10	1.66	2.23	1.02
168	1.16	1.76	1.12	1.88	1.03
336	0.16	0.51	0.17	0.56	0.97
504	0.02	0.12	0.02	0.11	1.06
672	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1251.30	719.48	1246.10	736.55	1.00
AUCT	1193.07	689.98	1194.07	714.48	1.00
CMAX	25.42	5.40	24.86	6.04	1.02
KE	0.02	0.01	0.02	0.01	0.96
LAUCI	1114.60	0.46	1107.48	0.46	1.01
LAUCT	1062.88	0.46	1060.55	0.46	1.00
LCMAX	24.82	0.23	24.15	0.25	1.03
THALF	39.91	18.06	37.80	16.62	1.06
TMAX	6.44	1.48	6.40	0.81	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1251.30	1246.10	1.00	97.20	103.64
AUCT	1193.07	1194.07	1.00	96.59	103.24
CMAX	25.42	24.86	1.02	98.86	105.64
LAUCI	1114.60	1107.48	1.01	97.56	103.83
LAUCT	1062.88	1060.55	1.00	97.02	103.53
LCMAX	24.82	24.15	1.03	99.62	106.00

Table 3

MEAN PLASMA NORFLUOXETINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.07	0.21	0.05	0.21	1.23
2	1.62	0.91	1.53	0.91	1.06
3	3.42	1.50	3.14	1.80	1.09
4	5.60	2.35	4.63	1.81	1.21
5	7.13	2.66	6.29	2.29	1.13
6	8.80	3.12	8.01	2.63	1.10
7	9.13	3.08	8.56	2.83	1.07
8	9.75	3.23	9.05	3.11	1.08
10	10.78	3.26	10.12	3.61	1.07
12	11.55	4.03	10.86	3.54	1.06
16	12.57	4.61	11.58	3.66	1.09
24	12.39	4.21	11.91	3.66	1.04
36	15.66	4.83	15.39	4.60	1.02
48	15.53	5.04	15.76	4.84	0.99
60	16.44	4.74	16.16	4.83	1.02
72	15.98	5.01	15.08	4.61	1.06
84	16.05	4.79	15.89	4.79	1.01
96	15.12	4.41	15.06	4.38	1.00
120	13.91	4.11	13.80	4.36	1.01
144	13.19	3.90	12.13	3.48	1.09
168	11.73	3.56	11.25	3.87	1.04
336	5.26	2.46	5.08	2.70	1.04
504	2.15	1.92	2.14	1.87	1.00
672	0.70	1.13	0.74	1.09	0.95

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	4846.80	1865.68	4726.53	1937.94	1.03
AUCT	4571.43	1608.47	4443.20	1681.59	1.03
CMAX	18.15	5.34	17.35	4.90	1.05
KE	0.01	0.00	0.01	0.00	1.00
LAUCI	4545.02	0.37	4388.91	0.39	1.04
LAUCT	4296.59	0.37	4150.51	0.38	1.04
LCMAX	17.33	0.32	16.60	0.32	1.04
THALF	128.75	42.73	129.86	47.38	0.99
TMAX	66.81	21.06	65.21	20.83	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	4846.80	4726.53	1.03	100.36	104.73
AUCT	4571.43	4443.20	1.03	100.47	105.30
CMAX	18.15	17.35	1.05	99.54	109.66
LAUCI	4545.02	4388.91	1.04	101.25	105.92
LAUCT	4296.59	4150.51	1.04	100.76	106.35
LCMAX	17.33	16.60	1.04	99.87	109.19

Table 4

MEAN PLASMA FLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, n=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	0.97	0.84	1.18	2.08	1.65	2.43	0.82
2.5	9.40	3.98	10.14	8.92	9.33	8.01	0.93
4	16.56	6.22	16.26	5.64	14.27	7.00	1.02
5	19.31	4.87	18.78	4.26	17.76	7.27	1.03
6	21.51	4.69	22.56	5.80	21.73	5.50	0.95
7	21.45	4.42	23.32	4.87	21.93	5.71	0.92
8	20.06	3.91	22.10	4.53	20.79	5.31	0.91
9	19.27	3.14	21.36	4.68	19.92	5.72	0.90
11	18.05	3.87	19.88	3.83	18.78	4.55	0.91
16	15.79	3.50	16.82	4.33	16.54	4.74	0.94
24	12.99	3.58	12.90	3.83	13.14	3.84	1.01
36	10.13	3.60	11.35	4.20	10.83	3.98	0.89
48	8.04	3.44	8.35	3.92	7.60	3.37	0.96
60	6.21	3.54	6.87	4.02	6.36	3.28	0.90
72	5.08	3.37	5.28	3.51	5.26	3.32	0.96
84	4.15	3.04	4.52	2.97	4.06	2.64	0.92
96	3.42	2.73	3.72	3.18	3.50	2.92	0.92
120	2.33	2.43	2.74	2.95	2.39	2.37	0.85
144	1.67	2.22	1.88	2.41	1.82	2.40	0.89
168	1.23	2.08	1.39	2.36	1.27	2.18	0.89
336	0.33	1.01	0.40	1.10	0.33	1.03	0.83
504	0.08	0.33	0.15	0.50	0.11	0.48	0.51
672	0.05	0.20	0.05	0.21	0.06	0.25	0.92

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN PLASMA FLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	0.58	0.71
2.5	1.01	1.09
4	1.16	1.14
5	1.09	1.06
6	0.99	1.04
7	0.98	1.06
8	0.96	1.06
9	0.97	1.07
11	0.96	1.06
16	0.95	1.02
24	0.99	0.98
36	0.94	1.05
48	1.06	1.10
60	0.98	1.08
72	0.97	1.00
84	1.02	1.11
96	0.98	1.07
120	0.97	1.15
144	0.92	1.03
168	0.97	1.09
336	0.99	1.20
504	0.68	1.33
672	0.78	0.85

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 5

FLUOXETINE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	1211.11	871.31	1315.00	971.94	1243.11	916.07	0.92
AUCT	1140.11	805.28	1258.44	930.88	1166.33	840.70	0.91
CMAX	22.40	4.32	24.31	4.93	23.17	5.47	0.92
KE	0.02	0.01	0.02	0.01	0.02	0.01	1.10
LAUCI	1031.98	0.53	1103.02	0.56	1045.13	0.56	0.94
LAUCT	978.74	0.52	1054.95	0.57	987.42	0.55	0.93
LCMAX	21.99	0.20	23.84	0.20	22.51	0.25	0.92
THALF	45.48	35.05	46.96	33.02	47.01	36.72	0.97
TMAX	6.45	1.10	6.47	1.38	6.61	1.58	1.00

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.97	1.06
AUCT	0.98	1.08
CMAX	0.97	1.05
KE	1.09	0.99
LAUCI	0.99	1.06
LAUCT	0.99	1.07
LCMAX	0.98	1.06
THALF	0.97	1.00
TMAX	0.98	0.98

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1176.28	1273.66	1205.03	0.92	0.98	1.06
AUCT	1109.09	1219.94	1131.57	0.91	0.98	1.08
CMAX	22.13	23.98	22.87	0.92	0.97	1.05
LAUCI	994.18	1057.08	1004.22	0.94	0.99	1.05
LAUCT	944.43	1011.93	949.98	0.93	0.99	1.07
LCMAX	21.73	23.53	22.24	0.92	0.98	1.06

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 6

MEAN PLASMA NORFLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, n=18

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	0.03	0.13	0.03	0.13	0.12	0.27	1.02
2.5	2.23	1.12	2.27	2.12	2.17	2.33	0.98
4	4.96	2.18	4.72	2.46	4.31	2.84	1.05
5	6.88	3.10	6.00	2.87	6.02	3.85	1.15
6	8.75	3.78	8.15	3.96	7.95	3.92	1.07
7	9.42	3.86	9.08	4.16	8.89	4.47	1.04
8	9.78	3.85	9.88	4.63	8.73	4.09	0.99
9	10.31	4.58	10.39	4.92	9.04	4.29	0.99
11	11.18	4.71	10.76	4.77	10.10	4.44	1.04
16	12.90	5.64	12.35	5.15	12.17	5.16	1.04
24	12.88	5.06	11.71	4.52	12.18	4.93	1.10
36	15.86	6.18	16.44	6.21	16.12	6.82	0.96
48	15.21	5.16	14.99	4.94	14.75	5.30	1.01
60	16.46	5.98	17.14	6.23	16.54	6.42	0.96
72	15.57	5.46	14.78	5.09	14.84	4.71	1.05
84	16.42	5.78	16.72	5.78	15.57	5.13	0.98
96	14.51	5.01	14.90	4.67	14.57	4.33	0.97
120	14.24	5.06	14.36	4.49	13.80	4.76	0.99
144	13.32	4.54	13.43	3.90	12.73	3.98	0.99
168	12.51	4.56	11.83	3.51	10.91	3.29	1.06
336	5.48	2.65	5.43	2.87	5.16	2.26	1.01
504	2.03	1.74	2.12	2.05	1.98	1.46	0.96
672	0.80	1.27	0.79	1.50	0.74	1.07	1.02

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN PLASMA NORFLUOXETINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	0.27	0.27
2.5	1.03	1.05
4	1.15	1.10
5	1.14	1.00
6	1.10	1.02
7	1.06	1.02
8	1.12	1.13
9	1.14	1.15
11	1.11	1.07
16	1.06	1.01
24	1.06	0.96
36	0.98	1.02
48	1.03	1.02
60	1.00	1.04
72	1.05	1.00
84	1.05	1.07
96	1.00	1.02
120	1.03	1.04
144	1.05	1.05
168	1.15	1.08
336	1.06	1.05
504	1.03	1.07
672	1.08	1.06

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 7

NORFLUOXETINE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=18

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	4983.50	1952.62	4974.39	1800.80	4708.83	1456.80	1.00
AUCT	4665.17	1688.98	4582.17	1434.64	4405.28	1317.09	1.02
CMAX	18.13	6.10	19.21	6.63	18.31	6.18	0.94
KE	0.01	0.00	0.01	0.00	0.01	0.00	1.03
LAUCI	4608.22	0.42	4694.30	0.35	4473.83	0.34	0.98
LAUCT	4330.69	0.42	4351.63	0.34	4185.60	0.35	1.00
LCMAX	16.92	0.41	17.83	0.43	17.11	0.41	0.95
THALF	130.49	53.57	136.10	57.24	132.06	51.61	0.96
TMAX	64.26	28.38	66.59	25.38	67.34	29.43	0.97

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

PARAMETER	RMEAN13	RMEAN23
AUCI	1.06	1.06
AUCT	1.06	1.04
CMAX	0.99	1.05
KE	1.02	0.98
LAUCI	1.03	1.05
LAUCT	1.03	1.04
LCMAX	0.99	1.04
THALF	0.99	1.03
TMAX	0.95	0.99

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	4933.20	4917.74	4655.36	1.00	1.06	1.06
AUCT	4641.92	4553.55	4379.35	1.02	1.06	1.04
CMAX	18.38	19.38	18.52	0.95	0.99	1.05
LAUCI	4578.25	4657.66	4441.82	0.98	1.03	1.05
LAUCT	4316.41	4331.24	4168.89	1.00	1.04	1.04
LCMAX	17.16	18.01	17.32	0.95	0.99	1.04

1= Test fasting
2= Test non-fasting
3= Reference non-fasting

Table 8. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg and 20 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 24, 1998
File Name: 75465SDW.998

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac® (Dista)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 001A Strength(mg) 10			Reference Product Lot # OAR04A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.0		16.9	90.5		4.2
20	98.8		3.5	93.6		2.7
30	98.9		2.1	97.5		5.0
45	99.2		3.9	96.3		3.6

Sampling Times (Minutes)	Test Product Lot # 001 Strength(mg) 20			Reference Product Lot # 1AD33A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.3		13.6	80.4		6.6
20	97.2		2.4	93.3		3.3
30	97.8		1.3	94.4		2.6
45	99.0		1.4	95.2		2.7

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 10 and 20 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:
>
> Not less than %(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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.

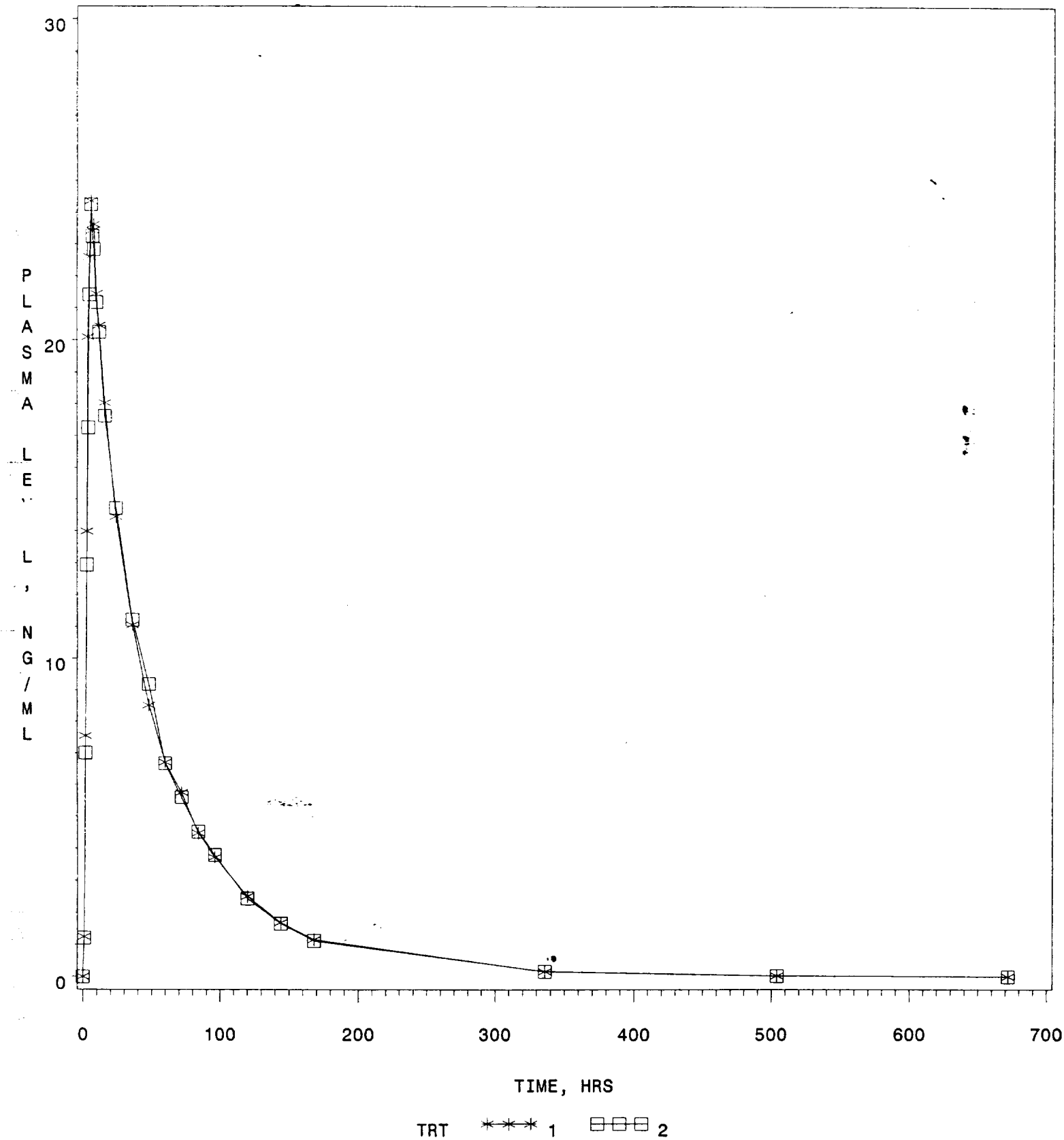
Sincerely yours,

/S/

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

FIG 1. PLASMA FLUOXETINE LEVELS

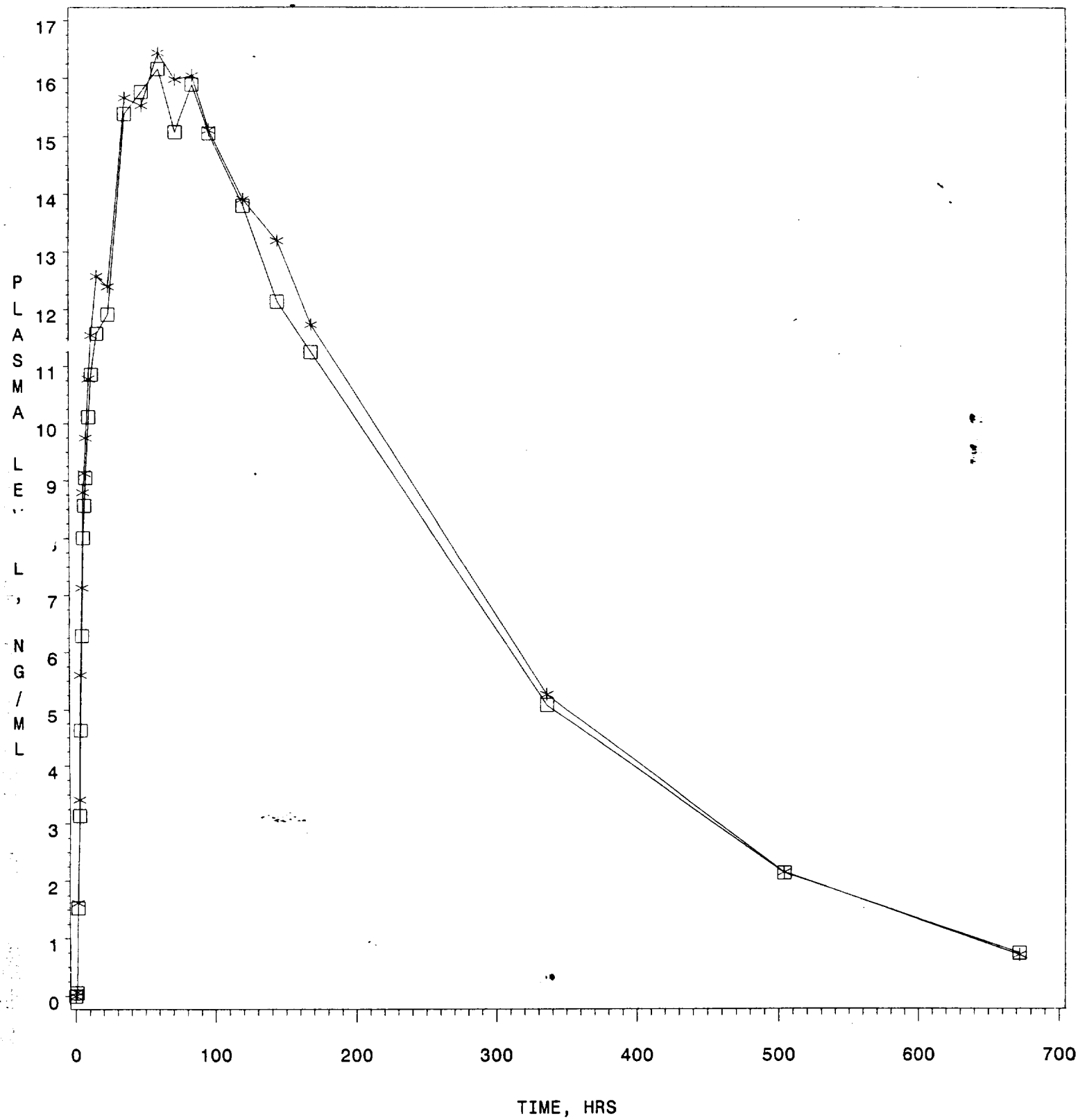
FLUOXETINE HCl CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(CHEMINOR) 2=REF(DISTA)

FIG 2 PLASMA NORFLUOXETINE LEVELS

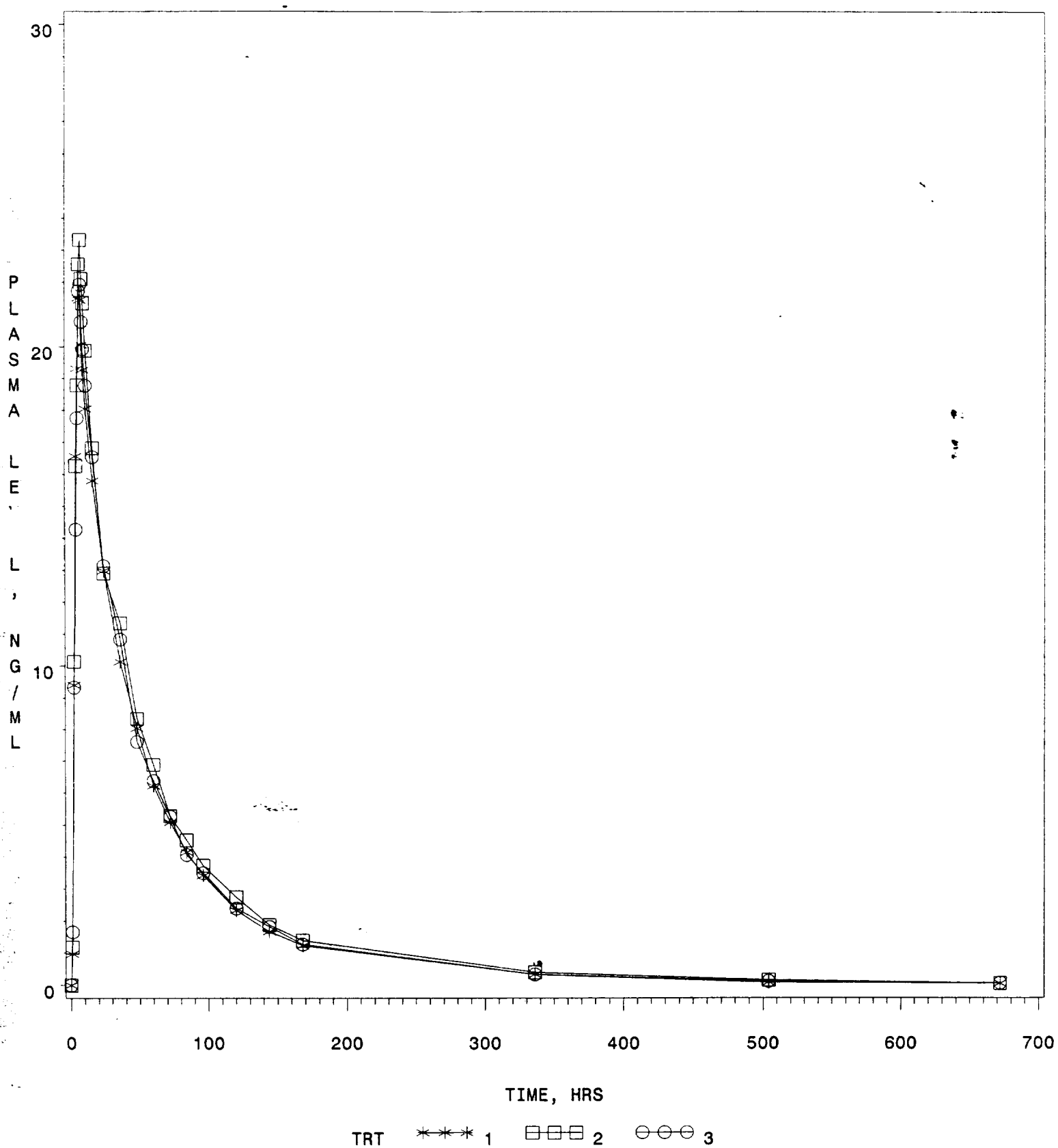
FLUOXETINE HCl CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(CHEMINOR) 2=REF(DISTA)

FIG 3. PLASMA FLUOXETINE LEVELS

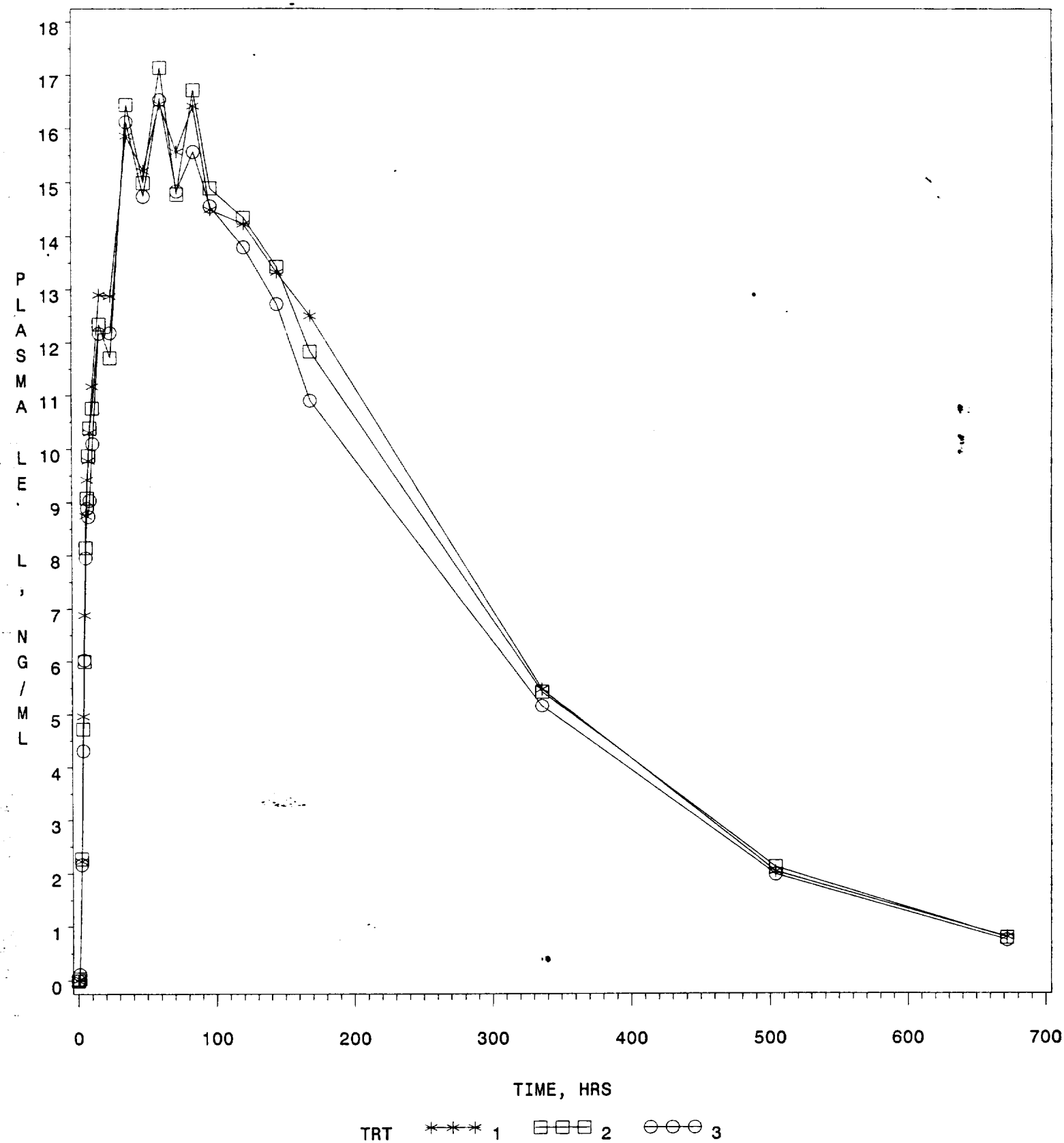
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING/NONFASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(FAST) 2=TEST(FED) 3=REF(FED)

FIG 4. PLASMA NORFLUOXETINE LEVELS

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 MG, ANDA #75-465
UNDER FASTING/NONFASTING CONDITIONS
DOSE=2 X 20 MG



1=TEST(FAST) 2=TEST(FED) 3=REF(FED)

3.1

DAVU

NOV 24 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsule
10 mg, 20 mg, 40 mg

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

If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.

Sincerely yours,

/S/

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

Fluoxetine Hydrochloride
10 mg, 20 mg and 40 mg Capsules
ANDA #75-465
Reviewer: Kuldeep R. Dhariwal
File name: 75465SDW.999

Cheminor Drugs Limited
7-1-27 Ameerpet
Hyderabad 500 016
India
Submission Date:
September 20, 1999

Review of an amendment to include Fluoxetine Capsules, 40 mg as additional dosage strength

September 24, 1998: Fasting and Non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
December 10, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsules granted.
September 20, 1999: This submission containing waiver request for an additional strength, 40 mg.

Reference Listed Drug: Prozac® by Lilly (Dista).
Available as:
Capsules 10 mg, 20 mg, and 40 mg
Tablet 10 mg
Oral solution 20 mg/5 mL

Comments:

1. The comparative formulation of the test 10 mg, 20 mg, and 40 mg capsules is given in Table 1. The formulation of the reference drug is given in Table 2.
2. The dissolution profile of all three strengths is given in Table 3. All three strengths meet specification of NLT % (Q) in 30 minutes. The bio-study was done on 20 mg strength and therefore 10 and 40 mg strengths are compared with this strength for F_2 comparisons:

Test 20 mg vs. Test 10 mg	74.92
Test 20 mg vs. Test 40 mg	60.41
Ref 20 mg vs. Ref 10 mg	63.35
Ref 20 mg vs. Ref 40 mg	**43.75**
Test 20 mg vs. Ref 20 mg	59.39
Test 10 mg vs. Ref 10 mg	53.82
Test 40 mg vs. Ref 40 mg	79.68

3. **NOT TO BE RELEASED UNDER FOI**

The innovator, Lilly (Dista) requested for biowaiver for approval of Prozac® 40 mg capsule in June 1998. The Agency denied the waiver based on failed dissolution profile comparison, nonlinear kinetics and compositional disproportionality between the proposed strength and the approved strengths (10 and 20 mg). The 40 mg strength was approved in June 1999 based on biostudy.

The 10 and 20 mg test capsules have identical total weights. The proposed 40 mg capsule is proportionally formulated to 20 mg capsule. The 10 and 40 mg capsules pass F_2 test when compared with 20 mg capsule. However, the reference 20 and 40 mg capsules are not proportionally formulated and the reference 40 mg capsule fails F_2 test when compared with reference 20 mg capsule.

Cheminor's 10 and 20 mg fluoxetine hydrochloride capsules are not yet approved. The status of this ANDA is 'pending review'.

The waiver of *in vivo* biostudy for test 40 mg capsule will be denied for following reasons:

a. The reference 20 and 40 mg capsules are not proportionally formulated like the test 20 and 40 mg capsules.
b. The F_2 test between 20 and 40 mg reference capsules fails.
c. The approval of reference 40 mg capsule was based on biostudy.

4. The firm may conduct a fasting study on 40 mg strength. The non-fasting study on this strength is not necessary. The firm has conducted a non-fasting study on 20 mg capsule (dose 2x20 mg) for the approval of 20 mg strength.

Recommendations:

The waiver of *in vivo* bioequivalence study requirements for fluoxetine hydrochloride 40 mg capsule manufactured by Cheminor Drugs is denied. The firm may conduct a fasting study on 40 mg strength.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 10/22/1999

Concur: /S/ Date 11/16/99
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

NOT TO BE RELEASED UNDER FOI

Table 1

Comparative Formulation of Fluoxetine Capsules (Test Drug)

Ingredient	Strength 10 mg		20 mg		40 mg	
	mg	%	mg	%	mg	%
Fluoxetine Hydrochloride	11.18*	5.08	22.36**	10.16	44.72***	10.16
Pregelatinized starch						
Total Fill Weight						

*equivalent to 10 mg fluoxetine, ** equivalent to 20 mg fluoxetine, *** equivalent to 40 mg fluoxetine

Hard gelatin capsule components: FD&C Blue #1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate

10 mg: opaque light blue capsule imprinted "FLUOXETINE 10 mg" and "SHN"

20 mg: opaque light blue and light turquoise blue imprinted "FLUOXETINE 20 mg" and "SHN"

40 mg: opaque light blue and opaque white imprinted "FLUOXETINE" 40 mg" and "SHN"

NOT TO BE RELEASED UNDER FOI

Table 2

Comparative Quantitative Composition of Prozac Capsules (Reference Drug)#

Ingredient	Strength					
	10 mg		20 mg		40 mg	
	mg	%	mg	%	mg	%
Fluoxetine Hydrochloride	11.18*	4.86	22.36**	9.72	44.71***	16.75
Pregelatinized starch						
Total Fill Weight						

taken from bio-pharm review dated 11/23/98

*equivalent to 10 mg fluoxetine, ** equivalent to 20 mg fluoxetine, *** equivalent to 40 mg fluoxetine

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

20 mg: opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body

40 mg: opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 20, 1999
File Name: 75465SDW.999

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac® (Dista)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 001A Strength(mg) 10			Reference Product Lot # OARO4A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.0		16.9	90.5		4.2
20	98.8		3.5	93.6		2.7
30	98.8		2.1	97.5		5.0
45	99.2		3.9	96.3		3.6

Sampling Times (Minutes)	Test Product Lot # 001 Strength(mg) 20			Reference Product Lot # 1AD33A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.3		13.6	80.4		6.6
20	97.2		2.4	93.3		3.3
30	97.8		1.3	94.4		2.6
45	99.0		1.4	95.2		2.7

Table 3 Continued... In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 20, 1999
File Name: 75465SDW.999

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac® (Dista)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # E001 Strength(mg) 40			Reference Product Lot # 2 ND49M Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
10	58		20.9	54		27.8
20	95		2.3	94		6.4
30	95		1.6	97		2.5
45	96		1.5	97		3.5

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsule
10 mg, 20 mg, 40 mg

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

If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.

Sincerely yours,

/S/

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

6.1

#8

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-465 SPONSOR : Cheminor

DRUG AND DOSAGE FORM : Fluoxetine Hydrochloride Capsules

STRENGTH(S) : 10 mg, 20 mg, 40 mg

TYPES OF STUDIES : Fasting study on 40 mg capsule

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : The fasting study is acceptable.

DISSOLUTION : The dissolution testing was conducted by the USP method. The test product meets the USP specifications.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Kuldeep R. Dhariwal BRANCH : II

INITIAL : KRD DATE : 11/8/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : /S/ DATE : 11/8/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 11/29/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-465 APPLICANT: Cheminor Drugs

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, USP
10 mg, 20 mg, 40 mg
Study Amendment, 9/26/2000

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

We acknowledge that dissolution testing as specified in USP 24, first supplement has been incorporated into your stability and quality control programs.

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,

/S/

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

Fluoxetine Hydrochloride
10 mg, 20 mg and 40 mg Capsules
ANDA #75-465
Reviewer: Kuldeep R. Dhariwal
File name: 75465S.900

Reddy-Cheminor, Inc.
66 South Maple Avenue
Ridgewood, NJ 07450
Submission Date:
September 26, 2000

Review of an Amendment: Fasting Study on 40 mg Capsules

September 24, 1998: Fasting and non-fasting studies on 20 mg capsules, dissolution data and waiver request for 10 mg strength.
December 10, 1998: Biostudies and dissolution data were acceptable. Waiver for 10 mg capsule granted.
September 20, 1999: Waiver request for an additional strength, 40 mg.
November 16, 1999: The following deficiencies were communicated to the firm: If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.
March 30, 2000: The firm submitted the response to November 16, 1999 deficiencies. The firm was again requested to conduct a fasting study on its 40 mg capsules. The firm earlier conducted a non-fasting study on 20 mg capsule (dose 2x20 mg) for the approval of 20 mg strength and therefore a non-fasting study on 40 mg strength was not requested.
This submission: Fasting study on 40 mg capsules.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #: 000632
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site:

Analytical Site:

Principal Investigator:
Study Dates: Period I March 25, 2000
Period II June 17, 2000

Analysis Dates: July 18 to July 31, 2000

Study Design: Randomized, two-way crossover design with a washout period of 12 weeks

Randomization Scheme: AB: 3,4,5,6,10,12,14,15,18,19,21,22,25
BA: 1,2,7,8,9,11,13,16,17,20,23,24,26

Treatments:

A= Fluoxetine Hydrochloride, 1x40 mg capsules; Cheminor Drugs; Batch #E001; Batch size: capsules; Manufacture Date: August 1999; Assay: %

B= Prozac®, 1x40 mg capsules; Lilly (Dista); Batch #2ND49M; Expiry Date: February 2001; Assay: %

Formulation of Test Product: Table 1

Subjects: 26 male subjects were enrolled according to the criteria specified in the protocol

Housing: From the evening before dosing until after the 36 hour blood draw

Dosing: After 10 hour fast, with 240 mL water

Sample Collection: Blood samples (10 mL) were collected at predose (0 h) and at following times after dosing:1,2,3,4,5,6,7,8,9,10,12, 24,36,48,60,72,84,96,120,144,168,336, 504 and 672 hours.

B. Study Results:

1. Clinical:

Drop-outs: Subject #13, 22, and 25 elected to withdraw after period I for personal reasons.

Adverse Events:

Subject	Complaint	Treatment	Relationship/Intensity
6	Erectile dysfunction, Headache	Test	Possible/Mild
7	Headache	Test	Possible/Mild
12	Difficulty to sleep	Test	Probable/Mild
16	Loose stool	Test	Possible/Moderate
19	Constipation, Loose stool, Dizziness, Nausea, Stomach cramps	Test	Probable/Mild
20	Headache	Test	Probable/Mild
25	Headache	Test	Probable/Mild
7	Headache	Reference	Probable/Mild
16	Loose stool	Reference	Possible/Mild
24	Headache	Reference	Probable/Mild

Protocol Deviations: There were a few sampling time deviations. The pharmacokinetic parameters were calculated using actual sampling times.

2. Analytical:

Method:
Internal Standard:
Linearity:

Regression:

Accuracy:

Precision:

Reassays:

The firm has provided following pre-study method validation results:

Linearity:

Accuracy:

Precision:

Recovery:

Stability:

3. Pharmacokinetics/Statistics:

FLUOXETINE:

Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	91.41-104.31%
	$LAUC_{0-inf}$	90.71-104.09%
	LC_{max}	92.82-106.60%
Test/Reference Ratio:	AUC_{0-t}	0.99 (0.58-1.32)
	AUC_{0-inf}	0.99 (0.56-1.31)
	C_{max}	1.01 (0.59-1.33)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.91-0.98)
	Reference	0.95 (0.81-0.98)

NORFLUOXETINE:

Mean Plasma Concentrations:	Table 3 and Figure 2	
Pharmacokinetic Parameters:	Table 3	
90% Confidence Intervals:	$LAUC_{0-t}$	95.98-105.76%
	$LAUC_{0-inf}$	94.14-104.57%
	LC_{max}	94.53-102.66%
Test/Reference Ratio:	AUC_{0-t}	1.02 (0.75-1.35)
	AUC_{0-inf}	1.00 (0.76-1.42)
	C_{max}	0.99 (0.71-1.20)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.92 (0.67-0.99)
	Reference	0.91 (0.56-0.98)

Comments:

1. Fluoxetine: The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer. Norfluoxetine: The least squares means and 90% confidence intervals calculated by the reviewer are different than those reported by the firm:

	Firm	Reviewer
$LAUC_{0-t}$	95.3-105.3%	95.98-105.76%
$LAUC_{0-inf}$	93.5-104.0%	94.14-104.57%
LC_{max}	84.6-103.1%	94.53-102.66%

   The reviewer used two different SAS programs and got the same results. The study is acceptable either way.
2. No subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits. There was no

statistically significant period, sequence or treatment effect for any of these parameters.

4. The semi-log plots of the individual subject plasma concentrations are satisfactory. The firm has not submitted the linear plots of individual subject plasma concentrations. The DBE management decided that these graphs will not be requested unless they are absolutely required to complete the review. The review of the study can be completed without the linear plots.
5. The fasting study is acceptable.

In Vitro Dissolution Testing:

The dissolution testing was done using the USP method: 900 mL water, apparatus II (paddles) at 50 rpm. The test and reference products used in the dissolution testing were from the same lots used in the *in vivo* bioequivalence study. The test and reference products dissolve more than % in 30 minutes (Table 4).

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Cheminor Drugs on its fluoxetine hydrochloride capsules, 40 mg, lot #E001, comparing it to the reference product Prozac® capsules 40 mg, lot #2ND49M manufactured by Dista (Lilly) is acceptable to the Division of Bioequivalence. The study demonstrates that Cheminor's fluoxetine hydrochloride 40 mg capsule is bioequivalent to the reference product, Prozac® 40 mg capsule manufactured by Dista (Lilly).

2. The dissolution testing conducted by Cheminor on its fluoxetine hydrochloride 40 mg capsules is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL water at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % of the labeled amount of fluoxetine in the dosage form is dissolved in 30 minutes.

3. From the bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

/S/ 11/8/00
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 11/8/2000

Concur: /S/ Date 11/29/00
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

\\CDS008\WP51F99\FIRMSAM\CHEMINOR\LTRS&REV\75465S.900

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Table 1

Comparative Formulation of Fluoxetine Capsules

Ingredient	Strength 10 mg		20 mg		40 mg	
	mg	%	mg	%	mg	%
Fluoxetine Hydrochloride	11.18*	5.08	22.36**	10.16	44.72***	10.16
Pregelatinized starch						
Total Fill Weight						

*equivalent to 10 mg fluoxetine, ** equivalent to 20 mg fluoxetine, *** equivalent to 40 mg fluoxetine

Hard gelatin capsule components: FD&C Blue #1, titanium dioxide, gelatin, silicon dioxide, sodium lauryl sulfate

10 mg: opaque light blue capsule imprinted "FLUOXETINE 10 mg" and "SHN"

20 mg: opaque light blue and light turquoise blue imprinted "FLUOXETINE 20 mg" and "SHN"

40 mg: opaque light blue and opaque white imprinted "FLUOXETINE" 40 mg" and "SHN"

Table 2

MEAN PLASMA FLUOXETINE LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=23

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.15	1.08	1.03	0.65	1.12
2	6.28	3.91	7.38	4.42	0.85
3	12.01	5.12	14.44	7.20	0.83
4	16.93	6.10	18.27	7.05	0.93
5	22.03	6.30	22.27	6.79	0.99
6	24.70	7.45	24.42	6.41	1.01
7	24.48	7.11	24.44	6.27	1.00
8	23.67	6.13	24.39	5.20	0.97
9	22.43	6.50	22.66	5.01	0.99
10	20.84	5.85	21.35	5.15	0.98
12	20.69	5.86	20.78	5.30	1.00
24	15.51	5.48	15.79	5.25	0.98
36	12.61	5.78	12.22	5.49	1.03
48	9.74	5.37	10.08	5.27	0.97
60	8.07	5.58	8.05	5.42	1.00
72	6.98	5.12	6.83	4.88	1.02
84	5.65	4.92	5.86	4.92	0.96
96	4.99	4.69	4.92	4.60	1.02
120	3.69	4.26	3.62	4.03	1.02
144	2.77	3.52	2.76	3.60	1.00
168	2.11	3.10	2.27	3.16	0.93
336	0.56	1.13	0.54	1.07	1.04
504	0.15	0.35	0.17	0.34	0.90
672	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1598.74	1256.58	1626.65	1218.36	0.98
AUCT	1525.91	1199.58	1548.96	1184.06	0.99
CMAX	26.35	7.48	26.23	6.18	1.00
KE	0.02	0.01	0.02	0.01	0.99
LAUCI	1285.76	0.63	1324.57	0.62	0.97
LAUCT	1227.03	0.63	1257.78	0.62	0.98
LCMAX	25.36	0.28	25.54	0.24	0.99
THALF	50.30	30.57	50.75	30.41	0.99
TMAX	6.83	0.94	7.17	1.37	0.95

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1611.17	1636.91	0.98	93.07	103.78
AUCT	1537.44	1558.92	0.99	94.00	103.24
CMAX	26.45	26.28	1.01	94.40	106.86
LAUCI	1292.17	1329.81	0.97	90.71	104.09
LAUCT	1232.97	1262.73	0.98	91.41	104.31
LCMAX	25.44	25.58	0.99	92.82	106.60

Table 3

MEAN PLASMA NORFLUOXETINE LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=23

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	1.29	0.90	1.52	1.03	0.85
3	2.79	1.68	3.46	1.99	0.81
4	4.51	2.36	5.04	2.96	0.90
5	6.28	3.09	6.41	3.31	0.98
6	7.85	3.96	7.78	3.71	1.01
7	8.47	3.85	8.56	3.93	0.99
8	9.04	4.32	9.39	4.69	0.96
9	9.01	4.23	9.41	4.69	0.96
10	9.31	4.29	9.88	4.90	0.94
12	10.71	4.72	10.91	5.45	0.98
24	11.88	5.11	12.30	5.64	0.97
36	15.77	6.33	15.63	7.33	1.01
48	14.29	5.36	14.98	6.86	0.95
60	15.68	5.90	15.59	6.25	1.01
72	15.70	5.76	15.95	6.41	0.98
84	15.93	5.49	16.23	6.22	0.98
96	14.90	5.02	15.02	5.52	0.99
120	13.94	4.91	13.81	4.93	1.01
144	13.05	4.53	12.98	4.51	1.01
168	11.47	3.77	12.37	4.56	0.93
336	6.26	2.83	5.72	2.54	1.09
504	2.92	2.20	2.79	1.95	1.05
672	1.27	1.44	1.33	1.58	0.96

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	5351.91	2094.79	5421.78	2266.67	0.99
AUCT	4869.26	1790.41	4853.04	1945.53	1.00
CMAX	17.11	6.12	17.59	7.16	0.97
KE	0.01	0.00	0.01	0.00	1.02
LAUCI	4917.93	0.44	4957.40	0.45	0.99
LAUCT	4502.78	0.43	4470.73	0.43	1.01
LCMAX	15.93	0.41	16.17	0.43	0.99
THALF	154.93	77.19	163.36	95.98	0.95
TMAX	63.65	26.20	78.80	33.12	0.81

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	5357.36	5426.13	0.99	93.13	104.34
AUCT	4869.19	4850.21	1.00	94.84	105.94
CMAX	17.08	17.55	0.97	91.69	102.93
LAUCI	4920.49	4959.44	0.99	94.14	104.57
LAUCT	4501.04	4467.31	1.01	95.98	105.76
LCMAX	15.89	16.13	0.99	94.53	102.66

Table 4. In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine Hydrochloride
Dose Strength: 10 mg, 20 mg, 40 mg
ANDA No.: 75-465
Firm: Cheminor Drugs
Submission Date: September 26, 2000
File Name: 75465S.900

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT % (Q) in 30 minutes
Reference Drug: Prozac®
Assay Methodology:

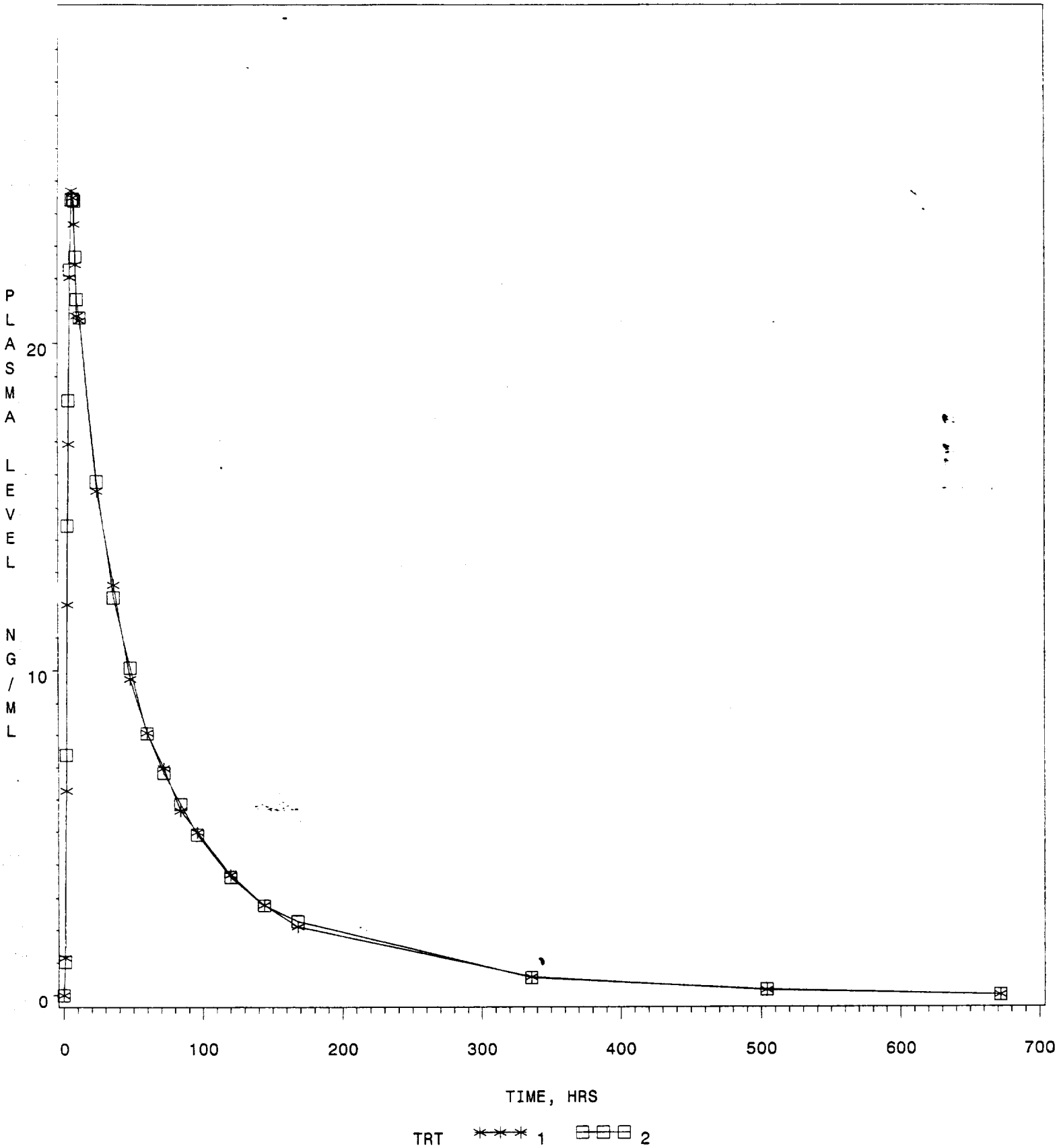
II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # E001 Strength(mg) 40			Reference Product Lot #2 ND49M Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
5	13		33.8	19		34.2
10	58		20.9	54		27.8
15	87		9.9	81		20.1
20	95		2.3	94		8.4
30	95		1.6	97		2.5
45	96		1.5	97		3.5

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

FIG 1. PLASMA FLUOXETINE LEVELS

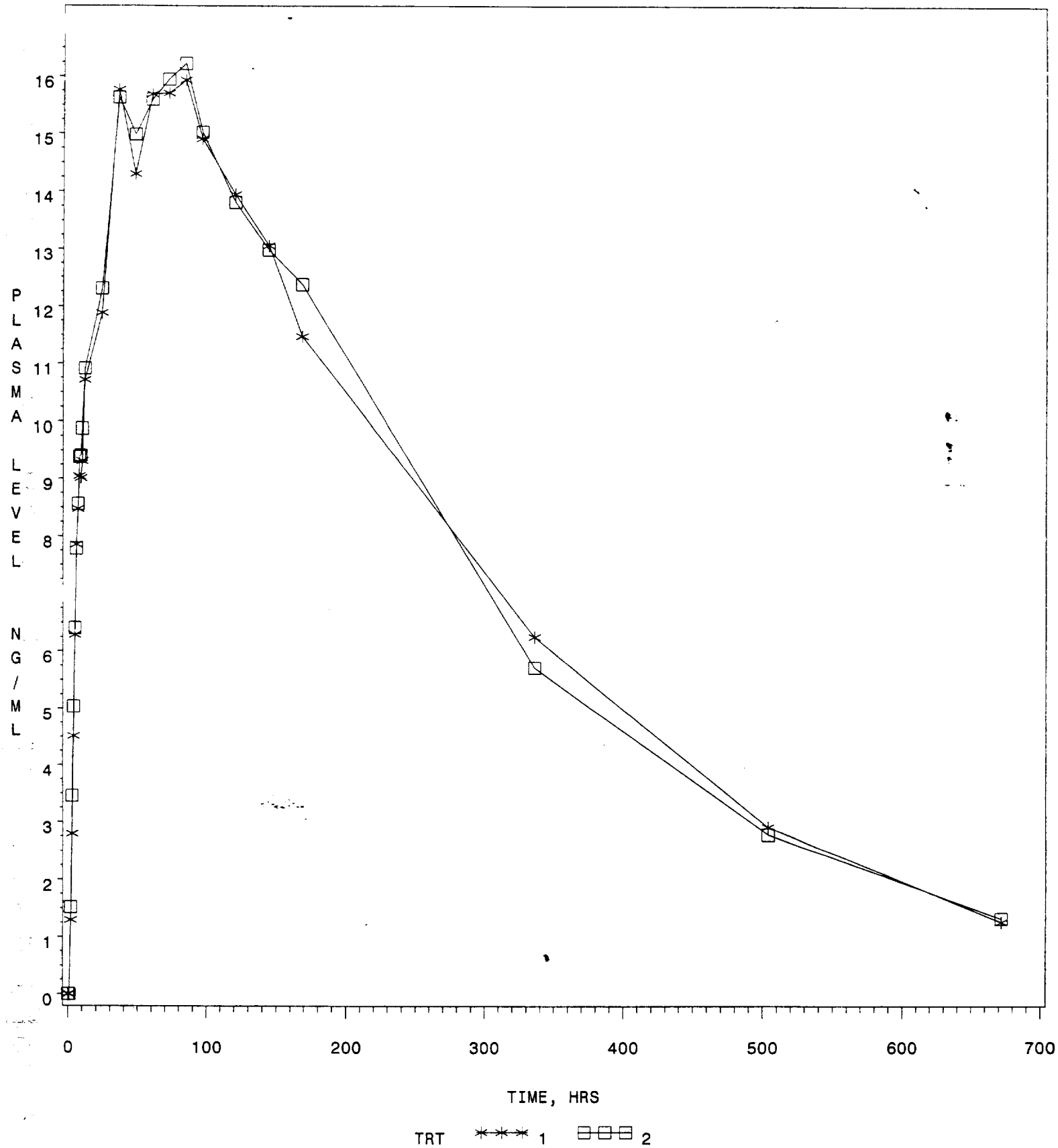
FLUOXETINE HYDROCHLORIDE TABLETS, 40 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=1 X 40 MG



1=TEST(CHEMINOR) 2=REF(DISTA)

FIG 2. PLASMA NORFLUOXETINE LEVELS

FLUOXETINE HYDROCHLORIDE TABLETS, 40 MG, ANDA #75-465
UNDER FASTING CONDITIONS
DOSE=1 X 40 MG



1=TEST(CHEMINOR) 2=REF(DISTA)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-465 SPONSOR : Cheminor

DRUG AND DOSAGE FORM : Fluoxetine Hydrochloride Capsules

STRENGTH(S) : 10 mg, 20 mg, 40 mg

TYPES OF STUDIES : Fasting study on 40 mg capsule

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : The fasting study is acceptable.

DISSOLUTION : The dissolution testing was conducted by the USP method. The test product meets the USP specifications.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal BRANCH : II

INITIAL : _____ DATE : 11/8/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : /S/ DATE : 11/8/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 11/29/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **75-465** Date of Submission: **May 9, 2000**

Applicant's Name: **CHEMINOR DRUGS LIMITED**

Established Name: **Fluoxetine Capsules USP, 10 mg, 20 mg and 40 mg**

Labeling Deficiencies:

1. CONTAINER 30s and 100s (10 mg, 20 mg and 40 mg) - 500s (40 mg) - 1000s (20 mg)

   Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

2. INSERT

   We acknowledge your amendment dated May 9, 2000. 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 Paragraph IV certification to patent 4,626,549 and we believe there should be clarification regarding this patent, 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 application with your letter to HFD-90. Please also provide a desk copy to Adolph Vezza.

/S/

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

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

ANDA Number: **75-465** Date of Submission: **September 24, 1998**

Applicant's Name: **CHEMINOR DRUGS LIMITED**

Established Name: **Fluoxetine Capsules USP, 10 mg and 20 mg**

Labeling Deficiencies:

1. CONTAINER 30s, 100s (10 mg and 20 mg) 1000s (20 mg)

   a. Each capsule contains:

      Fluoxetine Hydrochloride equivalent to ___ mg Fluoxetine.

   b. "**Usual Dosage:**" rather than "**Dosage:**".

2. INSERT

   a. GENERAL COMMENTS

      i. Delete "hydrochloride" throughout the text of the insert except in the DESCRIPTION section.

      ii. Italicize "*in vivo*" and "*in vitro*" throughout the text of the insert.

      iii. We acknowledge your comment that you have included only the depression indication in your labeling at this time due to ongoing patent litigation between the patent holder and other companies. However, we ask you to include information regarding the obsessive-compulsive disorder in your labeling as this exclusivity has expired.

      Also, you will be required to include information on the bulimia nervosa disorder if your drug product is approved after the expiration date of the exclusivity for this indication (November 21, 1999).

iv. Since you have elected to leave out the bulimia indication from your insert labeling, please delete all references to bulimia throughout the text of the insert.

b. CLINICAL PHARMACOLOGY

Absorption, Distribution, Metabolism, and Excretion - Age, second sentence -
... nonlinear ... (one word)

c. INDICATIONS AND USAGE

Please include the indications for "Obsessive-Compulsive Disorder" as seen below:

... (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 reevaluate the long-term usefulness

of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

d. PRECAUTIONS

i. General, Anxiety and Insomnia, last paragraph - ... 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 US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications), and nervousness (1% in depression)(see Table 3, below).

ii. Drug Interactions

A). CNS Active Drugs - The subsections "Anticonvulsants" through "Other Antidepressants" are all subsections of "CNS Active Drugs". Please distinguish the titles as such.

B). Antipsychotics, last sentence - "pimozide" rather than "primozide"

C). Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins, first sentence - delete "sodium"

e. ADVERSE REACTIONS

i. First paragraph - "i.e.," rather than "ie,"

ii. Associated with Discontinuation in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials) - ... in clinical trials collecting along a primary event associated with discontinuation) in depression and OCD.

iii. Table 3

A). Place (N=1108) under the title in the first column.

B). Delete "Nervousness (1%)" from the first column.

C). Place (N=392) under the title in the second column.

D). Delete "Insomnia (1%)" from the second column.

E). Delete "Nausea (1%)" from the second column.

F). Place (N=266) under the title of the third column.

G). Third column - "Rash (1%)" rather than "Rash (3%)".

iv. Postintroduction Reports - ...epidermal necrolysis, erythema nodosum, exfoliative dermatitis, ...

f. DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence, second sentence - ... drug seeking ... CNS active (delete the two hyphens)

g. DOSAGE AND ADMINISTRATION

i. Please add the information concerning dosage and administration for the obsessive-compulsive disorder as shown below:

... 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 **Usage in the Elderly** under **PRECAUTIONS**), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see *Liver Disease* and *Renal Disease* under **CLINICAL PHARMACOLOGY**, and *Use in Patients with Concomitant Illness* under **PRECAUTIONS**).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue 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.

ii. Switching Patients to a Tricyclic Antidepressant (TCA)

A). "may" rather than "mat"

B). ... under **PRECAUTIONS, Drug Interactions**).

h. HOW SUPPLIED

We encourage the use of the NDC number in this section.

i. ANIMAL TOXICOLOGY

We encourage you to relocate the "Rx only" symbol to immediately below the title of the insert.

Please revise your labels and 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 factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75465

CORRESPONDENCE

REDDY-CHEMINOR, INC. Rx-C

66 South Maple Avenue,
Ridgewood, NJ 07450
Phone: 201-444-4424
Fax: 201-444-1456

VIA HAND DELIVERY

July 30, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
AM

Reference: ANDA 75-465 Fluoxetine Capsules USP, 40 mg, 20mg and 10 mg
Minor Amendment

Request for Final ANDA Approval Subsequent to the Final Non Appealable Judgment of the United States District Court in Cause No. IP 01-442-CB/S, Consolidated Civil Action No. IP 98-1394 C-B/S and Expiration of Patent Number 4,314,081

Dear Sir/Madam:

This correspondence is being provided by the US Agent, Reddy-Cheminor, Inc. on behalf of Dr. Reddy's Laboratories Limited, Bachepalli, India, 502 325. Dr. Reddy's Laboratories Limited is hereby submitting a minor amendment to the abbreviated new drug application ("ANDA") for Fluoxetine Capsules USP, 40 mg, 20 mg and 10 mg tentatively approved on June 26, 2001. Dr. Reddy's Laboratories is hereby requesting final approval of its Fluoxetine Capsules USP, 40 mg, 20 mg and 10 mg.

On or about January 11, 1999, Eli Lilly filed Civil Action No. 99-0024 C-B/S, relating to Dr. Reddy's Laboratories (formerly known as Cheminor Drugs Ltd.) ANDA for Fluoxetine Capsules, USP 10 mg and 20 mg. On May 3, 1999, that case was consolidated with cases involving Zenith-Goldline Pharmaceuticals and Teva Pharmaceuticals USA under Civil Action No. IP 98-1394 C-B/S.

On or about November 3, 1999, Eli Lilly filed a second complaint relating to Dr. Reddy's Laboratories (formerly known as Cheminor Drugs Ltd.) Fluoxetine Capsules USP, 40 mg, Civil Action No. 99-1697 C-B/S. On December 1, 1999, this second case was consolidated into Civil Action No. IP 98-1394 C-B/S.

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RECD
JUL 30 2001
OGD

On or about April 2, 2001, a third complaint was filed against Dr. Reddy's Laboratories (formerly known as Cheminor Drugs Ltd.) relating to Fluoxetine Tablets, 10 mg, Civil Action No. 01-0442 C-B/S. This third case was not consolidated.

On July 18, 2001, the Court of Appeals for the Federal Circuit denied Lilly's second combined petition for rehearing and rehearing en banc in Appeal Nos. 99-1262, -1264, and -1303; Eli Lilly and Company v. Barr Laboratories, Inc. Thereafter, Lilly asked the Federal Circuit to stay its mandate; however, Lilly's motion was denied and the Federal Circuit issued its mandate on July 26, 2001.

As a result of the Federal Circuit's decision regarding Barr Laboratories, the United States District Court, Southern District of Indiana, Indianapolis Division issued a Final Judgment on July 27, 2001, in the first and second action that had been consolidated under Civil Action No. IP 98-1394 and in the third case under Civil Action No. 01-0442. As reflected in those Final Judgments, copies of which are attached hereto, Eli Lilly agreed not to appeal the Final Judgments and the Court's Judgments therefore provide "this Judgment is a final Judgment from which no appeal has been or can be taken and the right to appeal lapses concurrently with entry hereof."

All three of Eli Lilly's complaints asserted patent infringement based on claims 6 and 7 of U.S. Patent Number 4,626,549. Judgment was entered in favor of defendants and against Eli Lilly on claims 6 and 7 of U.S. Patent Number 4,626,549 based on the Federal Circuit's finding of invalidity of claim 7 and the District Court's finding of claim preclusion arising from the Federal Circuit decision. Therefore, Lilly's patent infringement claims were dismissed with prejudice.

Thus, based on the issuance of a non-appealable Final Judgment by the District Court, we are submitting this minor amendment so that our ANDA for Fluoxetine Capsules USP, 40 mg, 20 mg and 10 mg can reach final approval.

Dr. Reddy's Laboratories intends to market Fluoxetine Capsules USP, 20 mg and 10mg upon the expiration of the period of 180-day market exclusivity afforded to another manufacturer who was the first to file paragraph IV certifications for those dosage strengths.

Further, Dr. Reddy's Laboratories will not market its Fluoxetine Capsules USP, 40 mg until after Patent Number 4,314,081's pediatric exclusivity extension expires on August 2, 2001.

Please be advised that there are no changes, other than those previously submitted with respect to labeling, in the conditions under which Fluoxetine Capsules USP, 40 mg, 20 mg and 10 mg was tentatively approved.

Based upon the information presented in this minor amendment, Dr. Reddy's Laboratories Limited hereby requests final approval of its application for Fluoxetine Capsules USP, 40 mg, 20 mg and 10 mg be granted.

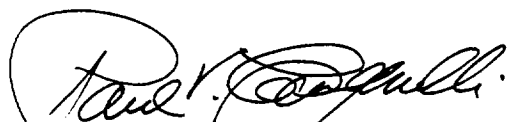
This information is provided as a single volume in an archival copy and duplicate copy.

This concludes our minor amendment submission. We request that this information be reviewed expeditiously so that full approval of Dr. Reddy's ANDA may be granted as soon as possible.

Should you have any additional questions I can be contacted at (201) 444-4424.

Very truly yours,

REDDY-CHEMINOR, INC.



Paul V. Campanelli
Vice President, Formulations Business

Attachments

cc Duplicate Chemistry Jacket
Reddy-Cheminor File Copy
Dr. Reddy's Laboratories Limited File Copy

REDDY-CHEMINOR, INC. Rx-C

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

labeling review
draft 5/16/00
A. Vezza

May 9, 2000

NDA ORIG AMENDMENT
N/AC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Major Amendment

Reference : Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg
ANDA 75-465

Dear Sir/ Madam:

This is in reference to your letter dated March 20, 2000 regarding our pending ANDA 75-465 for Fluoxetine Capsules, USP, 10 mg, 20 mg submitted on September 24, 1998 and subsequent Major Amendment to include Fluoxetine Capsules, USP, 40 mg filed on September 20, 1999. Reddy-Cheminor, Inc., US Agent for Cheminor Drugs Limited (CDL), herewith submits an amendment to the above referenced ANDA to include the following information in response to the Agency's comments:

A. Chemistry Deficiencies:

FDA Comment:

1) Regarding Components and Composition:

We note that empty hard gelatin capsule size "0" is used in the components and composition statement for the 40 mg strength. Please include the sizes for the 10 mg and 20 mg in the components and composition statement.

Response:

The components and composition statement of Fluoxetine Capsules USP, 10 mg and 20 mg have been revised to include the size of the empty hard gelatin capsules and are provided in *Exhibit I.*

FDA Comment

2) We note that there is no potential Organic Volatile Impurities to be present in the manufacture of the drug substance. However, the specifications of Organic Volatile Impurities were listed in the drug substance. Please update your specifications for Organic Volatile Impurities in the drug substance (Fluoxetine Hydrochloride) and Pregelatinised Starch NF per USP 24 requirements and resubmit.

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REC'D
MAY 10 2000
CGD

Response:

The specifications for Organic Volatile Impurities in the drug substance (Fluoxetine Hydrochloride, USP) and Pregelatinized Starch,NF, have been updated as per USP 24 requirements and are provided in *Exhibit II.*

FDA Comment

3) Regarding Gelatin Capsules:

We note that the specifications on description of hard gelatin capsule shells for 10 mg (page 45 of September 14, 1999 amendment) and 20 mg (page 48 of September 14, 1999 Amendment) and 40 mg (page 339 of September 20, 1999 Amendment) is not acceptable. Please clearly identify the color, shape and printing and color of ink and resubmit.

Response:

The Specifications on description of hard gelatin capsule shells for Fluoxetine Capsules, USP 10 mg, 20 mg and 40 mg have been revised to identify the color, size, printing and color of ink. The revised specifications are provided in *Exhibit III.*

FDA Comment

4) Submit the following information for the unit dose (e.g. blister) package:
- **i. Light transmission test**
- **ii. Physico – chemical tests**
- **iii. Permeation tests**
- **iv. Acceptance specification**
- **v. Leak test**

Response:

i. Light Transmission Test

The packaging components used in the unit dose blisters for Fluoxetine Capsules, USP 40 mg are, PVC Film with Aclar (Base Film) and Aluminum Foil Paper backed peelable (Lidding Foil). Cheminor requests a waiver to perform the above tests due to following reasons:

- PVC Film with Aclar (Base Film): This blister component is not intended to be light resistant, as the unit dose blister card is packaged in an outer carton.

- Aluminum Foil Paper Backed Peelable: Aluminum Foil is an opaque material and due to the nature of Aluminum, it is impossible for the light to pass through the foil.

ii. *Physico – Chemical Tests*

- Physico – Chemical Tests have been included in the specifications for the Base Film (PVC Film with Aclar). The updated specifications and the test data are provided in *Exhibit IV.*

iii. *Permeation Tests*

- Permeation test data for the unit dose blisters as per USP <671> are provided in *Exhibit V.*

iv. *Acceptance specification*

- The Acceptance Specifications are provided in *Exhibit VI.*

v. *Leak Test*

- The leak test on unit dose blisters is performed as in-process test during blister packing operation. The data on the leak test for Fluoxetine Capsules, USP 40 mg have been provided in the Executed Batch Production Record page 602 and 604 of our Major Amendment dated 20th September, 1999. The procedure for leak test is provided in the General Test Procedure (GTP) No.: GP077-01. Please refer *Exhibit VII.*

FDA Comment

5) We note that moisture content tests or loss on drying (LOD) tests have replaced brittleness tests in the stability studies. Please include the same tests in the finished product release specifications for each strength also.

Response:

The finished product release specifications and test procedures of Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg have been revised to include Loss on drying (LOD) of capsule shells and the Loss on drying (LOD) of contents of capsules. The revised finished product specifications and test procedures are provided in *Exhibit VIII.*

B. On March 30, 2000, Reddy-Cheminor, Inc., U.S. Agent for CDL, submitted a response to the Bioequivalence deficiencies contained in the Agency's fax dated November 24, 1999. This response did not require any chemistry, manufacturing and controls changes.

C. Labeling Deficiencies

Reddy-Cheminor, Inc., U.S. Agent for CDL, has modified the labeling in response to the Agency's comments and in accordance with the June, 1999 Drug Labeling Changes for PROZAC [June 16, 1999: Lilly] as obtained via the FDA Medical Products Reporting Program (http://www.fda.gov/medwatch). Four draft copies of the proposed labeling are supplied as follows: the bottle labeling for Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg is included in *Exhibit IX*; the unit dose labeling for Fluoxetine Capsules, USP, 40 mg is included in *Exhibit* X; and the outsert labeling is included in *Exhibit XI*. In addition, a side-by-side comparison of the proposed labeling with the last submission with all differences annotated and explained is submitted in *Exhibit XII*.

Additional Information

In addition to the aforementioned responses to the deficiencies cited by the agency, Reddy-Cheminor, Inc., U.S. Agent for CDL, is taking this opportunity to include the following information in the ANDA:

1) The dissolution method has been revised as per USP 24, Supplement 1 in the test procedure for the finished product (release) of Fluoxetine Capsules, USP 10 mg, 20 mg and 40 mg. The dissolution parameters and specifications have not been revised. For revised finished product (release) specifications and test procedure, please refer to *Exhibit VIII*. Comparative dissolution data obtained from the previous finished product (release) dissolution test procedure and the USP 24, Supplement 1 test procedure is also included in Exhibit VIII.

Pursuant to 21 CFR 314.440(a)(4), a third copy of this application is enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d)(1).

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456 if you have any questions concerning this submission.

Sincerely,

Paul V Campanelli
Vice President, Formulations Business
Reddy-Cheminor Inc.
US Agent for Cheminor Drugs Limited

REDDY-CHEMINOR, INC.

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
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lybelin review
drafted 11/15/99
A. Vezza

September 14, 1999

NDA ORIG AMENDMENT
N/AC

Office of Generic Drugs
Food and Drug Administration
Center for Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Major Amendment

Reference: Fluoxetine Capsules, USP, 10 mg and 20 mg
ANDA 75-465

Dear Sir/Madam:

This is in reference to your letters dated June 15, 1999 and July 28, 1999 regarding pending ANDA 75-465 for Fluoxetine Capsules, USP, 10 mg and 20 mg, submitted on September 24, 1998. Reddy-Cheminor, Inc., U.S. Agent for Cheminor Drugs Limited (CDL) is providing the following information in response to the Agency's correspondence:

A. Chemistry Deficiencies (June 15, 1999)

FDA Comment:

1. Regarding components and composition:

a. We note that Ferric Oxide black are present in the formulation of the 10 mg and 20 mg. Please provide the amount of iron oxide per capsule for the 10 mg and 20 mg capsule. This is required in order to comply with 21 CFR 1200 which limits the amount of elemental iron to not more than 5 mg per day.

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REC'D
SEP 15 1999
OGD

b. **Please include the empty capsule weight for each strength in the composition statement.**

c. **Submit the revised composition of the drug product based on the above comments.**

Response: 1a. Ferric Oxide Black (Iron Oxide Black) is present in the black printing ink used for the Fluoxetine Capsules, USP, 20 mg as described in the original ANDA in Section VIII, pages 3177 - 3187. Ferric Oxide Black is not present in the white printing ink used for the Fluoxetine Capsules, USP, 10 mg as described in the original ANDA in Section VIII, pages 3168 - 3175. Information provided on page 260 in Section VI of the ANDA erroneously implied that Ferric Oxide Black was used in the printing inks for both the 10 mg and 20 mg potencies. This page has been corrected to reflect the appropriate printing ink ingredients and is provided in Exhibit I.

CDL's formulations for Fluoxetine Capsules, USP, 10 mg and 20 mg are in compliance with 21 CFR § 73.1200(c) which restricts the amount of iron oxide ingested to not more than (NMT) 5 mg elemental iron per day. Please see Exhibit II for a summary of the maximum daily intake of iron for Fluoxetine Capsules, USP, 10 mg and 20 mg. Also included in Exhibit II is a letter from the capsule shell manufacturer, indicating the amount of elemental iron present in the ink used for printing the empty capsules for Fluoxetine Capsules, 20 mg.

1b. The Quantitative Statements of the Composition of the Drug Products have been revised to include the empty capsule weights and are provided in Exhibit III.

1c. The revised composition statements are included in Exhibit III.

FDA Comment:

2. **Regarding gelatin capsules:**

Submit the tests and specifications for imprinting inks. Also, provide information along with certification that the ink meets all the requirements of the indirect food additives regulation 21 CFR parts 174-178, 181 and 182.

Response: The empty capsule shells used in the manufacture of Fluoxetine Capsules, USP, 10 mg and 20 mg are imprinted by the capsule manufacturer, and then shipped to CDL.

The tests and specifications for the imprinting inks, obtained from the ink manufacturer, can be found on pages 3174 (white), 3184 (, black) and 3185 (black) of the original ANDA submission. The product specifications from the ink manufacturer certify that the ink ingredients meet the requirements listed in USP, F.C.C. or 21 CFR for the intended use in food and drugs.

Quantitative disclosures of the inks' contents can be found on pages 3175 white), 3186 black) and 3187 black). For your convenience copies of these pages are provided in Exhibit II.

FDA Comment:

3. **The submission fails to provide a complete formula card and satisfactory batch records. In this regard:**

   a. **Please provide the control limit of empty capsule weight variation, weight variation of filled capsule and content for each strength (pages 3311-3326 for 10 mg and pages 3389-3404 for 20 mg) in the blank batch records.**

   b. **We note that in-process specifications for blend uniformity were provided as 90% to 110.0% with relative standard deviation not more than 6% (pages 3605 & 3634 of the original submission). However, we recommend blend uniformity analysis acceptance criteria as 90% to 110.0% (mean of individual test results) with a relative standard deviation (RSD) of NMT 5.0%.**

   c. **Blend homogeneity testing should be specified for the production batches.**

Response: 3a. At present, the average weight of the empty capsules is being checked during the release of the empty capsule shells and therefore weight variation of the empty capsules is not included in the manufacturing records. However, the Hard Gelatin Capsule Shells standard test specifications and method have been revised to include a test and control limit for weight variation of the empty

capsule shells and are provided in Exhibit IV. The empty capsule shell analysis reports, RC0046 (10 mg) and RC0047 (20 mg), were updated in compliance with the revised test method and are also included in Exhibit IV.

The limits for weight variation of the filled capsules and the capsule contents are provided in the text of the proposed commercial batch manufacturing records (10 mg: ANDA page 3306 and 20 mg: ANDA page 3384). In addition, the in-process check records included in these master manufacturing records have been revised to include product-specific information and the limits for weight variation and capsule contents (Exhibit V).

3b. The in-process specifications for Fluoxetine Capsule Blend have been revised to meet the criteria of 90.0% to 110.0% (mean of individual test results) with a relative standard deviation (RSD) of NMT 5.0%. Revised specifications for the 10 mg and 20 mg capsule blends are provided in Exhibit VI.

3c. CDL commits to perform Blend Uniformity testing on all production batches of Fluoxetine Capsules, USP, 10 mg and 20 mg. Please refer to the revised sampling/testing protocol plans included in Exhibit VI.

FDA Comment:

4. We note that 85 cc HDPE and 950 cc HDPE bottles were used for packaging 30's, 100's and 1000's package size for Fluoxetine Capsules, 10 mg and 20 mg. However, 60 cc, HDPE bottle, 100 cc HDPE, 200 cc HDPE, 300 cc HDPE, 500 cc HDPE, 750 cc HDPE bottles were provided in Annexure-1 (Pages 3770-3782) for container diagrams. Please clarify use of those containers.

Response: Pages 3770 – 3781 are attachments to the Standard Test Procedure (STP) No. PP001-02 for High Density Polyethylene (HDPE) Containers, which is a common test procedure for all of the sizes of HDPE containers. The STP, along with all of the attachments, is included in the ANDA, even though some are not relevant for the present submission. Only the 85 cc and 950 cc HDPE bottles will be used to package these products, as described on pages 3697 – 3701 of the original ANDA.

FDA Comment:

5. **Submit the actual torque test for cap removal covering the 30's, 100's and 1000's capsules package sizes for each strength.**

Response: The actual torque test results for cap removal for the 30, 100 and 1000 capsule fill packages, for each strength, are included in Section XII of the original ANDA on the following pages:

Strength	Fill Count	Capacity	Page #
10 mg	30	85 cc	3523
	100	85 cc	3525
20 mg	30	85 cc	3578
	100	85 cc	3582
	1000	950 cc	3590

The Torque test operating instruction OI No. OPD057-00 is provided in Exhibit VII.

FDA Comment:

6. **Regarding the finished product:**

   a. **USP 23 Supplement 7 and COA of your finished product indicates that "not more than 0.25% of any individual impurity is found, and not more than 0.40% of total impurities is found" of drug product Chromatographic Purity. Please revise your related substances specifications in in-process testing in capsule filling stage to be consistent with current compendial requirements and your own finished product specifications and resubmit the COA in the capsule filling stage (see pages 2624, 4228, 4233, and etc.)**

   b. **Please provide complete description of drug product in the finished dosage form (pages 4228 & 4231) to be consistent with those in the stability protocol (pages 4285 & 4286).**

   c. **Please include brittleness tests in the finished dosage form and stability studies.**

Response: **6a.** Chromatographic Purity testing is conducted on finished product samples for release and stability. In-process samples will not be tested for Chromatographic Purity for commercial production batches, however for the exhibit batches this in-process testing was performed. Pages 3624 and 3658 represent COAs for pooled

samples taken during the encapsulation stage. For commercial production batches, these samples would be considered as finished product release samples, however for these exhibit batches the samples were compared against the in-process specifications including Related Substances. At that time the Chromatographic Purity limits were NMT 0.25% for individual impurities and NMT 0.7% for total impurities. As Chromatographic Purity testing will not be performed for in-process samples for commercial batches, there are no revised specifications or in-process COAs to submit.

Two sets of finished product release COAs were submitted in the original ANDA for the exhibit batches. For the 10 mg product, one COA represents testing for the pooled sample taken during the encapsulation stage (Pages 3896 and 4228). At that time the Chromatographic Purity limits were NMT 0.3% for individual impurities and NMT 1.0% for total impurities. Subsequently, the specifications were revised as per USP 23, Supplement 7, the product was retested and a second COA was provided (Pages 3897-3898 and 4226-4227). Similarly, for the 20 mg product, one COA (Pages 3901 and 4233) represents testing conducted prior to USP 23 Supplement 7 and the second COA provided (Pages 3902-3903 and 4231-4232) represents the retest data.

6b. The post-approval stability protocol contains the capsule descriptions to be used for all commercial batches (Exhibit XII). The proposed imprint for production batches is as follows:

For 10 mg	Cap: FLUOXETINE 10 mg	Body: SHN
For 20 mg	Cap: FLUOXETINE 20 mg	Body: SHN

The finished product specifications have been revised to provide a complete description of the drug product to be consistent with the stability protocol and are provided in Exhibit VIII.

In addition, a complete description of the drug product in the finished dosage form has been provided on the revised analysis reports for Fluoxetine Capsules, USP, 10 mg and 20 mg which are also included in Exhibit VIII. Please note that the exhibit batches consist of capsules imprinted with "Capsugel" on the body and "Axial Print" on the cap, as explained on page 3165 of the original ANDA.

6c. Emptied capsule samples of Fluoxetine Capsules, 20 mg, from 21 months stability samples stored under controlled room temperature (CRT) conditions (25°C and 60% relative humidity), and emptied capsule samples of Fluoxetine Capsules, 10 mg, from 18 months CRT stability samples, were tested for loss on drying (LOD). As shown by the data included in Exhibit IX, the capsules did not undergo any significant loss in moisture content. Furthermore, accelerated and room temperature dissolution data were consistent and well within specification for all stability intervals tested. Updated stability reports are provided in Exhibit X. Capsugel, the manufacturer of the empty capsule shells, could not recommend a specific test for brittleness, but suggested using LOD testing, as moisture loss is the best indicator of brittleness. Therefore, we are proposing LOD specifications for capsule contents and capsule shells for the finished dosage form stability studies. The revised stability specifications for Fluoxetine Capsules, USP, 10 mg and 20 mg and the standard test procedures are included in Exhibit XI.

FDA Comment:

7. **Your application fails to contain a satisfactory stability protocol and supporting stability data. In this regard:**

   a. **Please include composition of the drug product in stability report.**

   b. **Please include brittleness tests in the stability studies.**

   c. **We note that the descriptions of the drug product in the stability protocol (pages 4285-4286) is different from those in the stability data report (4292-4313). Please be consistent.**

   d. **On page 4291 you have explained your reason for not including moisture test and specification in the stability protocol. However, it is included in the stability data report. Capsules products are more susceptible to moisture. We strongly recommend that you include a test and specification for moisture in the stability protocol. Please revise and resubmit.**

Response: 7a. The composition of the drug product is included in the updated stability reports provided in Exhibit X.

7b. Please refer to our response to comment 6c. The stability

specifications and procedures for the finished product have been revised to include Loss on Drying testing for empty capsules and capsule contents and are included in Exhibit XI.

7c. As noted in our response to comment 6b, the capsule shell descriptions in the stability protocol for the commercial batches differ from the descriptions in the stability data reports because the capsules used for the exhibit batches, for which the stability data is submitted, were imprinted with different text. The description provided in the post-approval protocol reflects the imprint that will be used for commercial batches.

7d. The stability protocols have been revised to include moisture (Loss on Drying) testing of capsule contents and empty capsule shells (Exhibit XII).

FDA Comment:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You are advised that microbiological testing should be conducted on each lot of components, prior to use in the manufacture of the drug product, for those components for which the microbial limits test is specified by USP/NF [21 CFR 211.84 (d) (6)]. A 12-month retest period is recommended.

2. DMF has been reviewed and found deficient. A letter outlining the deficiencies has been sent to Dr. Reddy's Laboratories LTD. This ANDA cannot be approved until these deficiencies have been resolved.

Response: 1. Microbiological testing is conducted on Pregelatinized Starch and Empty Hard Gelatin Capsules as per the microbial limit test specified in USP/NF for every lot. Retesting is done after 12 months as per our retesting schedules.

2. A response to the deficiencies found in DMF was submitted to the Agency by Dr. Reddy's Laboratories Limited on July 6, 1999.

Bioequivalency Comments (June 15, 1999):

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus II (paddles) at 50 rpm. The test product should meet the following specifications:

Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Response:

The dissolution testing as described above has been incorporated into our release and stability testing requirements. Please refer to Exhibits VIII and XI.

Labeling Deficiencies (June 15, 1999 and July 28, 1999)

Response:

The container labels and package insert labeling for Fluoxetine Capsules, USP, 10 mg and 20 mg have been revised to correspond with the Agency's comments received on June 15, 1999 and July 28, 1999. Revised labeling, including 12 final printed copies and a side by side comparison of the proposed labeling with the labeling submitted in the previous submission, is included in Exhibit XIII.

Additional Information

In addition to the aforementioned responses to the deficiencies cited by the Agency, CDL is taking this opportunity to respond to an observation concerning the powder fineness specification for Fluoxetine Hydrochloride, USP, made during the FDA's inspection of Cheminor's facility in Bachepally, India on October 5-9, 1998. Cheminor Drugs Limited has revised the powder fineness and solubility specifications for the Fluoxetine Hydrochloride, USP drug substance used in the manufacture of Fluoxetine Capsules, USP, as follows:

Powder Fineness: Original ANDA

Amendment

Solubility: Original ANDA

Amendment

CDL's revised specifications and test procedure are provided in Exhibit XIV.

Dr. Reddy's Laboratories, manufacturer of Fluoxetine Hydrochloride, USP, drug substance, has amended their DMF to include the revised powder fineness specifications.

Pursuant to 21 CFR § 314.440(a)(4), a third copy of this amendment is also enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR § 314.50(d)(1).

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456 if you have any questions concerning this submission.

Sincerely,

Paul V. Campanelli
Vice President, Formulations Business
Reddy-Cheminor, Inc.

U.S. Agent for Cheminor Drugs Limited

REDDY-CHEMINOR, INC. Rx-C

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March 30, 2000

ORIG AMENDMENT

N | AB

Office of Generic Drugs
Food and Drug Administration
Center for Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Bioequivalency Amendment

Reference: Fluoxetine Hydrochloride Capsules, USP, 10 mg, 20 mg and 40 mg
ANDA 75-465

Dear Sir/Madam:

This is in reference to your letter dated November 24, 1999 regarding pending ANDA 75-465 for Fluoxetine Hydrochloride Capsules, USP, 10 mg, 20 mg and 40 mg, submitted September 24, 1998. Reference is also made to our September 20, 1999 amendment. Reddy-Cheminor, Inc., U.S. Agent for Cheminor Drugs Limited (CDL), is providing the following information in response to the Agency's correspondence:

Bioequivalency Deficiencies

FDA Comment:

1. **If the product development research and dissolution data confirm that the innovator product strengths (20 mg and 40 mg capsules) are not proportional, an additional fasting bioequivalence study on your fluoxetine hydrochloride 40 mg capsule will be necessary.**

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MAR 31 2000
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Response:

As requested a copy of your correspondence is provided in Exhibit 1. In order to support our request for waiver of *in vivo* bioavailability/bioequivalence study for the CDL 40-mg capsule, we have examined and provide the following data:

Capsule Fill Weight Data:
The individual and average fill weight data for 20-mg and 40-mg innovator capsules are summarized in Exhibit 2. The average fill weights were found to be 227 mg and 267 mg per capsule for 20-mg and 40-mg innovator products respectively. Thus, from the composition standpoint, 20-mg and 40-mg innovator capsules are not weight proportional. The fill weights for CDL products are 220 mg and 440 mg respectively for 20-mg and 40-mg capsules.

IR Spectrum:
IR spectra of 20-mg and 40-mg innovator capsules were examined and are provided in Exhibit 3. The two spectra are similar indicating that the two strengths of innovator product contain same ingredients.

Dissolution:
CDL has conducted comparative dissolution studies on 2x20-mg, 1x40-mg Prozac® Capsules, and 1x40-mg CDL capsules. The data are presented in Exhibit 4. All the three products are greater than % dissolved in 20 minutes. The 40-mg innovator product and the 40-mg CDL product exhibit very similar dissolution profiles. The Prozac® Capsules 20-mg innovator product shows higher dissolution at 10 minutes time-point compared to both, Prozac® Capsules 40-mg and Cheminor's Fluoxetine HCl Capsules 40-mg. While Fluoxetine is well absorbed, Phoenix International has calculated that following a 40-mg dose; the predicted Tmax is 6.5 hours with a half-life of 38 hours. Hence, minor differences in dissolution profiles before the 20-minute time interval are unlikely to affect bioavailability.

It should be noted that all potencies (10, 20 and 40-mg) of both the CDL and the innovator products are greater than % dissolution in 20 minutes, indicating that they are all rapidly dissolving. All data are well within the USP and ANDA specifications.

Biostudies:
CDL's fasting and food effect bioequivalence studies were conducted using 2x20-mg doses of the test and reference product. Therefore a 40-mg dose of fluoxetine was tested *in vivo*. The products are immediate-release capsules and the only

excipient for both the test and reference products is starch. The starch is used as a diluent/filler and the fact that the innovator 20-mg and 40-mg products are not weight proportional should not cause a difference *in vivo* between administration of a 2x20-mg dose or 1x40-mg dose.

It should be noted that, CDL conducted the biostudies for the 20-mg product prior to the approval and availability of the 40-mg innovator product. CDL's exhibit batch of the 40-mg capsules was manufactured and tested prior to the availability of the innovator 40-mg product.

Inference from Reference Listed Drug:
The 40-mg product is listed in the Orange Book, as the Reference Listed Drug (RLD), the 10-mg and 20-mg products are not. This would indicate a level of similarity between the 10-mg, 20-mg and 40-mg innovator products, such that biostudy waivers may be granted within the product line.

Chronology of events leading to CDL's biowaiver request:
In addition to the attached scientific data, we would like to provide the Agency with a chronology of events leading toward CDL's biowaiver request for Fluoxetine HCl Capsules, 40-mg.

- August 26, 1999: Innovator lists and advertises Prozac Capsules, 40-mg on Lilly website (www.prozac.com/)

- September 3, 1999: Innovator launches Prozac Capsules, 40-mg. However, the most current *Orange Book Cumulative Supplement* 7 (July 99) available to Industry, indicates no change in the Reference Listed Drug. At this time, the current RLD is Prozac Capsules, 20-mg.

- September 20, 1999: CDL amends ANDA 75-465 to request inclusion of additional strength (Fluoxetine HCl Capsules, 40-mg). At the time of this amendment, there is no RLD for Prozac Capsules, 40-mg.

- October 18, 1999: *Orange Book Cumulative Supplement 8* (August 99), lists Prozac Capsules 40-mg as the RLD. This supplement, available to industry in October 1999, indicates the product was approved on June 15, 1999.

- November 24, 1999: Reddy-Cheminor (US Agent for CDL) receives Bioequivalency Amendment from the Agency.

In closing, we acknowledge that the innovator 20-mg and 40-mg capsules are not weight proportional, however we believe that based on the data provided, a biowaiver for CDL's Fluoxetine HCl Capsules, 40-mg is supported. We respectfully request that the Agency reconsider our request for a waiver of *in vivo* bioavailability/bioequivalence study requirements for CDL's Fluoxetine HCl Capsules, USP 40-mg.

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456 if you have any questions concerning this submission.

Sincerely,

Paul V. Campanelli
Vice President
Formulations Business
Reddy-Cheminor, Inc.

U.S. Agent for Cheminor Drugs Limited

cc: Jennifer Fan, Project Manager, Division of Bioequivalence, OGD (fax copy)
Dale Conner, Pharm.D., Director, Division of Bioequivalence, OGD (desk copy)

labeling review
drafted 7/25/01
A. Vega

REDDY-CHEMINOR, INC. Rx-C

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HAND DELIVERED

July 18, 2001

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N1Am

Reference: ANDA 75-465 Fluoxetine Capsules USP, 10, 20 and 40 mg
Minor Amendment: Labeling

Dear Sir/ Madam:

This submission is in reference to the Agency's Correspondence dated July 6, 2001 to our tentatively approved ANDA 75-465 for Fluoxetine Capsules, 10 mg, 20 mg and 40 mg. Reddy-Cheminor Inc., US Agent for Dr. Reddy's Laboratories Limited, here within submits a **Minor Amendment** to the above referenced ANDA to include the following information in response to the Agency's Comments.

A. Labeling Deficiencies:

FDA Comment:

1. GENERAL COMMENT

Please note that 12 copies of revised containers labels and insert labeling in FPL are required before full approval of this application. Submit the changes as explained in our 6-26-01 correspondence granting tentative approval for this application.

FDA Comments:

2. *INSERT*

a. *PRECAUTIONS*

i. *CNS Active Drugs – Decrease the prominence of the sub-section titles in this subsection ("Anticonvulsants" through "Sumatriptan") to be less than that of "CNS Active Drugs".*
ii. *Warfarin – "anticoagulant" and " coadministed" (delete hyphens)*
iii. *Geriatric Use – The title of this subsection should be in italics.*

b. *ADVERSE REACTION*

Other Events Observed in All U.S. Clinical Trials – The footnote beginning "Neuroleptic malignant..." should be the first footnote.

c. *HOW SUPPLIED*

Add the statement "Sarafem ™ is a trademark of Elly Lilly."

Response:

The Package Insert Leaflet (PIL) has been revised to include all the changes as recommended by the agency.

Twelve copies of the final printed labels (FPL) for the containers are provided in Section V.

Twelve copies each for the final printed inserts (10 mg, 20 mg, and 40 mg capsules combined) and also for 'only Fluoxetine Capsules, 40 mg' are provided in Section V.

A summary of changes is provided in Section IV.

Dr. Reddy's Laboratories Limited hereby declares that, since the time of tentative approval of our ANDA, we have not made any change in our application, except for the above referred response to the FDA labeling comments.

Please contact the undersigned at (410) 309-3145 or by fax at (410) 309-6145, if you have any questions concerning this submission.

Sincerely,

C. Jeanne Taborsky

C. Jeanne Taborsky
Regulatory Affairs

REDDY-CHEMINOR, INC.

66 South Maple Avenue
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May 1, 1998

NAF
C. Hulquist
11/17/98

NEW CORRESP
NC

Mr. Tim Ames, Project Manager
Regulatory Support Branch
FDA-Office of Generic Drugs
MPN II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

RE: PATENT AMENDMENT
ANDA 75-465
Fluoxetine Capsules USP, 10 mg and 20 mg

Dear Mr. Ames:

In accordance with 21 CFR 314.95(b), we hereby certify that notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

Further, in accordance with 21 CFR 314.95(e), enclosed please find documentation acknowledging receipt by Eli Lilly & Co. with respect to ANDA 75-465.

Please do not hesitate to contact us should you have any questions or require additional information.

With best regards,

REDDY-CHEMINOR, INC.

Paul V. Campanelli
Vice President, Formulations Business

Enclosure

cc: R. S. Prasad, Cheminor Drugs Ltd.

RECEIVED
DEC 07 1998
GENERIC DRUGS

Madhu
12.29

ANDA 75-465

Reddy-Cheminor, Inc.
Attention: Paul V. Campanelli
U.S. Agent for Cheminor Drugs Ltd.
66 South Maple Avenue
Ridgewood, NJ 07450

NOV 19 1998

Dear Sir:

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

NAME OF DRUG: Fluoxetine Capsules USP, 10 mg and 20 mg

DATE OF APPLICATION: September 24, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 25, 1998

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,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Cheminor Drugs Limited

Pharma Division

Date: September 24,1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Labeling review drafted 12/7/98

Reference : **Fluoxetine Capsules, USP, 10 mg and 20 mg**
Abbreviated New Drug Application

Dear Sir/ Madam:

Cheminor Drugs Limited herewith submits an abbreviated new drug application (ANDA) for Fluoxetine Capsules, USP, 10 mg and 20 mg pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, PROZAC® (Fluoxetine Hydrochloride) Capsules, 10 mg and 20 mg which is manufactured by Eli Lilly and Co., who is the holder of the approved application and which is listed in the 1998 Approved Drug Products with Therapeutic Equivalence Evaluations, 18th Edition. U.S Patent No.4,314,081 will expire on February 2,2001. U.S Patent No. 4,626,549 will expire on December 2, 2003. Cheminor Drugs Limited is not seeking to market the product until after the patents expire. The Exclusivity for the Indication for the treatment of Bulimia expires on November 21,1999. Cheminor Drugs Limited will not market the product with the Indication noted above until after the Market Exclusivity expires.

Fluoxetine Capsules, USP, 10 mg and 20 mg have been developed and will be manufactured, packaged and tested at Cheminor Drugs Limited, Via IDA Bollaram, Bachepalli - 502 325, INDIA in accordance with 21 CFR 210 and 211.

The manufacturer of the drug substance used to produce the ANDA batches of this product is Dr.Reddy's Laboratories, Hyderabad, INDIA, DMF No.

The required bioavailability / bioequivalence studies were conducted on Fluoxetine Capsules, USP, 20 mg and PROZAC® Capsules 20 mg by

These studies indicate that Fluoxetine Capsules, USP, 20 mg are bioequivalent to PROZAC® Capsules 20 mg.

The in-vitro dissolution profiles for Fluoxetine Capsules, USP, 10 mg and 20 mg are comparable to those of PROZAC® Capsules, 10 mg and 20 mg respectively. The 10 and 20mg formulations are proportionally similar therefore, a waiver of in-vivo bioavailability / bioequivalence study requirements for Fluoxetine Capsules, USP, 10 mg is requested.

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SEP 25 1998
GENERIC DRUGS

September 24, 1998

Food and Drug Administration
Fluoxetine Capsules, USP, 10 mg and 20 mg
Abbreviated New Drug Application

Fluoxetine Capsules, USP, 10 mg and 20 mg are stable and a two year expiration dating is requested. The two year expiration dating for this product is supported by one, two and three months accelerated stability data (40°C ± 2°C / 75% ± 5% relative humidity) in the smallest and largest fill size of each container/closure system proposed for marketing.The stability studies were conducted under a stability protocol that is in conformance with the current FDA stability guidelines.

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION,INDICATIONS AND USAGE and HOW SUPPLIED Sections) for Fluoxetine Capsules, USP, 10 mg and 20 mg are the same as those for PROZAC® Capsules, 10 mg and 20 mg.

This ANDA is submitted in thirteen volumes :

Volume I	:	Section I through Section V
Volume II through Volume IX	:	Section VI
Volume X	:	Section VII through Section XII
Volume XI	:	Section XI through Section XIII
Volume XII	:	Section XIV
Volume XIII	:	Section XV through Section XXI

Following this letter is a letter authorizing Reddy-Cheminor to act as the U.S agent for this ANDA. Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Cheminor Drugs Limited

Pharma Division

September 24, 1998

Food and Drug Administration
Fluoxetine Capsules, USP, 10 mg and 20 mg
Abbreviated New Drug Application

Pursuant to 21 CFR 314.440 (a) (4), a third copy of this application is also enclosed.This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

Sincerely,

Prakash V Mallya
Senior Manager-Regulatory Affairs

Dr. Reddy's Group
Regd. Office : 7-1-27, Ameerpet, Hyderabad - 500 016. INDIA, Phone : (040) 291946 (6 Lines); Telex : 0425-8091, 8124 CHEMIN Fax : (040) 3745807, 291955
Works : Via. IDA Bollaram, Bachepalli - 502 325. INDIA.

REDDY-CHEMINOR, INC. Rx-C

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

October 4, 1999

NEW CORRESP
NC

FDA-Office of Generic Drugs
Center for Drug Evaluation and Research
MPN II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

RE: PATENT AMENDMENT
ANDA 75-465
Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg

Dear Sir or Madam:

In accordance with 21 CFR 314.95(b), Reddy-Cheminor, Inc., a subsidiary of Cheminor Drugs Ltd., is amending ANDA 75-465 for Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg.

Reddy-Cheminor, Inc., hereby certifies that notice has been provided to each person identified under 314.95 (a) and that notice met the content requirements under 314.95 (c).

Further, in accordance with 21 CFR 314.95 (e) attached please find herewith documentation of receipt acknowledging receipt by Eli Lilly and Company, along with FDA 356h regarding ANDA 75-465.

Please do not hesitate to contact us if you have any questions or require additional information.

Very truly yours,
REDDY-CHEMINOR, INC.

Paul V. Campanelli
Vice President, Formulations Business
(US Agent for Cheminor Drugs Ltd.)

Attachments

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 05 1999
OGD

REDDY-CHEMINOR, INC. Rx-C

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

NAI
12/13/99 NEW CORRESP
NC

November 18, 1999

Patent / Suit info recorded!
12/13/99

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attention: Lieutenant Greg Davis

Patent Amendment

Reference: Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg
ANDA 75-465

Dear Sir or Madam:

Under the provisions of 21 CFR § 314.95(e), Reddy-Cheminor, Inc., a subsidiary of Cheminor Drugs Ltd., is amending our pending ANDA 75-465 for Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg, submitted on September 20, 1999, to provide for additional patent certification information.

Reddy-Cheminor hereby certifies it has complied with the requirements of 21 CFR § 314.95(a) & (b) by sending a Notice of Certification to Eli Lilly and Company, the owner of U.S. Patent No. 4,626,549 and holder of approved application NDA 18-936 for Prozac® (fluoxetine hydrochloride) capsules 10 mg, 20 mg and 40 mg and that Notice met the content requirement under 21 CFR § 314.95(c).

A Notice of Certification was sent to Eli Lilly and Company in Indianapolis, Indiana via U.S. Postal Certified Return Receipt. The return receipt shows that Eli Lilly received the Notice on September 28, 1999 (Exhibit 1).

On November 3, 1999, Schein Pharmaceutical, Inc., Cheminor Drugs Ltd., and Reddy-Cheminor, Inc. were served with a Complaint filed in the United States District Court for the Southern District of Indiana, Civil Action IP99-1697 C-B/S (Exhibit 2) by Eli Lilly and Company in response to Cheminor's ANDA for Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg.

Further, we would like to advise the FDA that this is a second complaint served to Schein, Cheminor and Reddy-Cheminor. Lilly's initial complaint was filed on

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NOV 19 1999
OGD

January 11, 1999 (Exhibit 3) with respect to Fluoxetine Capsules, USP, 10 mg and 20 mg.

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at 201-444-4424 or by fax at 201-444-1456 if you have any questions regarding this submission.

Sincerely,

REDDY-CHEMINOR, INC.

Paul V. Campanelli
Vice President, Formulations Business

Cheminor Drugs Limited

Pharma Division

labeling review drafted 11/15/99 A. Vezza

September 20, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FDA DRUG AMENDMENT
AA

Reference : **Major Amendment to Abbreviated New Drug Application Fluoxetine Capsules, USP, 10 mg and 20 mg # 75-465 to include Fluoxetine Capsules, USP, 40 mg as additional dosage strength**

Dear Sir/ Madam:

Cheminor Drugs Limited herewith submits an amendment to the above referenced abbreviated new drug application, to include Fluoxetine Capsules, USP, 40 mg as additional dosage strength.

This ANDA amendment refers to the listed drug, PROZAC® (Fluoxetine Hydrochloride) Capsules, 40 mg which is manufactured by ELI LILLY and Co. who is the holder of the approved application. U.S. Patent No. 4314081 will expire on Feb 02, 2001. Cheminor Drugs Limited is not seeking to market the product until after the patent expires. Cheminor Drugs Limited certifies that U.S. Patent No. 4626549 (expiration date Dec 02, 2003) is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of Fluoxetine Capsules, USP, 40 mg for which this amendment is submitted. The exclusivity for indication for the treatment of bulimia expires on Nov 21, 1999. Cheminor Drugs Limited will not market the product with the indication noted above until after the market exclusivity expires.

Fluoxetine Hydrochloride Capsules, USP, 40 mg have been developed at Cheminor Drugs Limited, Via IDA Bollaram, Bachepalli - 502 325, INDIA in accordance with 21 CFR 210 and 211.

The manufacturer of the drug substance used to produce the ANDA batch of this product is : Dr.Reddy's Laboratories, Hyderabad, INDIA, DMF No.

The required bioavailability / bioequivalence studies were conducted on Fluoxetine Capsules, USP, 20 mg and PROZAC® (Fluoxetine Hydrochloride) Capsules, 20 mg by

These studies indicate that Fluoxetine Capsules, USP, 20 mg is bioequivalent to PROZAC® (Fluoxetine Hydrochloride) Capsules, 20 mg.

CENTER FOR DRUG EVALUATION AND RESEARCH
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SEP 20 1999
OGD

Dr. Reddy's Group
Regd. Office : 7-1-27, Ameerpet, Hyderabad - 500 016. INDIA, Phone : (040) 291946 (6 Lines); Telex : 0425-8091, 8124 CHEMIN Fax [illegible]07, 291955
Works : Via. IDA Bollaram, Bachepalli - 502 325. INDIA.

Cheminor Drugs Limited

Pharma Division

September 20, 1999

Food and Drug Administration
Fluoxetine Capsules, USP, 40 mg
Abbreviated New Drug Application # 75-465

The bioequivalence / bioavailability study report for Fluoxetine Capsules, USP, 20 mg is already submitted in our original ANDA # 75-465. The total dose administered to subjects in both these studies was 40 mg (2 x 20 mg capsules).

The 40 mg formulation is dose proportional to our Fluoxetine Capsules, USP, 20 mg formulation, therefore a waiver of in-vivo bioavailability / bioequivalence study requirements for Fluoxetine Capsules, USP, 40 mg is requested.

The in-vitro dissolution profile for Fluoxetine Capsules, USP, 40 is comparable to PROZAC® (Fluoxetine Hydrochloride) Capsules, 40 mg.

The dosage form, route of administration, active ingredient, potency and labeling (except Description, How Supplied and text covered by patents/exclusivities) for Fluoxetine Capsules, USP, 40 mg is the same as PROZAC® (Fluoxetine Hydrochloride) Capsules, 40 mg.

This ANDA amendment is submitted in two volumes:

Schein Pharmaceutical, Inc. will be the distributor for these products. The proposed labeling has been prepared using the Schein Pharmaceutical logo, etc. Following this letter is a letter authorizing Reddy-Cheminor, Inc. to act as the U.S. agent for this ANDA. Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self addressed stamped envelope provided for your convenience.

Dr. Reddy's Group

Regd. Office : 7-1-27, Ameerpet, Hyderabad - 500 016. INDIA, Phone : (040) 291946 (6 Lines); Telex : 0425-8091, 8124 CHEMIN Fax : (040) 3745807, 291955
Works : Via. IDA Bollaram, Bachepalli - 502 325. INDIA.

Cheminor Drugs Limited

Pharma Division

Date September 20, 1999

Food and Drug Administration
Fluoxetine Capsules, USP, 40 mg
Abbreviated New Drug Application # 75-465

Page 3

Pursuant to 21CFR 314.440 (a) (4), a third copy of this application is also enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

Sincerely,

R.S. Prasad
Senior Vice President

ANDA 75-465

JUN 26 2001

Reddy - Cheminor Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
Attention: Paul V. Campanelli
66 South Maple Avenue
Ridgewood, New Jersey 07460

Dear Sir:

This is in reference to your abbreviated new drug application dated September 24, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluoxetine Capsules USP, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendments dated March 30 and September 26, 2000; and February 5, March 8, March 30, and May 25, 2001.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

The listed drug product (RLD) referenced in your application, Prozac® Capsules of Eli Lilly and Company, is currently subject to periods of patent protection which expire on August 2, 2001 (U.S. Patent No. 4,314,081 [the '081 patent]) and June 2, 2004 (U.S. Patent 4,625,549 [the '549 patent]). Your application contains a Paragraph III Certification under Section 505(j)(2)(A)(vii)(III) of the Act to the '081 patent stating that you will not market this drug product prior to the expiration of this patent. Your application also 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. However, litigation is underway in the United States District Court for the Southern District of Indiana, Indianapolis Division involving a challenge to the patent (Eli Lilly and Company v. Cheminor Drugs, Ltd. and Reddy-Cheminor, Inc., Civil Action No. IP99-0024 C B/S). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision [505(j)(5)(B)(iii)(I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

   c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

We also note that should the patent litigation be resolved in favor of Cheminor Drugs, Ltd. and Reddy-Cheminor, Inc. prior to the expiration of the '081 patent which is the subject of a Paragraph III Certification, final approval of this application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '081 patent has expired, currently August 2, 2001.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60-days (but not more than 90-days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing and controls data, as appropriate. This amendment also serves to reactivate this application prior to final approval and should be submitted even if none of these changes were made since the date of this tentative approval letter. This amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. With respect to the patent issues noted

above, this amendment should also provide information such as a copy of a final order or judgement from the court, a notice of a settlement agreement between the parties, a licensing agreement between you and the patent holder, or any other relevant information as appropriate to address these unexpired patents.

In addition to this amendment, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to June 2, 2004, you should amend your application accordingly.

At the time you submit any amendments, you should contact Bonnie McNeal, Project Manager, at 301-827-5849, for further instructions.

Sincerely yours,

/S/
Gary Buehler 6/26/04
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Indexing Review
drafted 1/10/01
G Lizzo

REDDY-CHEMINOR, INC.

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

December 26, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CENTER FOR DRUG EVALUATION AND RESEARCH
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NDA ORIG AMENDMENT
N/FA

Fax Amendment

Reference: Fluoxetine Capsules, USP, 10 mg, 20 mg and 40 mg, ANDA # 75-465.

Dear Sir/ Madam:

This is in reference to your letter dated Nov 16, 2000 regarding our pending ANDA 75-465 for Fluoxetine Capsules, 10 mg, 20 mg and 40 mg submitted on September 24, 1998. Cheminor Drugs Limited (CDL) herewith submits the following **"Fax Amendment"** that includes information in response to the Agency's Correspondence:

Chemistry Comments:

FDA Comment

1. **The proposed specification of 100 ppm for residual in the drug substance (Fluoxetine Hydrochloride) and Pregelatinized Starch NF release specifications is too high. Although the USP 24/NF 19 OVI test does not include a limit for for all compendial articles, the current office policy still requires assurance that is either absent or present at levels NMT 2 ppm in pharmaceutical components. Please tighten the limit for to 2 ppm. Alternatively, you may submit certification from the manufacturers of the pharmaceutical components for absence of**

Response:

As per agency's recommendation, the limits for OVI have been revised to 2 ppm in the specifications of Fluoxetine Hydrochloride, USP and Pregelatinized Starch, NF. The revised specifications are provided in *Exhibit – I.*

Please also note that, we have already submitted the declaration from the supplier of the active raw material (Fluoxetine HCl) stating that "No USP specified Organic Volatile Impurities have been used in the manufacturing process". (Please see page # 281 of our ANDA Amendment dated Sept. 20th, 1999).

Labeling Comments:

FDA Comment

1. CONTAINER 30s and 100s (10 mg, 20 mg and 40 mg) – 500s (40 mg) – 1000s (20 mg).

   Please note that for computer-generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please assure that these criteria are met prior to submission of final print.

Response:

We acknowledge the Agencies Comment that final labels are required for final approval. We request the agency to grant the tentative approval based on the draft labeling.

FDA Comment

2. INSERT

   We acknowledge your amendment dated May 9, 2000. 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 Paragraph IV certification to patent 4,626,549 and we believe there should be clarification regarding this patent, and that it should be specifically associated (or not associated) with the indications appearing in the labeling for the reference 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 application to HFD-90. Please also provide a desk copy to Adolph Vezza.

Response:

The obsessive compulsive Disorder is included in the insert and explained in the Side-by-Side Comparison between the previously submitted insert issued May, 2000 and our proposed insert December, 2000.

We confirm that, the Paragraph IV Certification to patent 4,626,549 is not associated with any indications appearing in the labeling. The revised insert and side-by-side comparison are provided in Exhibit – II.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456 if you have any questions regarding this submission.

Sincerely,

Paul V. Campanelli
Vice President
Formulations Business
Reddy-Cheminor, Inc.

REDDY-CHEMINOR, INC.

66 South Maple Avenue
Ridgewood, New Jersey 07450
Telephone (201) 444-4424
Telefax (201) 444-1456

September 26, 2000

NDA ORIG AMENDMENT
AB

Office of Generic Drugs
Food and Drug Administration
Center for Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Bioequivalency Amendment

Reference: Fluoxetine Hydrochloride Capsules, USP, 10 mg, 20 mg and 40 mg
ANDA 75-465

Dear Sir/Madam:

This is in reference to your letter dated May 17, 2000 regarding pending ANDA 75-465 for Fluoxetine Hydrochloride Capsules, USP, 10 mg, 20 mg and 40 mg, submitted September 24, 1998. Reddy-Cheminor, Inc., U.S. Agent for Cheminor Drugs Limited (CDL), is providing the following information in response to the Bioequivalency Deficiencies stated in the May 17, 2000 letter.

As requested CDL has conducted a fasting bioequivalence study on our Fluoxetine Hydrochloride Capsules, USP, 40 mg product. This study demonstrates that CDL's Fluoxetine Hydrochloride Capsules, USP, 40 mg are bioequivalent to Prozac® Capsules, 40 mg.

Dissolution studies comparing CDL's Fluoxetine Hydrochloride Capsules, USP, 40 mg (Lot E001) with the referenced listed drug, Prozac® Capsules, 40 mg (Lot 2ND49M) are included in Exhibit I. The dissolution method used in generating the profile data is located on pages 257-260, Section VI of the September 20, 1999 amendment to ANDA 75-465. Copies of the certificates of analysis for the respective drug product lots are provided in Exhibit II.

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SEP 27 2000
OGD
EVALUATION AND RESEARCH

The required bioavailability/bioequivalence study was conducted by

Certification: Financial Interests and Arrangements of Clinical Investigators, is located in Exhibit III.

The full report for bioequivalence Protocol No. 000632 "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioequivalence Study of CDL's Fluoxetine Hydrochloride Capsules, USP, 40 mg and Eli Lilly and Company's Prozac® Capsules, 40 mg in Healthy Adult Males Under Fasting Conditions" is provided in Exhibit IV.

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (201) 444-4424 or by fax at (201) 444-1456 if you have any questions concerning this submission.

Sincerely,

Paul V. Campanelli
Vice President
Formulations Business
Reddy-Cheminor, Inc.

U.S. Agent for Cheminor Drugs Limited

cc: Jennifer Fan, Project Manager, Division of Bioequivalence, OGD (fax copy)