

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74803

APPROVAL LETTER

ANDA 74-803

AUG 2 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated December 9, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluoxetine Capsules USP, 10 mg and 20 mg.

Reference is also made to the Tentative Approval letter issued on June 14, 2000 and to your amendments dated May 22, and July 19, 2001.

The listed drug product referenced in your application is subject to a period of pediatric exclusivity which expires on June 2, 2004. 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 Paragraph IV Certification on the challenged claim in United States District Court for the Southern District of Indiana (Eli Lilly and Company v. Barr Laboratories, Inc., Apotex Inc., Interpharm Inc., Bernard C. Sherman, and Geneva Pharmaceuticals, Inc., Civil Action No. IP 96-0491 C B/S). You have also notified us that you prevailed on one claim of the '549 patent in both the district court and in the court of appeals and a Method of Use Statement to another claim.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, because of the unique (split) 180-day generic drug exclusivity issues

associated with this drug product, the Agency is prohibited from approving both strengths at this time. **Thus, only the 20 mg strength of the drug product is approved at this time.** The 10 mg strength 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, 20 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Prozac® Capsules, 20 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 Barr Laboratories, Inc. (Barr) was the first to submit a substantially complete ANDA with a Paragraph IV Certification for the 20 mg strength only. Therefore, Barr is eligible for 180-days of market exclusivity for the 20 mg strength. Subsequent applications for the 20 mg strength will be eligible for final approval not earlier than one hundred eighty days after:

- (1) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing, or
- (2) the date of a decision of a court 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 strength at this time because an abbreviated application for Fluoxetine Capsules USP, 10 mg containing a Paragraph IV Certification for this strength was accepted for filing by OGD prior to the filing of your application. Subsequent applications for the 10 mg

strength may not be approved 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, 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)].

With respect to the "first commercial marketing" the Agency expects that you will begin commercial marketing of the 20 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 20 mg strength.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application for the 20 mg strength require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application for the 20 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 20 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 strength 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 strength, 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 strength 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 this strength 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 this strength 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 strength, 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 strength.

The 10 mg strength 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 strength 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

JUN 14 2000

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

This is in reference to your abbreviated new drug application dated December 9, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluoxetine Capsules USP, 10 mg and 20 mg.

Reference is also made to your amendments dated June 6, 1997; April 29, June 15, and August 18, 1998; April 12, April 30, May 14, May 21, June 7, August 26, and December 17, 1999; and February 2, March 7, March 17, and April 18, 2000. Reference is also made to your correspondence dated March 13, March 14, and April 17, 1996.

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 (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. This letter does not address the notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product (RLD) referenced in your application, Prozac Capsules of Eli Lilly & Co., is subject to periods of patent protection which expire on February 2, 2001, (U.S. Patent No. 4,314,081 [the '081 patent]), and December 2,

2003, (U.S. Patent No. 4,626,549 [the '549 patent]). Your application contains a Paragraph IV Certification to the '081 and '549 patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on these patents or that the patents are invalid or unenforceable. You have notified the agency that Barr Laboratories, Inc. has complied with the notification requirements of Section 505(j)(2)(B) of the Act. Subsequently, the patent and NDA holder initiated a patent infringement suit against Barr et al. in the United States District Court for the Southern District of Indiana (Eli Lilly and Company v. Barr Laboratories, Inc., Apotex Inc., Interpharm Inc., Bernard C. Sherman, and Geneva Pharmaceuticals, Inc., Civil Action No. IP 96-0491C B/S). On January 25, 1999, the district court entered a Final Judgment and Injunction in this case which states that the '081 and '549 patents were not proven to be invalid or unenforceable and that Barr et al. infringed the patents by filing the ANDA. Furthermore, the district court prohibited the agency from approving any ANDA for this drug product subject to the injunction before the expiration of the '549 patent, subject to further rulings by the courts. You have informed the agency that the district court decision was appealed to the U.S. Court of Appeals, Federal Circuit in Washington, D.C., and that oral arguments were heard before this court on March 8, 2000. The Appeals Court's decision is currently pending.

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. Your amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved and should include documentation such as a copy of a final order or judgement from the Court of Appeals, or a settlement agreement between the parties, whichever is applicable, a licensing agreement between you and the patent holder, or any other relevant information. The amendment should also provide updated information such as final-printed labeling, chemistry, manufacturing and controls data as appropriate. As your amendment serves to reactivate this application in OGD, an amendment should be submitted even if no changes were made to the application since the date of this tentative approval letter. This amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the agency may request at any time prior to

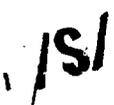
the date of final approval that you submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments, may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final 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.

The drug product that is the subject of this abbreviated application 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 before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list, (the "Orange Book").

Before you submit the amendment(s), please contact Timothy Ames, R.Ph., Project Manager, at (301) 827-5798, for further instructions.

Sincerely yours,


Gary Buehler 6/4/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

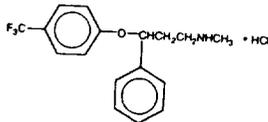
APPLICATION NUMBER:

74803

DRAFT FINAL PRINTED LABELING

DESCRIPTION:

Fluoxetine Hydrochloride is an antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-toilyloxy)propylamine hydrochloride. Fluoxetine Hydrochloride has the following structural formula:



C₁₇H₁₈F₃NO • HCl Molecular Weight: 345.79

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water. Each capsule, for oral administration, contains fluoxetine hydrochloride equivalent to 20 mg (64.7 μmol) of fluoxetine. In addition, each capsule contains the following inactive ingredients: butylparaben, carboxymethyl cellulose sodium, corn starch, D&C yellow no. 10 aluminum lake, D&C red no. 28, edetate calcium disodium, FD&C blue no. 1, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, gelatin, lactose monohydrate, methylparaben, microcrystalline cellulose, pharmaceutical glaze, propylene glycol, propylparaben, sodium lauryl sulfate, sodium propionate, stearic acid, 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 α₁-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently *in vitro* than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion:

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

The capsule, tablet, and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Protein Binding: Over the concentration range from 200 to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins, including albumin and α₁-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (see **PRECAUTIONS**).

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

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

Clinical Issues Related to Metabolism/Excretion: 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 P450ID6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of R-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the four active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable path-ways (non-ID6) 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 anti-depressants, involves the P450ID6 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 of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is, not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after 3rd dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are maintained at 4 to 5 weeks.



FLUOXETINE
CAPSULES, USP



SAMPLE

Revised MAY 2001
1008770101

AUG 2 2001

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

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

Clinical Trials:

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

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 end-point HAM-D score of ≤ 8 . Fluoxetine was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between fluoxetine (12%) and placebo (9%).

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

Obsessive Compulsive Disorder: The effectiveness of fluoxetine for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed fluoxetine doses of 20, 40, or 60 mg/day (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 two higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined:

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies				
Outcome Classification	Placebo	Fluoxetine		
		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 five of the following nine symptoms: depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

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

The efficacy of fluoxetine in maintaining an antidepressant response for up to 36 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 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 US fluoxetine clinical trials, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

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

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis and including 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 P4501D6 isozyme activity. Thus, this study suggests that drugs which inhibit P4501D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (see **PRECAUTIONS**).

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

PRECAUTIONS:

General:

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

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with 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 US 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 US 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 US 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 US 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 US fluoxetine clinical trials, 0.7% of 10,782 patients reported mania/hypomania.

Seizures: In US placebo-controlled clinical trials for depression, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with fluoxetine and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for OCD. In all US 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 of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

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

Use in Patients with Concomitant Illness: Clinical experience with fluoxetine in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received fluoxetine in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis. Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (see **Renal Disease** under **CLINICAL PHARMACOLOGY**). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (see **DOSAGE AND ADMINISTRATION**).

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

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

Information for Patients:

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

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

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

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 and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m² basis). Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery:

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

Nursing Mothers:

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

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

U.S. fluoxetine clinical trials (10,782 patients) included 687 patients ≥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 US clinical trials as of May 8, 1995. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories. In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative (Over)

contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials):

Table 1 enumerates the most common treatment-emergent adverse events associated with the use of 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 US controlled clinical trials.

**TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS:
INCIDENCE IN US DEPRESSION AND OCD PLACEBO-CONTROLLED CLINICAL TRIALS**

Body System/ Adverse Event	Percentage of patients reporting event			
	Depression		OCD	
	- 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				
Impotency†	2	--	--	--
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 US 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 EVENTS ASSOCIATED WITH DISCONTINUATION IN
US 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 sexual experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US 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 US Clinical Trials:

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials (10,782 patients) except (1) those listed in the body or footnotes of 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 one patient treated with fluoxetine and which did not have a substantial probability of being acutely life-threatening.

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

Body as a Whole: **Frequent:** 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, thrombocytopenia, thrombocytopenia.

Metabolic and Nutritional: **Frequent:** weight gain; **Infrequent:** dehydration, generalized edema, gout, hypercholesterolemia, 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 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 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths. Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after 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 arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience:

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

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

Among six dogs purposely overdosed with oral fluoxetine, five experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically. In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (see **Management of Overdose**).

Management of Overdose:

Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known. A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see **Other Antidepressants under PRECAUTIONS**). Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

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

DOSAGE AND ADMINISTRATION:

Depression:

Initial Treatment: In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 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 co-administered or has been recently discontinued (see **Other Antidepressants** under **Drug Interactions**).

Switching Patients to or from a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with 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 is equivalent to 20 mg (64.7 µmol) of fluoxetine are available as:

20 mg: Blue clear cap/gray opaque body capsule filled with white to off-white powder. Imprinted in black ink ⁶⁸⁷⁷ 877. Each 20 mg capsule contains fluoxetine present as fluoxetine hydrochloride. Available in bottles of:

100 NDC 0555-0877-02

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

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

Protect from light.

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
BARR LABORATORIES, INC.
POMONA, NY 10970

BR-877
Revised MAY 2001

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74803

MEDICAL REVIEW

ANDA APPROVAL SUMMARY

ANDA: 74-803

DRUG PRODUCT: Fluoxetine Hydrochloride USP

FIRM: Barr

2 Quaker Road

P.O. Box 2900

Pomona, New York 10970-051

DOSAGE FORM: Capsule

STRENGTHS: 10 mg

20 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 09-00026) in original submission. Paragraph 306(k) certification submitted (p. 01-00006).

EIR acceptable for drug product manufacturer (withhold, 7-26-99) and drug substance manufacturer (OK, 5/27/98).

Facilities included:

Compounding and encapsulation:

Barr Laboratories, Inc.
265 Livingston Street
Northvale, New Jersey 07647-0008.

Packaging and labeling:

Barr Laboratories, Inc.
246 Pegasus Avenue
Northvale, New Jersey 07647-0008.

Shipping:

Barr Laboratories, Inc.
Arco Building
232 Pegasus Avenue
Northvale, New Jersey 07647-0008.

Analytical and stability testing:

Barr Laboratories, Inc.
Building #1
2 Quaker Road
Pomona, New York 10970-0591.

Drug Substance Manufacturer:

BIO STUDY:

Bioequivalence study conducted on 20 mg capsule Lot #5R87719, batch size capsules, was found acceptable by the Division of Bioequivalence per Z. Wahba, 8/21/98.

Waiver granted for the 10 mg product as it has been shown to be proportional to the 20 mg product.

In-vitro dissolution study was found acceptable, Z. Wahba, 8/21/98.

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

Drug substance and drug product compendial.

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

Stability for the following included:

<u>Lot #</u>	<u>Batch Size</u>	<u>Sample</u>	<u>Test Conditions</u>
5R87618	capsules	100's	40°C/75% RH/3 months 25°C/60% RH/24 months
5R87719	capsules	100's	40°C/75% RH/3 months 25°C/60% RH/24 months
308769R01	capsules	100's	40°C/75% RH/3 months 25°C/60% RH/6 months
308779R01	capsules	100's	40°C/75% RH/3 months 25°C/60% RH/6 months

Container/Closure system, 10 mg and 20 mg capsules:

100 capsules/container - 60 cc round white HDPE bottle, 33 mm metal screw cap or 33 mm metal/plastic child resistant cap with polyethylene coated paper liner, PS-22 Innerseal.

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months based on accelerated stability data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, A. Vezza,

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

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

Bio batch: 20 mg product, Lot #5R87719, batch size capsules, stability data included.

DMF Fluoxetine Hydrochloride, Laboratori MAG, satisfactory, L. Tang, 5/16/2000.

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

See above.

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

Executed batch records for the 10 mg x capsules Lot #5R87618 and the 20 mg x capsules Lot #5R87719 (bio/stability batches) included. Blank batch records were submitted in the application for 195.000 kilogram granulation and filling for 10 mg x capsules and 20 mg x capsules. All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST: Lucia C. Tang *[Signature]*

DATE: 5-16-2000 *6-7-2000*

SUPERVISOR: U.V. Venkataram *[Signature]*

DATE: 5-18-2000 *6/8/00*

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74803

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 7
2. ANDA # 74-803
3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories, Inc.
2 Quaker Road
P.O. Box 2900
Pomona, New York 10970-051

4. LEGAL BASIS FOR SUBMISSION

Prozac® 20 mg
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46258

The drug substance is currently covered by two U.S. patents; #4314081, expiration date 2/2/01 and #4626549, expiration date 12/2/03. The applicant filed a Paragraph IV Certification and notified the innovator as required. The innovator has filed an action for patent infringement (4/10/96) and requested that approval not be made effective until at least the expiration of the thirty-month period provided by 21 USC ' 355(j)(4)(B)(iii), subject to an appropriate ruling by the court.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Fluoxetine Hydrochloride USP

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

9. AMENDMENTS AND OTHER DATES:

Firm:

12/9/95 Original submission.
2/22/96 New Correspondence - Submission of additional copies of analytical methods.
3/13/96 New Correspondence - Paragraph IV Notification Certification.
3/14/96 New Correspondence - Addendum to 3/13/96 correspondence.
6/15/98 Amendment - Response to Agency's letter of 7/9/96.
8/18/98 Bioequivalence Amendment.

4/12/99 Amendment - Response to Agency's letter of 3/12/99.
 5/21/99 Telephone Amendment.
 6/7/99 Telephone Amendment.
 7/23/99 New Correspondence.
 3-7-2k Minor amendment, later withdrawn
 3-17-2k Minor amendment with withdrawn 3-7-2k amendment
 4-18-2k Telephone amendment
 5-22-01 Minor amendment
 7-19-01 Labeling amendment

FDA:

2/21/96 Receipt acknowledged.
 4/17/96 Notification of Filing of Legal Action for Patent Infringement from innovator.
 6/10/96 Issuance of Bioequivalence Deficiency letter.
 7/9/96 Issuance of Not Approvable letter.
 3/12/99 Issuance of Not Approvable facsimile.
 3-15-2k request to withdraw 3-7-2k amendment
 4-5-2k Telephone NA letter

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
 DMF
 DMF
 DMF
 DMF
 DMF

13. DOSAGE FORM

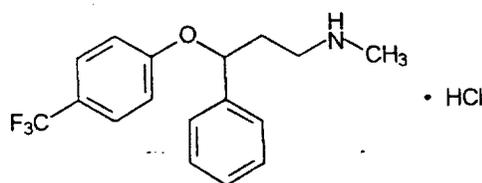
Hard Gelatin Capsule
 for oral administration

14. POTENCIES

10 mg, 20 mg

15. CHEMICAL NAME AND STRUCTURE

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



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

16. RECORDS AND REPORTS

5/15/96 - Bioequivalency review, Z. Wahba.
 5/20/96 - Chemistry review #1, G.J. Smith.
 6/17/96 - Labeling review, C. Hoppes.
 8/18/98 - Labeling review, A. Vezza.
 8/21/98 - Bioequivalency review, Z. Wahba.

17. COMMENTS

The ANDA was Tentatively Approved on 6-14-2000. Firm provides the following changes in the minor amendment dated 5/22/01: site changes, test method and specification changes, manufacturing and packaging changes, and labeling changes before the final approval.

Status:

a. EER status: Pending

EER was requested for Barr _____, by B. McNeal on July 18, 2001 and found acceptable on July 24, 2001 for the control testing laboratory. However, an inspection is scheduled for August for the site as a finished dosage packager, labeler and stability tester. Pat Beers-Block sent an E-Mail to EES questions on 7/30/01 asking that the inspection be cancelled.

b. Method Validation status:

Methods validation not required since drug substance and product are compendial.

c. Bio-review status: Satisfactory

The Division of Bioequivalence found the 20 mg drug product equivalent to RLD and granted waiver for the 10 mg product.

d. Labeling review status: Satisfactory
Satisfactory per A. Vezza reviewed on 7-30-01.

e. DMF Satisfactory

DMF was reviewed and found satisfactory per L.
Tang reviewed on 5-16-2000.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER:

DATE COMPLETED:

Lucia C. Tang

7-25-2001

AUG 2 1999

Chemistry Comments to be Provided to the Applicant

AADA/ANDA: 74-803 APPLICANT: Barr Laboratories

DRUG PRODUCT: Fluoxetine HCl Capsules USP, 10 mg & 20 mg

The deficiencies presented below represent
MINOR deficiencies.

Reference is also made to your amendments dated June 6, 1997; April 29, June 15, and August 18, 1998; April 12, April 30, May 14, May 21, and June 7, 1999, and your correspondence dated July 23, 1999.

Review of the data submitted in your correspondence dated July 23, 1999 shows that your drug product fails to meet compendial specifications through the proposed expiry dating when the amounts of Impurity I ((±) 1-Phenyl-3-methylamino-1-propanol) are included in the determination of Individual and Total Impurities. Please submit stability data demonstrating conformance to compendial requirements in support of the proposed 24 month expiration date.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74803

BIOEQUIVALENCY REVIEW(S)

JAN 8 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, - 20 mg

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

Your dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

Please conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

Sincerely yours,


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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #74-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine HCL Capsules, 20 mg and 10 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 Apparatus #2 (Paddle) 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.

Important Note: Please submit dissolution testing data (for the 20 mg and 10 mg strengths) from your first three production batches using the above mentioned dissolution method. The dissolution profile which you submit should be accompanied by dissolution data from a current batch of the reference listed drug.

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

Sincerely yours,


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

Fluoxetine Hydrochloride
20 mg Capsules
ANDA #74-803
Reviewer: Z.Z. Wahba
File #74803fa.697

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
June 06, 1997

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE
STUDY UNDER FASTING CONDITIONS

AND

REVIEW OF IN VIVO BIOEQUIVALENCE STUDY
UNDER NON-FASTING CONDITIONS AND
IN VITRO DISSOLUTION TESTING DATA

I. Amendment to a Reviewed In Vivo Bioequivalence Study Under
Fasting Conditions

BACKGROUND

The firm has previously submitted an in vivo bioequivalence study (single dose) under fasting conditions comparing its test drug product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated May 15, 1996, ANDA #74-803) due to deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1

Limited Food Effect Study:

Due to the fact that the labeling of reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug". Therefore, a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under fasting and non-fasting conditions.

The single-dose post-prandial bioequivalence study using a three-way crossover study design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

Note: A standard breakfast should be as follows:

- one buttered English muffin
- one fried egg
- one slice of American cheese
- one slice of Canadian bacon
- one serving of hashed brown potatoes
- eight fluid ounces (240 mL) of whole milk
- six fluid ounces (180 mL) of orange juice.

Response to Comment #1

The firm has submitted a non-fasting study which is included in this report. The non-fasting study was reviewed and found acceptable (see the part "review of in vivo bioequivalence study under non-fasting conditions" of this report).

The firm's response to comment #1 is acceptable.

Comment #2

The following items are missing from the submission:

- a. Stability data regarding effect of room temperature during handling of the samples.
- b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products, in addition, the date of manufacture of the test product should be included.

Response to Comment #2.a.

The firm stated that the requested data were not included in the original submission because at the time the bioequivalence study (under fasting conditions) was conducted the firm thought that data obtained from standard and control samples

of each analytical run were enough to validate the analytical methodology.

In the present supplement, the firm provided the information needed (see the analytical methods section for the bioequivalence study under non-fasting conditions, pages #1582-1583, Vol.B2.5):

The firm's response to comment #2.a. is acceptable.

Response to Comment #2.b.

The batch/lot size of the test product was capsules.
Assay potency of the test product = 99.1%
Assay potency of the reference product = 100.6%
Content uniformity of the test product = 99.0%
Content uniformity of the reference product = 99.9%
The date of manufacture of the test product was the date of mixing 6/28/95 while the encapsulation date was 7/6/95 to 7/7/95.

The firm's response to comment #2.b. is acceptable.

Comment #3

Submit a comparative dissolution study for both the test and reference drug products, performed simultaneously. The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number that was used in the in vivo bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis.

Response to Comment #3

The firm has submitted comparative dissolution data for its drug product, Fluoxetine HCl Capsules, 20 mg and the reference listed drug, Eli Lilly's Prozac® Capsules, 20 mg. The firm's dissolution conditions are summarized below:

Method: USP 23 apparatus II (Paddle) at 50 rpm
Medium: 900 mL 0.1N HCL

Temperature: 37°C ± 0.5°C
 No. Units Tested: 12 Capsules
 Specification: NLT % (Q) is dissolved in 30 minutes
 Reference product: Eli Lilly's Prozac® Capsules, 20 mg.

Table . In Vitro Dissolution Testing

Drug (Generic Name): Fluoxetine HCl
 Dose Strength: 20 mg
 ANDA No.: 74-803
 Firm: Barr Laboratories
 Submission Date: June 06, 1997
 File Name: 74803fa.697

I. Conditions for Dissolution Testing:

USP 23 Method Basket: Paddle: X RPM: 50
 No. Units Tested: 12 Capsules
 Medium: 0.1N HCl
 Volume: 900 mL
 Specifications: NLT % (Q) is dissolved in 30 minutes
 Reference Drug: Eli Lilly's Prozac® Capsules, 20 mg

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #5R87719 Strength(mg) 20			Reference Product Lot #8AM94A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.4		12.8	78.5		8.6
15	89.7		8.7	95.6		5.8
30	95.2		4.2	102.0		2.2
45	97.6		3.4	102.5		2.4

COMMENTS

1. The dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.
2. The firm should conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.
3. The dissolution results should meet the following specifications: Not less than % of the labeled amount of the

drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

The firm's response to comment #2.b. is not acceptable.

Comment #4

The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:

- * A dose of 20 mg/day, administered in the morning, is recommended as the initial dose.
- * Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.
- * Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.

In the study, the firm administered three capsules of 20 mg fluoxetine at the same time to each subject. Therefore, the firm should respond to the following item:

- a. The rationale of administering dosage which is three times higher than the recommended dose.

Response to Comment #4.a.

Barr Laboratories reviewed data obtained from a previous study experience with the 60 mg single dose conducted by _____ and found no significant deleterious adverse effects. Both the Physicians Desk Reference and the AHFS indicated that variable blood concentrations could be expected to occur after dosing with fluoxetine. Since the expected LLOQ was 1 ng/mL and the metabolite could very conceivably produce data which might not exceed peak levels of 10 ng/mL, a 40 mg dose was deemed unacceptable and the dose of 60 mg was selected. Barr Laboratories, Inc. and _____ investigators, medical personnel and IRB all agreed to proceed with the 60 mg dose.

The firm's response to comment #2.b. is acceptable.

Comment #5

Provide a brief description on the analytical methodology procedure.

Response to Comment #5

The analytical methodology used for Barr's Fluoxetine 20 mg Capsule fasting study is entitled "Analysis of Fluoxetine and Norfluoxetine in Human Plasma." A brief summary of this follows. A 1.0 mL sample volume is required for analysis. The sample is kept frozen at -20°C prior to analysis. At the time of analysis fluoxetine, norfluoxetine and the internal standard protryptiline are extracted from basic, heparinized human plasma using
The compounds are then acid back-extracted into % phosphoric acid. separation is achieved by

Fluorescence detection with an excitation wavelength of 230 nm and an emission wavelength of 305 nm is used to detect fluoxetine and norfluoxetine. This method is validated with a minimum quantifiable level of 2.00 ng/mL for fluoxetine and 2.00 ng/mL for norfluoxetine. The upper level is 500 ng/mL for each analyte. A linear weighted (1/concentration squared) least squares regression analysis is used to quantitate unknown samples.

II. REVIEW OF IN VIVO BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS AND IN VITRO DISSOLUTION TESTING DATA

OBJECTIVE:

To review:

Barr's in vivo bioequivalence study (single dose) under non-fasting conditions comparing its 20 mg strength Fluoxetine HCl Capsules to the reference listed drug, Eli Lilly's Prozac® Capsules, 20 mg.

BACKGROUND:

Fluoxetine is a selective serotonin reuptake inhibitor. It is primarily indicated for the treatment of depression. The exact mechanism of action is still not completely understood.

Following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from ng/mL are observed after 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 administered with or without food. It is extensively metabolized in the liver to norfluoxetine and a number of unidentified metabolites. The only identified, active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. Fluoxetine has an elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration. Norfluoxetine has an elimination half-life of 4 to 16 days after acute and chronic administration.

Fluoxetine HCL is currently marketed as Prozac® oral Capsules, 20 mg and 10 mg; and Prozac® oral solution, 20 mg/5 mL, manufactured by Dista (Eli Lilly).

A dose of 20 mg/day, administered in the morning, is recommended as the initial dose. The maximum fluoxetine dose should not exceed 80 mg/day.

III. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (clinical study project #P96-150)

A. Sponsor:

Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970

Clinical Facility:

Principle Investigator:

Analytical Facility:

Statistical Analysis:

Clinical Study Dates:

Period I: August 10, 1996

Period II: October 12, 1996

Period III: January 04, 1997

Analysis Schedule Dates:

Analysis of samples began on March 10, 1997 and completed on April 14, 1997.

B. STUDY DESIGN:

Randomized, three-way crossover, single dose study, under non-fasting and fasting conditions.

C. SUBJECTS:

Twenty-four (24) healthy male subjects were enrolled in the study and all subjects completed the study (subjects #1-24). The subjects were 18 to 40 years of age, and their body weights were within $\pm 10\%$ of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Inclusion, Exclusion and Restriction Criteria:

Same as in study #P95-251 under fasting conditions

D. Treatment Plan:

Test Product:

Treatment A: Fasting Conditions, 3 X 20 mg Barr's Fluoxetine HCL, Lot #5R87719, Lot size capsules, assay 99.1%, content uniformity 99.0%.

Treatment B: Non-fasting conditions, 3 X 20 mg Barr's Fluoxetine HCL, Lot #5R87719, Lot size capsules, assay 99.1%, content uniformity 99.0%.

Reference Product:

Treatment C: Non-fasting conditions, 3 X 20 mg Eli Lilly's Prozac® Capsules, Lot #8AM94A, assay 100.6%, content uniformity 99.9%, expiration date: Oct./97.

Washout period: at least 9 weeks

E. DRUG, FOOD AND FLUID INTAKE:

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments B and C) only fasted for 9.5 hours. Treatments B and C differed from treatment A in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was not permitted for 1 hour before and 2 hour after dosing, but was allowed at all other times. Standard meals were provided at appropriate times thereafter (at 4.5 and 9.5 hours after dosing).

F. ASSAY METHODOLOGY:

Precision and accuracy of the method (for both fluoxetine and norfluoxetine) are shown in Tables #1-4.

Table #1
Precision and Accuracy of the Assay Method
from Calibration Standards Samples
(Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	48	2.01	3.79	0.571
5.0	48	4.93	4.55	-1.36
10.0	48	9.99	4.82	-0.130
25.0	48	25.1	4.09	0.263
50.0	48	49.7	3.36	-0.607
100.0	46	99.3	3.51	-0.661
250.0	46	254	3.68	1.14
500.0	47	503	3.85	0.550

Table #2
Precision and Accuracy of the Assay Method
from Calibration Concentrations Samples
(norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	48	2.01	3.02	0.285
5.0	48	4.95	3.41	-0.960
10.0	48	10.0	5.39	0.257
25.0	48	25.2	3.24	0.704

50.0	48	50.0	3.18	-0.092
100.0	46	99.6	3.28	-0.428
250.0	45	252	4.01	0.655
500.0	47	498	4.86	-0.408

Table #3

Inter-Assay Precision and Accuracy of
the Assay Method from the Quality Control Samples
(Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	72	5.05	5.67	1.02
40.0	72	40.1	4.16	0.141
400.0	72	402	4.18	0.500

Table #4

Inter-Assay Precision and Accuracy of
the Assay Method from the Quality Control Samples
(Norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	71	4.86	5.72	-2.72
40.0	72	39.0	4.72	-2.39
400.0	72	396	5.63	-1.10

5. Recovery: (pp 1577-1579, Vol. B2.5)

The overall percent recovery of fluoxetine and norfluoxetine were 43.5% and 38.6% with CV% range of 1.57%-13.4% and 2.52-12.7%, respectively.

6. Stability:

(The stability data are presented on pages #1554-1555, #1580-1585; Vol. B2.5).

1. Fluoxetine and norfluoxetine were stable at room temperature during 3 freeze/thaw cycles conducted over 48 hours.

2. Long term stability data showed that fluoxetine and

norfluoxetine were stable for 365 days at -20 °C.

G. BLOOD SAMPLING:

Blood samples were collected at 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, 192, 240, 312, 408, 504, 600 and 696 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -20 °C until analysis.

H. ADVERSE EVENTS: (pp #510-518; Vol. B2.2)

One hundred forty-two adverse events were reported in twenty subjects out of twenty-four subjects. The summary of the adverse events are presented in Attachment #1. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

I. IN VIVO BE STUDY AND STATISTICAL ANALYTICAL:

Twenty-four (24) healthy male subjects were enrolled in the study and all subjects completed the study (subjects #1-24).

Adverse Events:

The adverse reactions are reported on page #510-519, Vol. B2.2. The following are the adverse events summary for study subjects under non-fasting conditions. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

Parameter	Treat A (# of Subjects)	Treat B (# of Subjects)	Treat C (# of Subjects)
Headache	19	40	21
Respiratory Disorder (such as nasal congestion, stuffy head, chest congestion)	8	6	7
Rhinitis (runny nose, sneezing)	6	15	7

Dyspepsia (heartburn)	--	3	4
Pharyngitis (sore throat)	3	5	5
Conjunctivitis (itchy eyes)	--	2	1
coughing	2	5	6
Pain (sore ribs, chest, neck, knee, eye, back)	5	6	4
Myalgia (muscles ache)	4	4	2
Right Wrist Sprain			1
Vomiting*	--	4	2
Abdominal Pain and upset stomach	2	6	6
Nausea	--	--	2
Rigors (chills)	--	1	1
Hot Flushes (head hot)	--	2	2
Tremors (shakiness)	--	-	2
Earache	--	--	2
Tooth Disorder (Toothache)	-	2	--
Tendinitis	2	--	--
Fever (Feverish)	--	1	--
Dizziness	4	3	4
Fatigue	--	--	2
Urinary Retention	2	--	--
Diarrhea	3	2	--
Sinusitis	--	3	-

Edema (swollen right wrist or arm)	2	--	--
------------------------------------	---	----	----

* Vomiting occurred after 11:35 hours post-dosing.

The pharmacokinetic parameters of fluoxetine and norfluoxetine were analyzed using

The pharmacokinetic parameters for the plasma fluoxetine and norfluoxetine concentrations, as well as the following parameters, AUct, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #5
Fluoxetine Mean Plasma Concentrations (ng/mL)
in 24 Subjects Following 3X20 mg Oral Dose of
Fluoxetine HCL Under Non-Fasting Conditions
 (Test Lot #5R87719, Reference Lot #8AM94A)

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
0	0.00	0.00	0.00	0.00	0.00	0.00	
2	13.88	10.48	3.35	3.73	0.98	2.15	4.15
4	31.16	11.53	21.27	10.09	14.96	9.58	1.47
5	38.00	11.54	33.65	10.59	29.72	11.98	1.13
6	43.21	11.39	42.92	12.94	41.92	11.98	1.01
7	44.67	11.50	43.78	11.67	42.04	9.92	1.02
8	44.56	11.11	44.02	10.40	42.88	10.05	1.01
10	42.24	9.77	41.99	11.03	42.52	11.25	1.01
12	39.44	10.09	39.57	10.15	40.97	10.49	1.00
24	28.12	8.48	28.15	8.55	29.39	8.48	1.00
36	25.30	9.78	25.69	11.07	25.05	7.86	0.98
48	18.88	8.80	19.31	8.46	19.77	8.51	0.98
60	18.07	9.69	17.99	9.46	18.85	11.57	1.00
72	13.86	8.24	13.35	7.46	13.66	7.52	1.04
96	10.31	7.30	9.81	7.07	9.81	6.37	1.05
120	7.40	6.28	7.35	6.05	7.27	6.06	1.01
144	5.22	5.83	5.24	5.74	5.32	6.25	1.00
192	3.01	4.89	2.51	4.55	2.80	4.51	1.20
240	1.73	3.55	1.62	3.87	1.68	3.93	1.07
312	1.24	3.27	0.78	2.67	0.90	2.96	1.58
408	0.48	1.92	0.48	1.84	0.50	1.89	1.02
504	0.27	1.31	0.29	1.44	0.28	1.35	0.91
600	0.19	0.95	0.21	1.05	0.23	1.11	0.91
696	0.16	0.78	0.15	0.72	0.18	0.86	1.09

(CONTINUED)

TIME HR	RMEAN13	RMEAN23
0		
2	14.17	3.42
4	2.08	1.42
5	1.28	1.13
6	1.03	1.02
7	1.06	1.04

8	1.04	1.03
10	0.99	0.99
12	0.96	0.97
24	0.96	0.96
36	1.01	1.03
48	0.95	0.98
60	0.96	0.95
72	1.01	0.98
96	1.05	1.00
120	1.02	1.01
144	0.98	0.98
192	1.07	0.90
240	1.03	0.97
312	1.38	0.87
408	0.97	0.95
504	0.97	1.06
600	0.86	0.94
696	0.91	0.84

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
MEAN23=Mean T/R (under non-fasting conditions)
Unit: Plasma Level=NG/ML Time=HRS

Table #6
Summary of Pharmacokinetics Parameters (Fluoxetine)
in 24 Subjects Following 3X20 mg Oral Dose of
Fluoxetine HCL Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
AUCI	3198.50	2402.10	3063.08	2287.28	3125.96	2349.39	1.04
AUCT	2949.25	2165.21	2835.75	2117.53	2896.83	2116.29	1.04
C _{MAX}	47.02	12.49	46.77	11.08	46.62	11.45	1.01
KE	0.02	0.01	0.02	0.01	0.02	0.01	0.99
*LAUCI	2636.62	0.60	2560.67	0.57	2612.11	0.57	1.03
*LAUCT	2439.79	0.60	2357.74	0.58	2426.95	0.57	1.03
*LC _{MAX}	45.55	0.26	45.58	0.23	45.30	0.25	1.00
THALF	53.02	37.60	51.34	37.43	52.62	40.43	1.03
T _{MAX}	7.38	1.34	7.38	1.64	8.00	2.27	1.00

(CONTINUED)

PARAMETER	RMEAN13	RMEAN23
AUCI	1.02	0.98
AUCT	1.02	0.98
C _{MAX}	1.01	1.00
KE	0.99	1.00
*LAUCI	1.01	0.98
*LAUCT	1.01	0.97
*LC _{MAX}	1.01	1.01
THALF	1.01	0.98
T _{MAX}	0.92	0.92

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
RMEAN23=Mean T/R (under non-fasting conditions)
UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma fluoxetine levels for the test and reference products reached a maximum level of concentration around 8.0 hours (Table #5 and Figures #1&2).
2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi and Cmax were all within the acceptable range of 0.8 to 1.25 (Table #6).
3. The average values of T1/2, Tmax and Kel for the test product were comparable to the reference product values under the same conditions (Table #6).

NORFLUOXETINE DATA:

Table #7
Mean Plasma Concentrations (ng/mL)
of Norfluoxetine in 24 Subjects
Following 3X20 mg Oral Dose of Fluoxetine HCL
Under Non-Fasting Conditions
 (Test Lot #5R87719, Reference Lot #8AM94A)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
2	1.34	1.45	0.00	0.00	0.12	0.57	.
4	5.55	1.90	3.81	2.15	2.36	2.02	1.46
5	7.55	2.37	6.27	2.26	5.28	2.24	1.20
6	9.42	3.38	8.29	2.70	8.02	3.20	1.14
7	10.45	3.39	9.18	3.07	8.80	3.27	1.14
8	11.35	3.54	10.26	3.99	9.75	3.87	1.11
10	12.80	4.48	11.31	4.10	11.19	3.95	1.13
12	13.54	4.40	12.65	4.48	12.91	4.80	1.07
24	15.52	4.65	14.82	4.80	15.16	4.92	1.05
36	20.65	5.88	19.98	5.89	20.15	6.61	1.03
48	18.98	4.92	19.42	6.10	19.75	5.51	0.98
60	23.03	6.02	22.32	5.62	23.68	7.63	1.03
72	20.47	4.98	19.77	5.10	20.19	5.08	1.04
96	21.04	4.87	20.59	5.20	20.65	5.52	1.02
120	20.37	4.62	20.12	4.99	20.36	4.92	1.01
144	19.41	4.66	19.30	4.70	19.81	5.23	1.01
192	17.51	5.14	16.72	4.14	17.74	5.27	1.05
240	14.40	4.91	14.92	3.92	15.42	5.66	0.97
312	11.44	4.40	11.07	4.30	11.84	4.42	1.03
408	8.52	8.50	7.42	3.67	7.49	4.23	1.15
504	5.08	4.69	4.71	3.69	4.63	4.27	1.08
600	2.61	3.48	2.59	3.54	2.56	3.56	1.01
696	1.58	2.90	1.44	2.51	1.71	3.27	1.09

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0		
2	11.48	0.00
4	2.36	1.62
5	1.43	1.19
6	1.17	1.03
7	1.19	1.04
8	1.16	1.05
10	1.14	1.01
12	1.05	0.98
24	1.02	0.98
36	1.02	0.99
48	0.96	0.98
60	0.97	0.94
72	1.01	0.98
96	1.02	1.00
120	1.00	0.99
144	0.98	0.97
192	0.99	0.94
240	0.93	0.97
312	0.97	0.93
408	1.14	0.99
504	1.10	1.02
600	1.02	1.01
696	0.92	0.85

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
 MEAN23=Mean T/R (under non-fasting conditions)
 Unit: Plasma Level=NG/ML Time=HRS

Table #8
Summary of Pharmacokinetics Parameters (Norfluoxetine)
in 24 Subjects Following 3X20 mg Oral Dose of
Fluoxetine HCL Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	8271.29	3551.92	8021.29	2886.94	8374.00	3749.93	1.03
AUCT	7343.38	2860.31	7106.42	2244.38	7322.75	2627.37	1.03
CMAx	24.25	7.31	22.94	5.73	24.95	7.52	1.06
KE	0.00	0.00	0.00	0.00	0.01	0.00	1.00
*LAUCI	7687.86	0.38	7578.61	0.34	7756.74	0.39	1.01
*LAUCT	6840.01	0.40	6697.10	0.38	6819.09	0.42	1.02
*LCMAx	22.77	0.42	21.73	0.41	23.23	0.46	1.05
THALF	156.01	61.45	165.14	89.10	164.30	93.37	0.94
TMAx	90.50	76.96	87.00	56.53	87.75	50.40	1.04

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.99	0.96
AUCT	1.00	0.97
CMAx	0.97	0.92

KE	0.96	0.96
*LAUCI	0.99	0.98
*LAUCT	1.00	0.98
*LCMAX	0.98	0.94
THALF	0.95	1.01
TMAX	1.03	0.99

MEAN1=Test-Fast MEAN2=Test-NonFast MEAN3=Ref.-NonFast
RMEAN23=Mean T/R (under non-fasting conditions)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

1. Under non-fasting conditions, the mean plasma norfluoxetine levels for the test and reference products reached a maximum level of concentration around 60 hours (Table #7 and Figures #3&4).
2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the log-transformed AUCt, AUCi and Cmax were all within the acceptable range of 0.8 to 1.25 (Table #8).
3. The average values of T1/2, Tmax and Kel for the test product were comparable to the reference product values under the same conditions (Table #8).

IV. COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg are bioequivalent. The 90% confidence intervals for the log-transformed AUCt, AUCi and Cmax for Fluoxetine and Norfluoxetine were all within the acceptable range of 80-125%.
2. Under non-fasting conditions: The firm's in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg are bioequivalent. The ratios of the test mean to the reference mean for the AUCt, AUCi, Cmax were within the acceptable range of 0.8-1.25.

V. DEFICIENCY:

The dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

The firm should conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

VI. RECOMMENDATION:

The in vivo Bioequivalence study conducted by Barr Laboratories under fasting conditions on its test product, Fluoxetine Hydrochloride Capsules, 20 mg, (Lot #5R87719) versus the listed reference product, Eli Lilly's Prozac® Capsules, 20 mg, (Lot #8AM94A) has been found to be incomplete by the Division of Bioequivalence due to the deficiency cited above.

The firm should be informed of the deficiency and recommendation.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 74-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine Hydrochloride Capsules, 20 mg

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

Your dissolution testing of the test product in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

Please conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

Sincerely yours,

JS

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

BIOEQUIVALENCY - DEFICIENCIES

- | | | |
|----|------------------------|------------------------|
| 1. | FOOD STUDY (STP) | Strength: <u>20 mg</u> |
| | Clinical: | Outcome: IC |
| | Analytical | |
| 2. | DISSOLUTION DATA (DIS) | Strength: 20 mg |
| | | Outcome: IC |
| 3. | STUDY AMENDMENT (STA) | Strength: <u>20 mg</u> |
| | | Outcome: IC |

OUTCOME DECISIONS: IC - Incomplete

ISI

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

RD INITIALED RMHATRE
FT INITIALED RMHATRE _____ 12/22/97

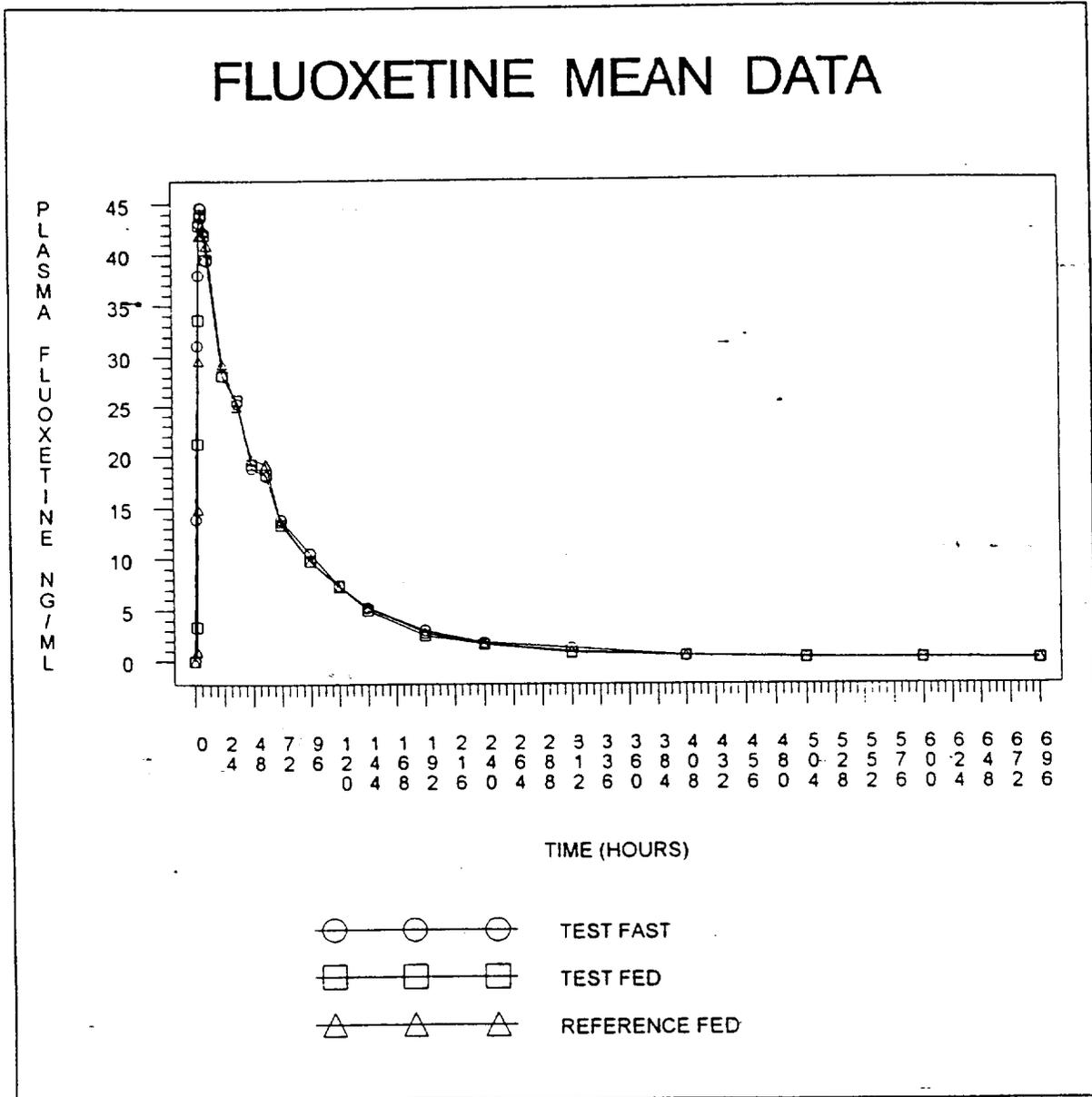
ISI

Concur: _____ Date: 12/24/97
Dale Conner, Pharm.D.
Acting Director
Division of Bioequivalence

ISI

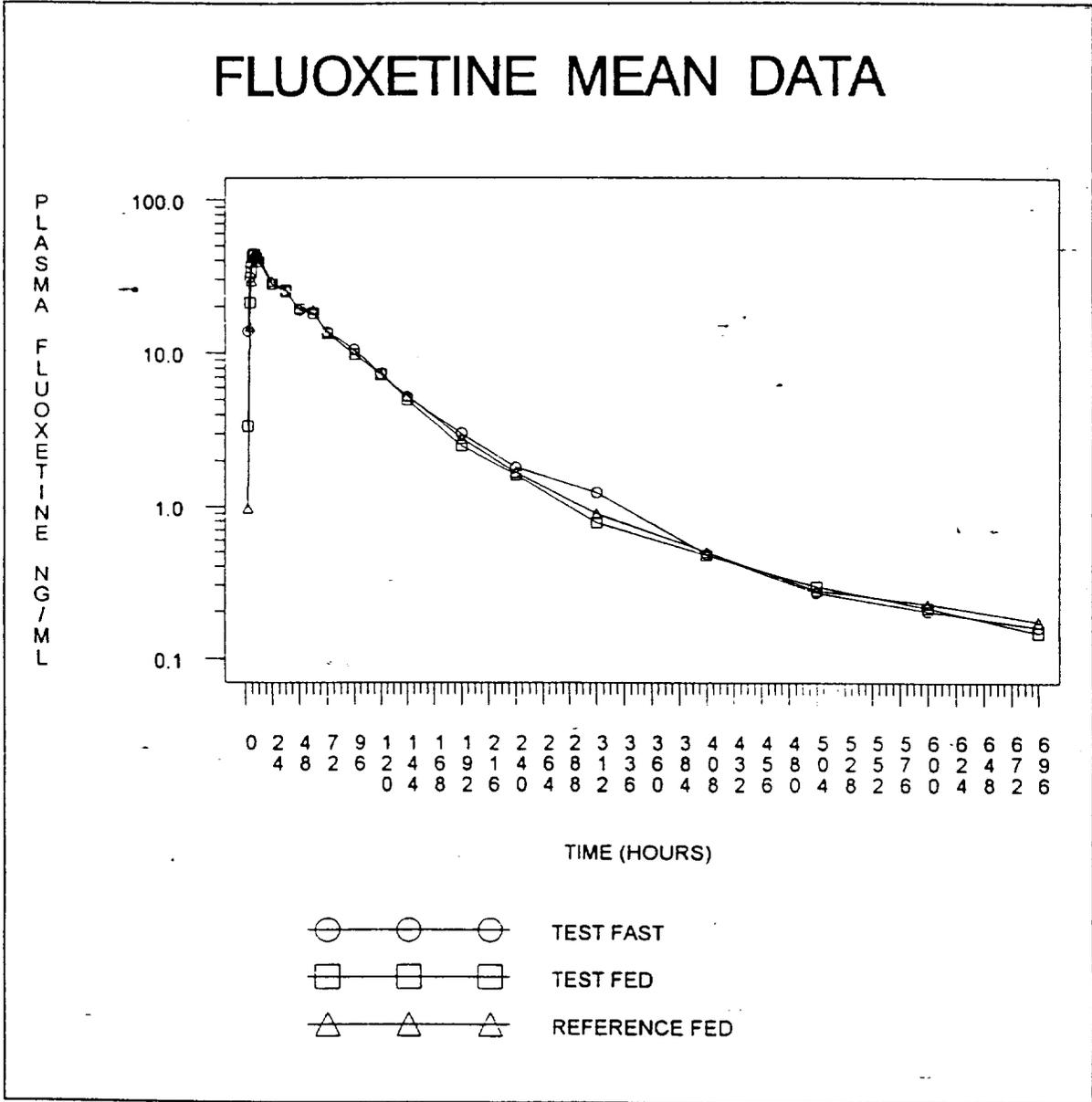
ANDA # 74-803

Figure #1 Linear Plot of Mean Plasma Fluoxetine Concentrations vs Time



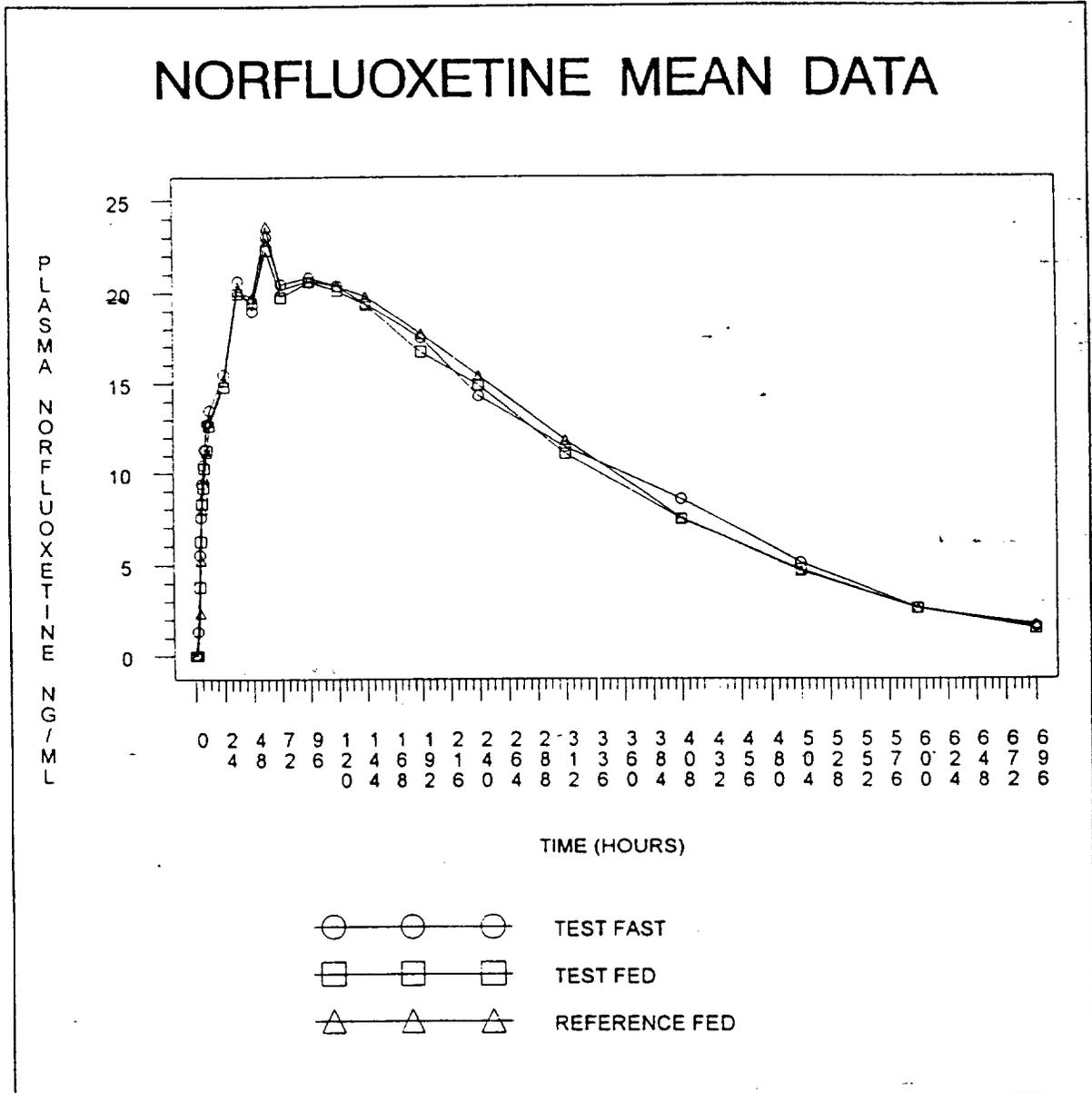
ANDA # 74-803

Figure #2 Semi-logarithmic Plot of Mean Plasma Fluoxetine Concentrations vs Time



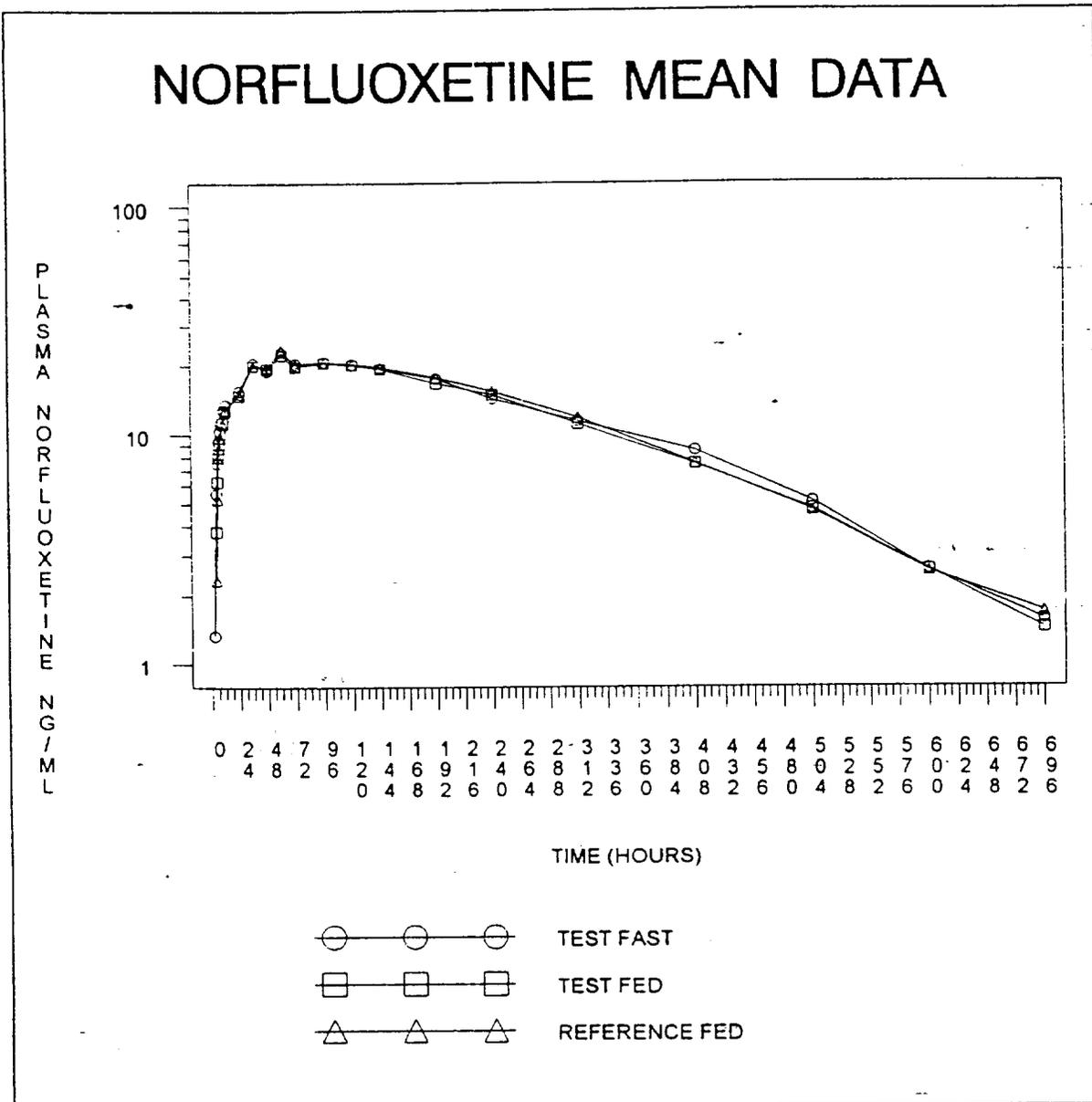
ANDA # 74-803

Figure #3 Linear Plot of Mean Plasma Norfluoxetine Concentrations vs Time



ANDA # 74-803

Figure # 4 Semi-logarithmic Plot of Mean Plasma Norfluoxetine Concentrations vs Time



Fluoxetine Hydrochloride
20 mg Capsules
ANDA #74-803
Reviewer: Z.Z. Wahba
File #74803a1.A98

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
April 29, 1998
June 15, 1998
August 18, 1998

REVIEW OF AN AMENDMENT AND A WAIVER REQUEST

I. BACKGROUND

1. The firm has previously submitted two in vivo bioequivalence studies (single-dose fasting and single-dose post-prandial) comparing its test drug product, Barr's Fluoxetine HCL Capsules, 20 mg to the reference product, Eli Lilly's Prozac® Capsules, 20 mg.
2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated December 24, 1997, ANDA #74-803) due to a deficiency regarding the dissolution data.
3. The firm has requested a waiver of in vivo bioequivalence study requirements for its drug product, Barr's Fluoxetine HCL Capsules, 10 mg. The reference listed product is Eli Lilly's Prozac® Capsules, 10 mg.

II. DEFICIENCY COMMENT:

The firm was asked to submit complete dissolution testing data using USP 23 apparatus #2 (Paddle) at 50 rpm in 900 mL of water.

THE FIRM'S RESPONSE TO COMMENT:

The dissolution testing for the test and reference products is summarized below:

Apparatus: USP 23 apparatus 2 (Paddles) at 50 rpm
Medium: 900 mL water
Test Product: Barr's Fluoxetine HCL Capsules, 20 mg, lot #5R87719
Barr's Fluoxetine HCL Capsules, 10 mg, lot

#5R87618

Ref. Product: Eli Lilly's Prozac® Capsules, 20 mg, lot #8AM94A

Eli Lilly's Prozac® Capsules, 10 mg, lot #8NE08M

Number of Units: 12 Capsules

The dissolution testing results are shown in the following table

Table. In Vitro Dissolution Testing						
Drug (Generic Name): Fluoxetine HCL Capsules Dose Strength: 20 mg and 10 mg ANDA No.: 74-803 Firm: Barr Laboratories, Inc. Submission Date: April 29, 1998 File Name: 74803a1.a98						
I. Conditions for Dissolution Testing:						
USP XXII Basket: Paddle: X RPM: 50 No. Units Tested: 12 Medium: 900 mL water Reference Drug: Eli Lilly's Prozac® Capsules, 20 mg and 10 mg						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Minutes)	Test Product Fluoxetine Lot # 5R87719 Strength(mg) 20			Reference Product Prozac® Lot #8AM94A Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
10	79		12.5	60		31.6
15	86		7.8	92		6.5
30	93		3.8	96		1.8
45	93		2.6	96		1.6
Sampling Times (Minutes)	Test Product Fluoxetine Lot #5R87618 Strength(mg) 10			Reference Product Prozac® Lot #8NE08M Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV

10	84		9.7	83		17.7
15	87		7.4	97		3.2
30	92		4.3	99		2.7
45	94		3.6	99		2.6

III. COMMENTS ON THE DISSOLUTION TESTING (NOT TO BE RELEASED UNDER FOI):

1. The firm conducted the dissolution testing on expired batches, test (20 mg strength, lot #5R87719, manufacturing date June 95, dissolution testing date 2/23/98) and reference (20 mg strength, lot #8AM94A, expiration date October 95, dissolution testing date 2/23/98) products. Also, the dissolution testing on the 10 mg strength was conducted on expired batches, test (lot #5R87618, manufacturing date June 95, dissolution testing date 2/23/98) and reference (lot #8NE08M, expiration date September 96, dissolution testing date 2/23/98) products.
2. In the original submission (6/6/97), the firm conducted the dissolution in 900 mL of 0.1N HCl, using USP 23, apparatus II (paddle), at 50 rpm which was not acceptable by the Division of Bioequivalence. The Division requested the firm conduct the dissolution testing in 900 mL of water, using USP 23, apparatus II (paddle), at 50 rpm.
3. On April 29, 1998, the firm resubmitted the dissolution data applying the Agency's dissolution specification on its bio-lot which had expired.
4. The firm's justification of using the expired bio-lot was due to ongoing patent litigation with Eli Lilly (the innovator of the drug). Therefore, the firm has not manufactured any validation batches.
5. The dissolution data for 10 mg and 20 mg strengths are acceptable.
6. Important note: The firm is required to submit dissolution

data (for the 20 mg and 10 mg strengths) from its first three production batches using the above-mentioned dissolution method. The test product dissolution data should be accompanied by dissolution data from a current batch of the reference listed drug.

IV. FORMULATION

(page 6-16 and 6-17, volume A3.2, under Part II, Section VI)

Barr's formulation of its drug product, Fluoxetine HCL Capsules, 10 mg and 20 mg is presented below.

Formulation Comparison

Ingredients	10 mg Capsule	20 mg Capsule
	mg/capsule	mg/capsule
Fluoxetine Hydrochloride	11.2*	22.4*
Lactose Monohydrate, NF (Fast-Flo)		
Microcrystalline Cellulose, NF (Avicel® PH-101)		
Starch, NF (Corn Starch-Purity 21)		
Stearic Acid, NF (Hystrene)		
Total Weight		

*22.4 mg and 11.2 mg of Fluoxetine Hydrochloride are equivalent to 20 mg and 10 mg Fluoxetine, respectively.

V. RECOMMENDATIONS

- The two in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, conducted by Barr Laboratories, Inc. on its Fluoxetine HCL Capsules, 20 mg (lot #5R87719), comparing it to the reference product, Eli Lilly's Prozac® Capsules, 20 mg (lot #8AM94A), have been found acceptable. The two studies demonstrate that under fasting and non-fasting conditions, Barr's Fluoxetine HCL Capsules, 20 mg is bioequivalent to the reference listed product, Eli Lilly's Prozac® Capsules, 20 mg.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #74-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Fluoxetine HCL Capsules, 20 mg and 10 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:

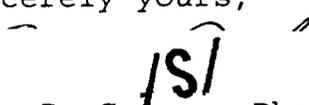
The dissolution testing should be conducted in 900 ml of water, at 37°C using Apparatus #2 (Paddle) at 50 rpm. The test product should meet the following specifications:

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

Important Note: You are required to submit dissolution testing data (for the 20 mg and 10 mg strengths) from your first three production batches using the above mentioned dissolution method. The dissolution profile which you submit should be accompanied by dissolution data from a current batch of the reference listed drug.

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

Sincerely yours,


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

BIOEQUIVALENCY - ACCEPTABLE

1. **STUDY AMENDMENT** dated 04-29-98 Strengths: 20 mg
Outcome: AC
2. **DISSOLUTION WAIVER** dated 06-15-98 Strengths: 10 mg
Outcome: AC
3. **STUDY AMENDMENT** dated 08-18-98 Strengths: 20 mg & 10 mg
Outcome: AC

OUTCOME DECISIONS: AC - Acceptable
WINBIO COMMENTS: Acceptable Biostudy

MAY 15 1996

Fluoxetine Hydrochloride
20 mg Capsules
ANDA #74-803
Reviewer: Z.Z. Wahba
File #74803s.d95

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
December 09, 1995

REVIEW OF AN IN VIVO BIOEQUIVALENCE STUDY

I. OBJECTIVE:

To review:

Barr's in vivo bioequivalence study (single dose) under fasting conditions comparing its 20 mg strength Fluoxetine HCl Capsules to the reference listed drug, Eli Lilly's Prozac® Capsules, 20 mg.

II. BACKGROUND:

Fluoxetine is a selective serotonin reuptake inhibitor. It is primarily indicated for the treatment of depression. The exact mechanism of action is still not completely understood.

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. 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. It is extensively metabolized in the liver to norfluoxetine and a number of unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. Fluoxetine has an elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration. Norfluoxetine has an elimination half-life of 4 to 16 days after acute and chronic administration.

Fluoxetine HCL is currently marketed as Prozac® Pulvules® oral Capsules, 20 mg and 10 mg; and Prozac® oral solution, 20 mg/5 mL, manufactured by Dista (Eli Lilly).

A dose of 20 mg/day, administered in the morning, is recommended as the initial dose. The maximum fluoxetine dose should not exceed 80 mg/day.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITIONS

(clinical study project #P95-251)

A. SPONSOR:

Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970

Clinical Facility:

Principle Investigator:

Analytical Facility:

Statistical Analysis:

Clinical Study Dates:

Period I: July 22 - September 12, 1995

Period II: September 23 - October 24, 1995

Analysis Schedule Dates:

Analysis of samples began on March 20, 1995 and ended on April 18, 1995.

B. STUDY DESIGN:

Randomized, two-way crossover, single dose study, under fasting conditions.

C. SUBJECTS:

Thirty eight (38) healthy male subjects were enrolled in the study but 37 subjects completed the clinical study. Subject #36 failed to return to the facility to complete Period 2. Therefore, the data set used for statistical analyses contained data from 37 subjects (subjects #1-35, 37 and 38).

Subject Inclusion Criteria:

1. The subjects were within 18 to 40 years of age, and their body weights were within $\pm 10\%$ of the ideal weight as defined by the Metropolitan Life Insurance Chart.
2. Only medically healthy subjects as determined by normal history, physical examination, laboratory profiles and EKG were enrolled in the study.

Subject Exclusion Criteria:

1. History of cardiovascular, respiratory, renal, gastrointestinal, immunologic, neurologic, hepatic, hematopoietic or psychiatric disease.
2. History of chronic alcohol consumption or drug addiction.
3. Tested positive for hepatitis B surface antigen screen or a reactive HIV 1 & 2 antibody screen.
4. Allergy to the class of drug being tested.
5. Use of tobacco in any form
6. Participated in a previous clinical trial or donated blood within the past 30 days.
7. Treatment with any known hepatic enzyme inducing or inhibiting agents within the past 30 days prior to dosing.

Subject Restrictions:

1. No subject took any medications, including OTC products for at least 2 weeks prior to the beginning of the study and until completion of the study.
2. No alcoholic, xanthine and caffeine containing foods and beverages were allowed during the study.

D. TREATMENT:

Test Product: 3 X 20 mg Barr's Fluoxetine HCL, Lot #5R87719, Lot size (not given), assay (not given), content uniformity (not given).

Reference Product: 3 X 20 mg Eli Lilly's Prozac® Capsules, Lot #8AM94A, assay (not given), content uniformity (not given), expiration date: Oct./97.

Washout period: 63 days

E. DRUG, FOOD AND FLUID INTAKE:

Subjects fasted for at least 10 hours (overnight) before dosing and for at least 4 hours after dosing. Each dose was followed by 240 mL of water according to randomized dosing schedule. Water intake was restricted from 1.0 hour prior to and 2.0 hours after drug administration. At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after the dose, water was allowed ad lib, if requested. Standard meals were provided at appropriate times thereafter.

F. SUBJECT MONITORING:

Vital signs (blood pressure and heart rates) were monitored predose (-1 hr) and at 12 and 24 hours post-dose (the values

were reported on pages #06-01577 to 06-01582, vol. #6).

G. ASSAY METHODOLOGY:

Table #1
Precision and Accuracy of the Assay Method
from Calibration Concentrations Samples
(Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	70	2.01	9.57	0.316
5.0	72	4.99	5.75	-0.172
10.0	72	9.93	2.94	-0.675
25.0	72	24.7	1.84	-1.12
50.0	72	49.7	1.67	-0.57
100.0	72	99.7	2.01	-0.275
250.0	72	253	1.83	1.14
500.0	72	507	1.98	1.36

Table #2
Precision and Accuracy of the Assay Method
from Calibration Concentrations Samples
(norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy (%Difference)
2.00	70	2.04	8.39	2.08
5.0	69	4.89	4.98	-2.12
10.0	70	9.63	2.61	-3.68
25.0	70	23.7	1.82	-5.30
50.0	70	48.4	2.05	-3.15
100.0	70	98.2	2.08	-1.79
250.0	70	262	1.78	4.90
500.0	70	545	2.08	9.03

Table #3
Pre-Study Validation of Inter-Assay Precision
and Accuracy of the Assay Method
from the Quality Control Samples
(Fluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	107	4.82	5.41	-3.53
40.0	108	39.6	2.81	-1.4
400.0	108	407	2.70	1.66

Table #4
Pre-Study Validation of Inter-Assay Precision
and Accuracy of the Assay Method
from the Quality Control Samples
(Norfluoxetine)

Theoretical Conc. ng/mL	N	Found Mean ng/mL	Precision (%CV)	Accuracy %Difference
5.0	105	5.53	5.71	10.7
40.0	105	43.1	3.33	7.76
400.0	105	435	3.05	8.83

Table #5
Within-Study Validation of Intra-Assay Precision
and Accuracy of the Assay Method
in Human Plasma Samples

Theoretical Conc. ng/mL	N	<u>(Fluoxetine)</u>		Accuracy %Difference
		Found Mean ng/mL	Precision (%CV)	
2.0	6	1.96	13.1	-1.77
5.0	6	5.01	4.61	0.25
40.0	6	38.9	2.13	-2.64
400.0	6	384	0.84	-4.04

Table #6
Within-Study Validation of Inter-Assay Precision
and Accuracy of the Assay Method
in Human Plasma Samples

Theoretical Conc. ng/mL	N	<u>(Fluoxetine)</u>		Accuracy %Difference
		Found Mean ng/mL	Precision (%CV)	
2.0	12	2.11	13.2	5.48
5.0	12	4.92	4.49	-1.50
40.0	12	39.0	4.69	-2.51
400.0	12	393	3.00	-1.71

Table #7
Within-Study Validation of Intra-Assay Precision
and Accuracy of the Assay Method
in Human Plasma Samples

Theoretical Conc. ng/mL	N	<u>(Norfluoxetine)</u>		Accuracy %Difference
		Found Mean ng/mL	Precision (%CV)	
2.0	6	2.08	10.2	4.00
5.0	6	4.54	4.29	-9.17
40.0	6	37.9	1.73	-5.24
400.0	6	361	0.76	-9.73

Table #8
Within-Study Validation of Inter-Assay Precision
and Accuracy of the Assay Method
in Human Plasma Samples

Theoretical Conc. ng/mL	N	<u>(Norfluoxetine)</u>		Accuracy %Difference
		Found Mean ng/mL	Precision (%CV)	
2.0	12	2.09	10.3	4.49
5.0	12	4.73	5.30	-5.42
40.0	12	36.8	5.03	-7.91
400.0	12	373	2.99	-6.87

5. **Stability:** The freeze/thaw cycles and long-term stability data are summarized in Tables #9&10. The stability data of control samples at room temperature has not been reported.

Table #9
Freeze/Thaw Cycles Stability Data

Storage Conditions	Stability as %Original		
	5.0 ng/mL	40 ng/mL	400 ng/mL

Freeze/thaw, 3-cycles

For Fluoxetine:

1st freeze/thaw cycle (n=2)			
	5.06(+1.2%)	39(-2.5%)	384(-4.0%)
2nd freeze/thaw cycle (n=2)			
	5.08(+1.6%)	38.9(-2.7%)	378(-5.5%)
3rd freeze/thaw cycle (n=2)			
	5.05(+1.0%)	38.6(-3.5%)	394(-1.5%)

For Norfluoxetine:

1st freeze/thaw cycle (n=2)			
	4.99(-0.2%)	36.8(-8.0%)	369(-7.7%)
2nd freeze/thaw cycle (n=2)			
	4.72(-5.6%)	37.4(-6.5%)	365(-8.7%)
3rd freeze/thaw cycle (n=2)			
	5.04(+0.8%)	37.7(-5.7%)	384(-4.0%)

Table #10
Long-Term Stability Samples

Storage Conditions	Stability as %Original		
	50.0 ng/mL	100 ng/mL	250.0 ng/mL

Long term freezing for approximately 12 months (n=6)

For Fluoxetine:

	52.4(+4.87%)	107(+6.93%)	267(+6.14%)
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For Norfluoxetine:

	50.4(+0.83%)	104(+3.89%)	262(+4.70%)
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I. BLOOD SAMPLING:

Blood samples were collected at 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 144, 240, 312, 408, 576 and 744 hours post-dosing. The plasma samples were separated, collected and promptly stored frozen at -20 °C until analysis.

J. ADVERSE EVENTS:

Adverse reactions have been reported (vol. #6, pages 06-01539 to 06-01542 and 06-01632 to 06-01637). Several subjects experienced adverse events during the study with some possibilities of linkage to the test or reference drug product. None of the adverse events was considered serious or resulted in terminating any subject from study participation.

K. Protocol Deviations:

The deviations are reported on page #06-01535, vol. #6). There were three deviations from the protocol instructions of no nonprescription medications of within 7 days of period I. Subjects #28, 37 and 38 consumed multivitamin (2 tablets), advil (400 mg) and multivitamin (1 tablet), respectively. These deviations were viewed as not clinically significant by the investigators.

L. Statistical analyses:

The statistical analyses were performed on the plasma fluoxetine (n=37) and norfluoxetine (n=37) data to compare the test and reference treatments. The pharmacokinetic parameters for fluoxetine and its metabolite norfluoxetine are summarized in the tables below:

Table #11
Mean Plasma Concentrations (ng/mL)
of Fluoxetine in 37 Subjects
Following 20 mg Oral Dose of Fluoxetine HCL
Under Fasting Conditions

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.00	0.00	0.00	0.00	.
2	10.95	5.76	8.03	4.37	1.36
4	27.61	7.68	25.35	8.24	1.09
5	33.59	7.82	32.12	7.87	1.05
6	37.24	8.06	36.36	8.08	1.02
7	37.74	8.56	37.07	8.46	1.02
8	36.37	7.48	36.84	8.20	0.99
10	34.04	6.91	33.84	7.86	1.01
12	32.07	7.19	31.85	7.87	1.01
16	26.98	6.85	26.62	7.16	1.01
24	22.16	6.55	22.38	6.34	0.99
36	18.95	6.75	18.94	6.99	1.00
48	14.34	5.96	14.19	6.17	1.01
72	9.24	5.03	9.15	5.32	1.01
96	5.87	4.64	5.87	4.88	1.00
144	2.60	3.44	2.29	3.65	1.14
240	0.49	1.77	0.59	1.90	0.83
312	0.17	1.02	0.19	1.15	0.89
408	0.09	0.56	0.09	0.57	0.99
576	0.00	0.00	0.00	0.00	.
744	0.00	0.00	0.00	0.00	.

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #12
Summary of Pharmacokinetics Parameters (Fluoxetine)
in 37 Subjects Following 20 mg Oral Dose of
Fluoxetine HCL Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	1829.62	1054.74	1809.68	1118.27	1.01
AUCI	2007.41	1142.10	1991.59	1199.16	1.01
C _{MAX}	39.12	8.02	38.36	8.58	1.02
KE	0.02	0.01	0.02	0.01	0.98
THALF	37.82	16.74	37.80	18.37	1.00
T _{MAX}	6.49	1.02	7.14	0.79	0.91
*LAUCT	1632.34	0.47	1588.37	0.50	1.03
*LAUCI	1795.77	0.46	1758.61	0.49	1.02
*LC _{MAX}	38.31	0.21	37.40	0.23	1.02

UNIT: AUC=NG HR/ML C_{MAX}=NG/ML T_{MAX}=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Table #13
LSMeans and 90% Confidence Intervals
(Fluoxetine)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	1835.98	1814.40	97.63	104.74
AUCI	2014.14	1996.64	97.54	104.21
CMAX	39.14	38.39	99.38	104.51
*LAUCT	1636.49	1590.99	99.35	106.49
*LAUCI	1800.26	1761.45	98.89	105.63
*LCMAX	38.32	37.41	99.94	104.99

LSMEAN1=LS mean test

LSMEAN2=LS mean ref.

Low CI 12=Lower C.I. for T/R

UPP CI 12=Upper C.I. for T/R

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

* The values represent the geometric means (antilog of the means of the logs).

Table #14
Test/Reference Products Ratios for
Pharmacokinetic Parameters for Individual Subjects
(Fluoxetine)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
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1=Test product 2=Reference product

Table #15
Summary of Mean and SD of Individual T/R Ratios
(Fluoxetine)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	37	1.04	0.14		
RAUCI12	37	1.03	0.13		
RCMAX12	37	1.03	0.09		
RTMAX12	37	0.92	0.18		
RKE12	37	1.00	0.12		
RTHALF12	37	1.02	0.13		

1. The mean plasma fluoxetine levels reached a maximum level of concentration around 7.0 hours (Table #11 and the attached Figures #1&2). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions.
2. The arithmetic test/reference mean ratios for AUC_{0-t} , AUC_{0-inf} and C_{max} were 1.01, 1.01 and 1.02, respectively. The geometric test/reference mean ratios for AUC_{0-t} , AUC_{0-inf} and C_{max} were 1.03, 1.02 and 1.02, respectively (Table #12). The 90% confidence intervals for the log-transformed AUC_{0-t} , AUC_{0-inf} and C_{max} were within the acceptable range of \pm (Table #13).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC and C_{max} .

3. The average values of $T_{1/2}$, T_{max} and K_{e1} for the test product were comparable to the reference product values (Table #12).

NORFLUOXETINE DATA:

Table #16
Mean Plasma Concentrations (ng/mL)
of Norfluoxetine in 37 Subjects
Following 20 mg Oral Dose of Fluoxetine HCL
Under Fasting Conditions

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.00	0.00	0.00	0.00	.
2	2.54	1.76	1.73	1.67	1.47
4	7.91	3.09	7.10	2.50	1.11
5	10.41	3.44	9.88	3.21	1.05
6	12.72	4.78	11.98	4.11	1.06
7	14.00	4.96	13.51	4.38	1.04
8	14.47	5.16	14.55	4.91	0.99
10	15.96	5.64	15.75	5.22	1.01
12	17.52	6.02	17.44	5.86	1.00
16	18.42	6.10	18.26	5.84	1.01
24	19.17	6.16	19.88	6.20	0.96
36	25.36	7.69	25.61	7.33	0.99
48	24.56	7.17	24.72	7.07	0.99
72	25.11	7.00	24.95	6.47	1.01
96	24.13	6.12	24.38	6.34	0.99
144	21.33	5.19	21.69	5.06	0.98
240	15.83	5.42	15.91	3.91	1.00
312	12.01	4.03	12.00	3.42	1.00
408	8.03	3.22	7.99	2.97	1.00
576	3.19	2.70	3.05	2.56	1.05
744	0.98	1.79	0.95	1.72	1.03

MEAN1=Test MEAN2=Reference MEAN12=Mean T/R

Table #17
Summary of Pharmacokinetics Parameters (Norfluoxetine)
in 37 Subjects Following 20 mg Oral Dose of
Fluoxetine HCL Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	8006.11	2446.93	7998.19	2248.36	1.00
AUCI	8879.86	2525.93	8909.65	2338.41	1.00
CMAX	27.13	7.25	26.88	6.80	1.01
KE	0.005	0.001	0.005	0.001	1.01
THALF	159.35	41.13	160.14	40.04	1.00
TMAX	64.22	41.97	69.08	33.87	0.93
*LAUCT	7596.51	0.35	7637.87	0.33	0.99
*LAUCI	8505.10	0.31	8566.02	0.30	0.99
*LCMAX	25.96	0.32	25.83	0.31	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR

* The values represent the geometric means (antilog of the means of the logs).

Table #18
LSMeans and 90% Confidence Intervals
(Norfluoxetine)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCT	8011.62	7999.22	97.89	102.42
AUCI	8886.73	8912.65	97.72	101.69
CMAX	27.12	26.88	98.60	103.20
*LAUCT	7596.30	7633.20	97.02	102.08
*LAUCI	8507.05	8564.17	97.34	101.37
*LCMAX	25.95	25.81	98.19	102.91

LSMEAN1=LS mean test LSMEAN2=LS mean ref.
 Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
 UNIT: AUC=NG HR/ML CMAX=NG/ML
 * The values represent the geometric means (antilog of the means of the logs).

Table #19
Test/Reference Products Ratios for
Pharmacokinetic Parameters for Individual Subjects
(Norfluoxetine)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
-----	-----	-----	---------	---------	---------	---------	-------	----------

1=Test product 2=Reference product

Table #20
Summary of Mean and SD of Individual T/R Ratios
(Norfluoxetine)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	37	1.00	0.09		
RAUCI12	37	1.00	0.07		
RCMAX12	37	1.01	0.08		
RTMAX12	37	1.00	0.48		
RKE12	37	1.01	0.11		
RTHALF12	37	1.00	0.12		

1. The mean plasma norfluoxetine levels reached a maximum level of concentration around 36.0 hours (Table #16 and the attached Figures #3&4). Mean blood levels-time profiles were comparable between the test and reference products under the same conditions.
2. The arithmetic test/reference mean ratios for AUC_{0-t} , AUC_{0-inf} and C_{max} were 1.00, 1.00 and 1.01, respectively. The geometric test/reference mean ratios for AUC_{0-t} , AUC_{0-inf} and C_{max} were 0.99, 0.99 and 1.01, respectively (Table #17). The 90% confidence intervals for the log-transformed AUC_{0-t} , AUC_{0-inf} and C_{max} were within the acceptable range of (Table #18).

There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC and C_{max} .

3. The average values of $T_{1/2}$, T_{max} and K_{e1} for the test product were comparable to the reference product values (Table #17).

IV. FORMULATION

Barr's formulation of its drug product, Fluoxetine HCL Capsules, 20 mg is presented in Table #21

Table #21
Formulation Comparison

Ingredients	mg/capsule
Fluoxetine Hydrochloride	22.4*
Lactose Monohydrate, NF (Fast-Flo)	
Microcrystalline Cellulose, NF (Avicel® PH-101)	
Starch, NF (Corn Starch-Purity 21)	
Stearic Acid, NF (Hystrene)	
Total Weight	mg/dose

*22.4 mg of Fluoxetine Hydrochloride is equivalent to 20 mg Fluoxetine
For the capsule shell components list (see page 07-00005, vol. C1.8).

V. COMMENT:

Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Barr's Fluoxetine HCL Capsules, 20 mg and the reference product, Eli Lilly's Prozac® Capsules, 20 mg are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} for Fluoxetine and Norfluoxetine were all within the acceptable range of $\pm 10\%$. However, the submission has been found incomplete by the Division of Bioequivalence for the deficiencies cited below.

VI. DEFICIENCIES:

1. Limited Food Effect Study:

Due to the fact that the labeling of reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug". Therefore, a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under fasting and non-fasting conditions.

The single-dose post-prandial bioequivalence study using a three-way crossover study design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

Note: A standard breakfast should be as follows:

- one buttered English muffin
- one fried egg
- one slice of American cheese
- one slice of Canadian bacon
- one serving of hashed brown potatoes
- eight fluid ounces (240 mL) of whole milk
- six fluid ounces (180 mL) of orange juice.

2. The following items are missing from the submission:

- a. Provide the Stability data regarding effect of room temperature during handling of the samples.
- b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products, in addition to the date of manufacturing the test product should be included.

3. Submit a comparative dissolution study for both the test and reference drug products, performed simultaneously. The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number that was used in the in vivo bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis.
4. The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:
 - * A dose of 20 mg/day , administered in the morning, is recommended as the initial dose.
 - * Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.
 - * Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.In the study, the firm administered three capsules of 20 mg fluoxetine at the same time to each subject. Therefore, the firm should respond to the following item:
 - a. The rationale of administering dosage which is three times higher than the recommended dose.
5. Provide a brief description on the analytical methodology procedure.

II. RECOMMENDATION:

The in vivo Bioequivalence study conducted by Barr Laboratories under fasting conditions on its test product, Fluoxetine Hydrochloride Capsules, 20 mg, (Lot #5R87719) versus the listed reference product, Prozac^R Pulvules, 20 mg (Lot #8AM94A), manufactured by Eli Lilly has been found to be incomplete by the Division of Bioequivalence for the deficiencies cited above (#1-5).

The firm should be informed of the deficiencies and recommendations.

/S/

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

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/

5/15/96

Concur: */S/* Date: *5/15/96*
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-803 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658
(Mhatre, Wahba), Drug File, Division File
ZWahba/041596/051496/file #74803s.d95

Figure #1 Linear Plot of Mean Plasma Fluoxetine Concentrations vs Time

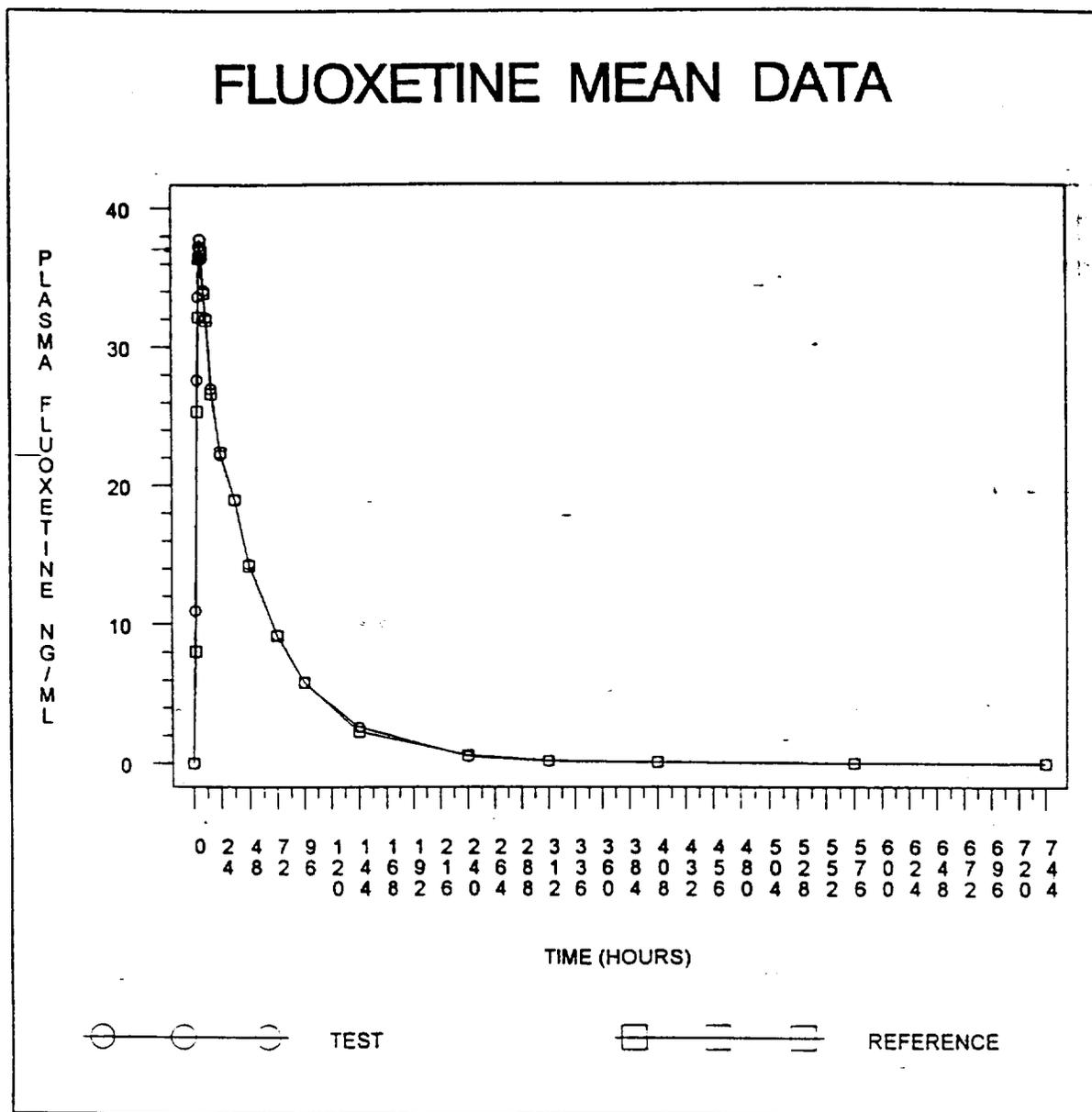


Figure # 2 Semi-logarithmic Plot of Mean Plasma
Fluoxetine Concentrations vs Time

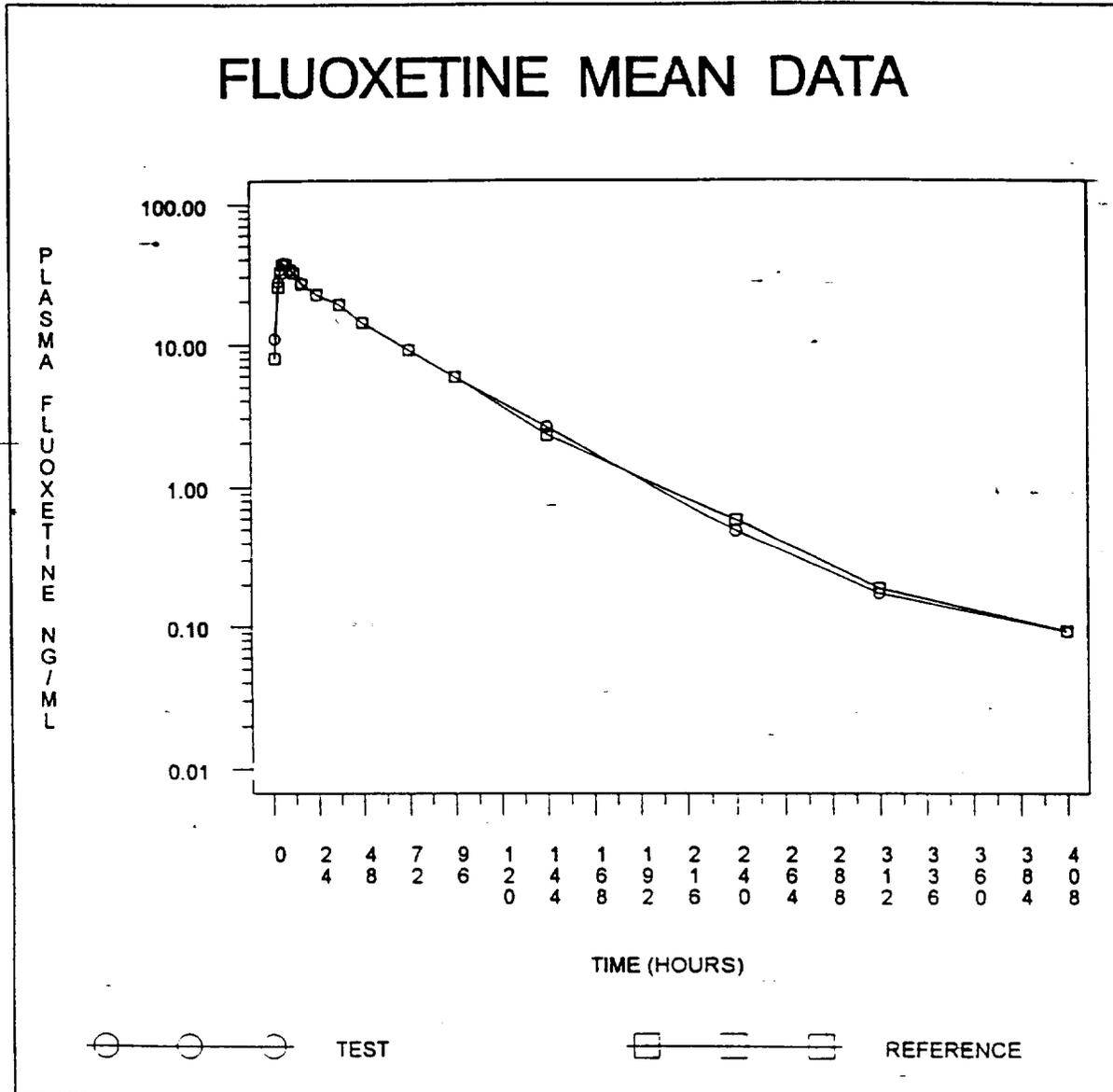


Figure #3 Linear Plot of Mean Plasma Norfluoxetine Concentrations vs Time

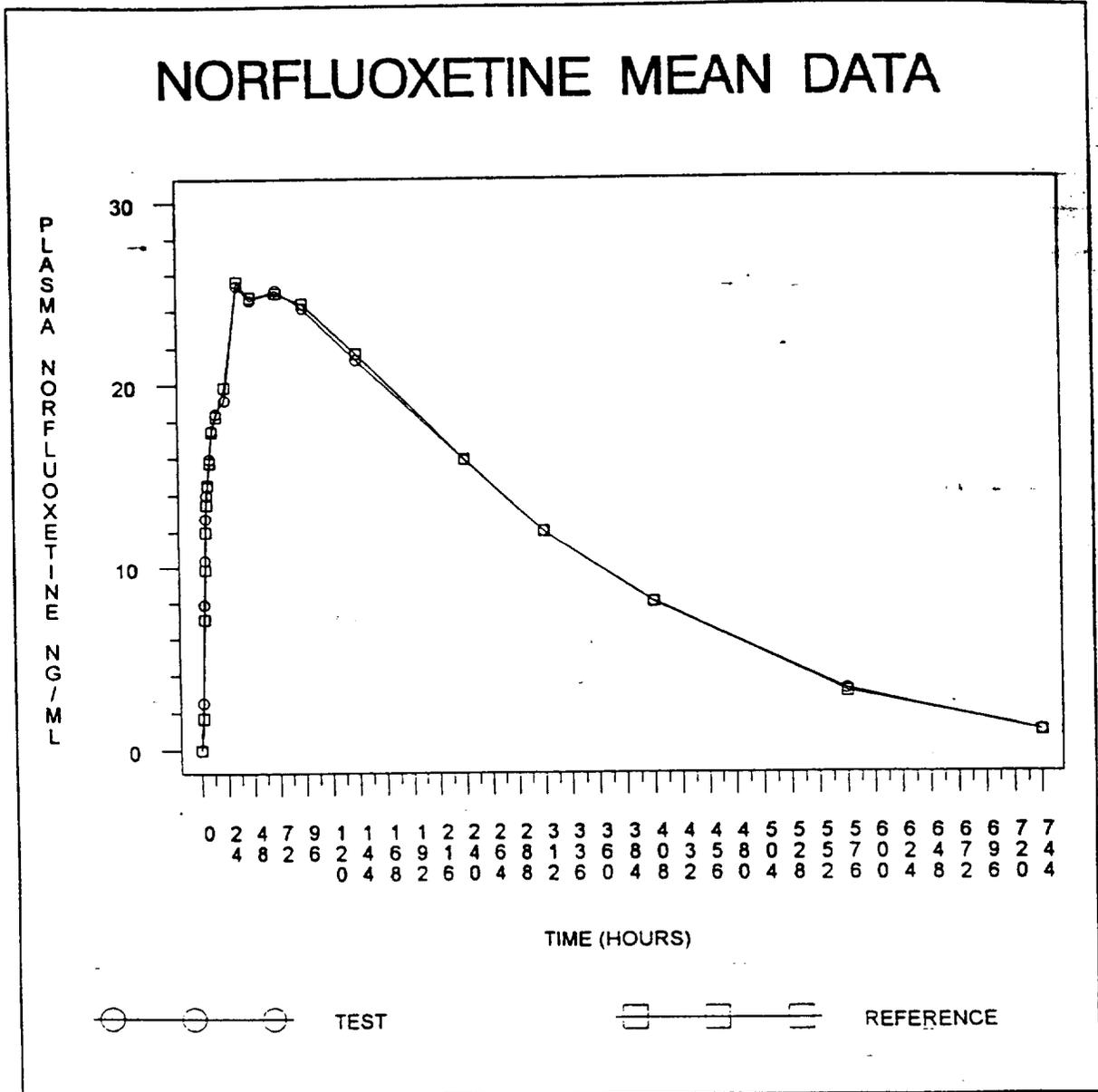
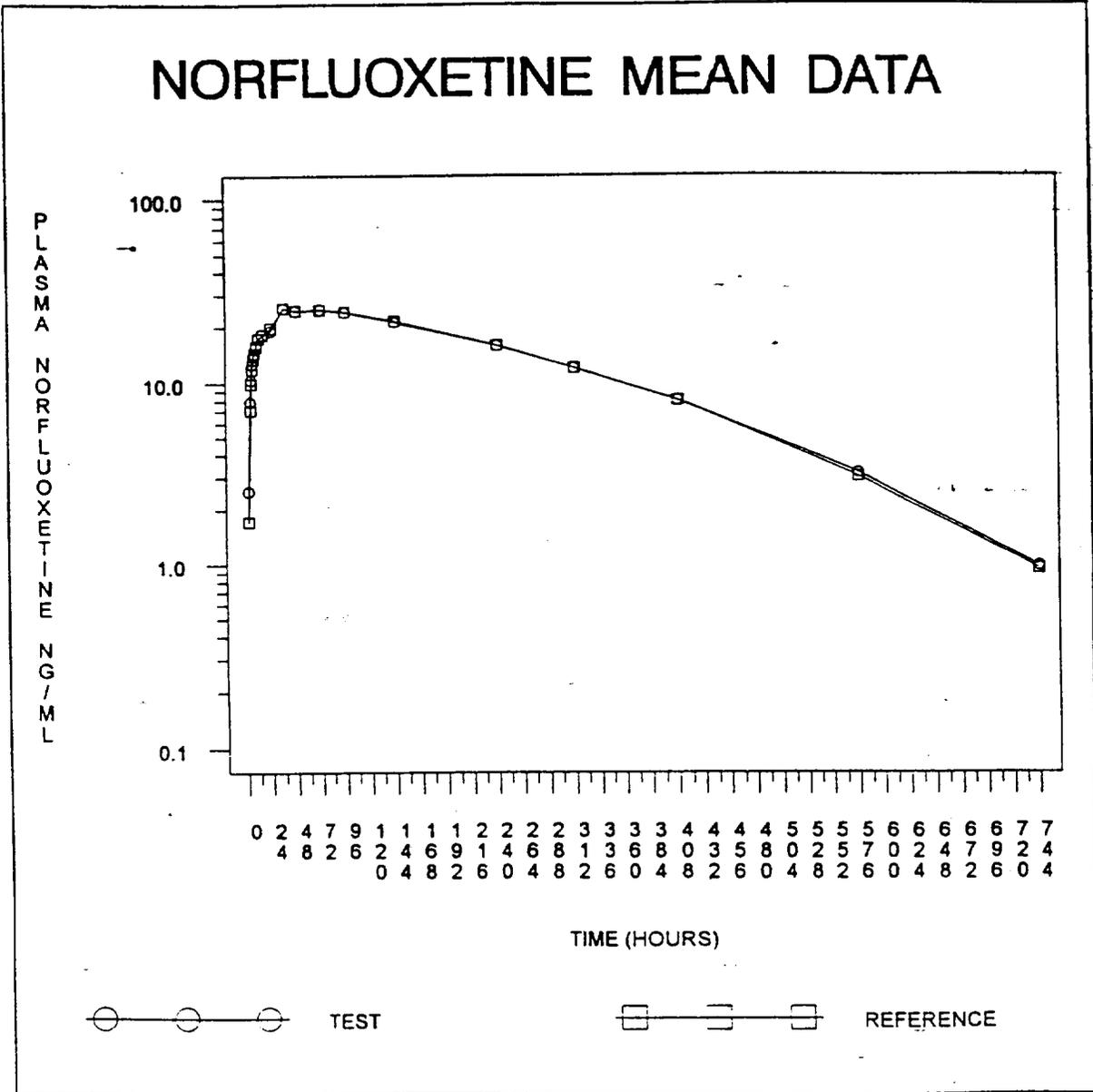


Figure #4 Semi-logarithmic Plot of Mean Plasma Norfluoxetine Concentrations vs Time



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74803

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

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

DATE: August 2, 2001

FROM: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

151
8/2/01

SUBJECT: ANDA 74-803
Fluoxetine Hydrochloride Capsules
Barr Laboratories, Inc.

TO: The Record Regarding U.S. Patent No. 6,258,853

July 10, 2001, U.S. Patent No. 6,258,853 (the '853 patent) was issued to Stowell, et.al. The abstract of the patent states "The present invention relates to novel pharmaceutical formulations and methods of using Form A of fluoxetine hydrochloride" .

On July 18, 2001, aai Pharma (aai) submitted a letter to the Agency under 21 C.F.R. 314.53(f) to advise the agency that the holder of NDA 18-936, Eli Lilly & Co. (Lilly) for Prozac® (fluoxetine hydrochloride) has failed to submit required patent information under 21 U.S.C. 355(c)(2) with respect to the '853 patent. aai claims that the patent meets all the legal requirements for listing and that Lilly must list the patent in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). aai requested that FDA contact Lilly to confirm the correctness of Lilly's omission of information with respect to the '853 patent. aai also stated that FDA has an obligation to effect the Congressional intent of protecting patent owner rights whether or not the patent owner or licensee is an NDA applicant.

On July 23, 2001, the FDA issued a letter to Lilly asking Lilly to review the patent challenge submitted under 314.53(f) and to confirm whether the patent information for NDA 18-936 is correct.

On July 31, 2001, Lilly replied to the FDA's July 23, 2001, letter and stated they reviewed the challenge and that the patent information contained in the Orange Book is correct. Lilly stated

that no changes need to be made to the patent and exclusivity information addendum of the Orange Book.

On August 2, 2001, the Agency fully approved applications for fluoxetine hydrochloride that were otherwise ready for approval. All scientific and regulatory issues had been resolved. All patent and exclusivity information currently listed in the Orange Book had been addressed.

The statute 21 U.S.C. 355(c)(2) states that the holder of an approved application shall file with the Secretary, the patent number and the expiration date of any patent which claims the drug for which the application was submitted, or which claims a method of using such drug, and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. Because the NDA holder, Lilly, declined to list the '853 patent, the Agency did not list the patent. The Agency's ministerial role in the patent listing process is limited. The statute requires the Agency to publish the patent after it is submitted to the Agency by the applicant. The Agency does not independently list patents, which are not submitted to it by the applicant for listing. The Agency fulfilled its ministerial role by forwarding the patent challenge submitted under 21 C.F.R. 314.53(f) for the '853 patent to the NDA applicant, Lilly.

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

ANDA Number: 74-803 Date of Submission: June 15, 1998

Applicant's Name: Barr Laboratories, Inc.

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

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. Revisions related to you previously via fax dated July 14, 1998 are preceded by an asterisk (*).

- b. Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: <http://www.fda.gov/cder/guidance/index.htm>. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

2. CONTAINER (100s) 10 mg and 20 mg

See GENERAL COMMENTS above.

3. INSERT

a. GENERAL COMMENTS

- i. See GENERAL COMMENTS above.

- *ii. Due to recent revision of the insert labeling of the reference listed drug, Prozac® (Fluoxetine) Capsules (NDA 18-936 -- Approved March 13, 1998; Revised January 1998), please make the following changes:
- iii. We recognize your intent to market this product before the patent expiration dates of the listed drug. Please note, however, that after November 21, 1999, the information regarding bulimia must be included in your labeling.
- iv. Delete "hydrochloride" throughout the text of the insert except in the following locations:
 - A). The chemical name.
 - B). The last sentence of the first paragraph.
 - C). The second paragraph.
 - D). The first sentence of the third paragraph.

b. CLINICAL PHARMACOLOGY

Absorption, Distribution, Metabolism, and Excretion

- i. Systemic Bioavailability, Second paragraph, first sentence - The capsule and oral solution dosage forms of fluoxetine are bioequivalent.
- ii. Renal Disease, last sentence - under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). [delete bold print from word "and").

c. INDICATIONS AND USAGE

Depression, third paragraph - The second sentence (The efficacy of ...) Begins a new paragraph.

d. PRECAUTIONS

i. General

- A). 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 U.S. ... were anxiety (2% in OCD), insomnia (1% in combined indications), and nervousness (1% in depression) (see Table 3, below).

- B). Altered Appetite and Weight, Last paragraph - Replace the last sentence with the following:

Patients treated with fluoxetine, 60 mg, on average lost 0.45 kg compared with a gain of .16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored throughout therapy.

- C). Seizures -- First paragraph, first sentence -- ... fluoxetine and 0.2% of patients treated ... ("0.2%" rather than "2%").

- ii. Carcinogenesis, Mutagenesis, Impairment of Fertility -- Second paragraph, last sentence - ... recommended human dose (MRHD) ...

e. ADVERSE REACTIONS

- i. Incidence in US Placebo-Controlled Clinical Trials (excluding data from extensions of trials), Table 2 - Indent the word "insomnia".
- *ii. Associated with Discontinuation in U.S. Placebo-Controlled Clinical Trials (excluding data from extensions of trials), Table 3
- A). Place (N=1108) beneath title of first column.
- B). Place (N=392) beneath title of second column.
- C). Place (N=266) beneath title of third column.
- D). Delete "Nervousness (1%)" from first column.
- E). Delete "Insomnia (1%)" and "Nausea (1%)" from second column.
- F). Revise "Rash (3%)" to read "Rash (1%)" in third column.
- iii. Other Events Observed in All US Clinical Trials.
- A). Cardiovascular System -- Rare - ... embolism,

cerebral ischemia, cerebrovascular ...

- B). Digestive System -- Rare - "biliary" rather than "bilary".
- C). Nervous System -- Frequent - "lability" rather than "liability".
- D). Skin and Appendages -- Infrequent - "eczema" rather than ecxema".
- E). Last sentence - ... disorder is the COSTART ... ("is" rather than "in").

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

f. DOSAGE AND ADMINISTRATION

Switching Patients to a Tricyclic Antidepressant (TCA):
-- Last sentence - under **PRECAUTIONS, Drug Interactions**).

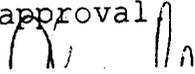
g. HOW SUPPLIED

Indicate that capsules contain fluoxetine present as fluoxetine hydrochloride.

Please revise your container labels and package insert labeling, as instructed above, and submit final print labeling.

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.

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




/S/

Jerry Phillips
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:
74803

CORRESPONDENCE

Barr Laboratories, Inc.
Attention: Herbert G. Luther, Ph.D.
2 Quaker Road
Pomona, New York 10970-0519

JUL 9 1996

Dear Dr. Luther:

This is in reference to your abbreviated new drug application dated December 9, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Fluoxetine Hydrochloride Capsules, 20 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding synthesis:

DMF has been found to be deficient. A letter has been sent to the holder identifying these issues. All deficiencies must be corrected before the approval of this application.

2. Regarding raw material controls:

- a. Please revise your specifications for Fluoxetine Hydrochloride to replace "Report Results" for Related Substances and "See Test Record for Limits" for Particle Size with specifications based on data accrued to date.
- b. Please revise your specifications for Fluoxetine Hydrochloride to include tests for Melting Point and Moisture.
- c. Since the drug substance exists as a racemic mixture, please revise your specifications to include testing for optical rotation to ensure that a racemic mixture is used.
- d. Your Assay specification (%) is not consistent with the supplier's specification of %. Please revise your specification to be consistent with the supplier or submit justification and supporting data for the wider specification.

- e. Regarding the Reference Standards for Fluoxetine Hydrochloride and Related Compounds:
 - i. Please indicate the source of reference standards for Fluoxetine Hydrochloride as well as all Related Compounds.
 - ii. Please describe any in-house qualification procedures or purification steps used for all reference standards prior to use.
 - iii. Please submit supplier and in-house (if applicable) Certificates of Analysis for your reference standards for Fluoxetine Hydrochloride as well as all Related Compounds.

- 3. Regarding manufacturing and processing:
 - a. Please revise your Master Batch Record to include the manufacturer, model, and mode of operation (Vertical or Horizontal) of the High Shear Mixer.
 - b. Please revise your Master Batch Record to include Oscillator/Mesh settings for screening the granulation.
 - c. Please revise your Master Batch Record to include the rate of encapsulation (nominal or range in capsules/hour) as well as any limits on environmental conditions (e.g. temperature, relative humidity) for the encapsulation process.

- 4. Regarding container/closure systems:
 - a. Please submit USP <671> Containers-Permeation testing results for the proposed container/closure system.
 - a. We strongly suggest that the smallest container/closure system included in the application be equipped with a child resistant closure. Please comment.

- 5. Regarding laboratory controls:
 - a. Regarding exhibit Lot #5R87719:
 - i. Please indicate the make, model and principle of operation (vertical or horizontal) of the high shear mixers.
 - ii. Please indicate nominal encapsulation speed and environmental parameters.

b. Regarding in-process controls:

- i. Please submit specifications for monitoring blend uniformity during normal production of drug product along with any applicable justification or supporting data.
- ii. Your Master Batch Record indicated that capsule fill weight will be monitored by aggregate fill weight and not individual fill weights, which will not provide control over fill weight variance. Please submit specifications for in-process monitoring of individual capsule fill weights, along with any necessary justification and supporting data to demonstrate acceptable capsule fill weight as well as fill weight variance.

c. We note that you have included copies of your validation SOP's as well as validation study results for exhibit Lot #5R87719. While the validation data submitted may be useful for clarification purposes, please note that approval of the application does not include approval of SOP's or validation protocols and reports which are the responsibility of the Field Investigator.

d. Section 1 of your Acceptance Tests for In-Process & Finished Products includes description and reference to a 10 mg capsule, which has not been included in this application. Please remove all references to the 10 mg capsule from the specifications and procedures in this application.

e. Your specifications for Related Compounds and Moisture ("Report Results") are unacceptable. Please revise these specifications to include limits based on data accrued to date.

f. Your final product specifications (Spec. #0877 - Rev. 2) fail to include Moisture as shown in the methods. Please revise the final product specifications to include Moisture or submit justification for the deletion.

6. Regarding stability:

You have indicated that a light yellow coloration was noted in the granulation where the granulation was in contact with the hard gelatin capsules for several of the samples taken during accelerated stability testing at one and three months. Close review of the individual capsule dissolution results submitted

revealed individual samples which exhibited dissolution values as low as ½ when the majority of the capsules exhibited values greater than ¾. Please discuss any possible relationship between the apparent low values for dissolution and the yellow coloration, as well as the potential for pellicle formation. All room temperature stability data accrued to date should be submitted in support of your discussion.

B. Labeling Deficiencies

1. GENERAL COMMENTS

We recognize your intent to market this product before the patent expiration dates of the listed drug. Please note, however, that after February 28, 1997, the information regarding obsessive compulsive disorder must be included in your labeling.

2. CONTAINER (100s)

The strength of this product is expressed in terms of fluoxetine, and we suggest clarifying it as such by adding an asterisk after the expression of strength on the main panel as follows:

FLUOXETINE HYDROCHLORIDE CAPSULES

20 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

*Each capsule contains: Fluoxetine Hydrochloride, equivalent to 20 mg fluoxetine.

3. INSERT

a. General

i. We recognize your intent to market this product before the patent expiration dates of the listed drug. Please note, however, that after February 28, 1997, the information regarding obsessive compulsive disorders must be included in your labeling.

ii. Italicize "*in vivo*" and "*in vitro*" where they appear in the insert labeling.

b. DESCRIPTION

- i. Regarding the use of the phrase "and other ingredients". We refer you to USP XXIII, General Information, Chapter <1091>, Labeling of Inactive Ingredients, which states that a trade secret may be omitted from the list of inactive ingredients if the list states "and other ingredients". The chapter further states that an ingredient is considered to be a trade secret only if its presence confers a significant competitive advantage AND its identity cannot be ascertained by the use of modern analytical technology. If you still elect to use the phrase "and other ingredients", please provide supporting data concerning the "trade secret" status of these ingredients, if not, revise your labeling at the time of next printing to include all ingredients in the list of inactive ingredients. Also, include any dye(s) with your listing of inactive ingredients.
- ii. Revise the first sentence in the third paragraph to read "Each capsule, for oral administration, contains...".

c. CLINICAL PHARMACOLOGY (Clinical Trials)

Revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this subsection.

d. INDICATIONS AND USAGE

- i. Delete the subsection heading, "Depression".
- ii. Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.

e. CONTRAINDICATIONS

- i. Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.
- ii. Make the following revision in the penultimate sentence, "...within a minimum of...".

iii. Make the following revision in the last sentence, "...doses [see *Accumulation and Slow Elimination* under **CLINICAL PHARMACOLOGY**]) should...".

f. WARNINGS

In the last sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride".

g. PRECAUTIONS

i. Except in the following locations, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

- the first sentence of this section.
- the "Suicide" subsection of the "General" subsection.
- the first sentence of the "Use in Patients with Concomitant Illness" subsection of the "General" subsection.
- the "Pregnancy" subsection.

ii. Revise the "Other Antidepressants" subsection of the "Drug Interactions" subsection as follows:

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

iii. Drug Interactions (Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins)

Revise to read "...warfarin...", rather than "...Coumadin...".

iv. Nursing Mothers

Make the following revision in the last sentence, "...were 340 ng/mL...".

v. Usage in Children

Revise the section heading to read, "Pediatric Use" and make the following revision, "...in pediatric patients have...".

h. ADVERSE REACTIONS

i. Except in the following locations, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

- the first sentence of the "Commonly Observed" subsection.
- the first sentence of the "Associated with Discontinuation of Treatment" subsection.
- the penultimate subsection title.

ii. Incidence of Controlled Clinical Trials

- A) Revise the first sentence to read, "The table that follows enumerates...".
- B) Make the following revision in the first sentence of the second paragraph, "...that these figures cannot...".
- C) Delete the title, "TABLE I".

iii. Other Events Observed During Premarketing Evaluation of Fluoxetine Hydrochloride

- A) Make the following revision in the third sentence of the second paragraph, "...already listed in the table, those...".
- B) Use formatting to increase the prominence of the terms, "frequent", "infrequent", and "rare".

iv. Postintroduction Reports

Revise as follows:

...the following: aplastic anemia, atrial fibrillation, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, priapism, pulmonary embolism, QT prolongation, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

i. DRUG ABUSE AND DEPENDENCE

Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.

j. OVERDOSAGE

Except in the third paragraph of the "Management of Overdose" subsection, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride".

k. DOSAGE AND ADMINISTRATION

i. Delete the subsection heading "Depression". Please note that "Initial Treatment" and "Maintenance/ Continuation/Extended Treatment" should appear with the same prominence as other subsections.

ii. Add the following text as the last two subsections:

Switching Patients to a Tricyclic Antidepressant (TCA):

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see *Other Antidepressants* under Drug Interactions of PRECAUTIONS).

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).

1. HOW SUPPLIED

Clarify that "20 mg" is equivalent to 20 mg fluoxetine and not of fluoxetine hydrochloride.

Please revise your container labels and package insert labeling, as instructed above, and submit final print labeling.

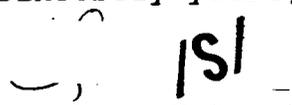
To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a

separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,


Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

7/5/96

ANDA 74-803 ✓
75-810

MAR 16 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

Dear Madam:

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

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

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

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

Sincerely,

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

ISI
for
3/16/2001

Ves...
JUN 10 1996

Barr Laboratories, Inc.
Attention: Herbert G. Luther
2 Quaker Road
Post Office Box D2900
Pomona, NY 10970-0519

|||||

Dear Dr. Luther:

Reference is made to the Abbreviated New Drug Application, submitted on December 9, 1995, for Fluoxetine Hydrochloride Capsules, 20 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Regarding the single dose fasting study, please provide the following information which was missing from the submission:
 - a. Stability data regarding the effect of room temperature storage during handling of the samples.
 - b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products. In addition, the date of manufacture of the test product should be included.
2. The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:
 - * A dose of 20 mg/day, administered in the morning, is recommended as the initial dose.
 - * Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.
 - * 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.

In your study, three capsules of 20 mg fluoxetine were administered to each subject. Please explain the rationale

for administering a dosage which is three times higher than the recommended starting dose.

3. Provide a brief description on the analytical methodology procedure.
4. Due to the fact that the labeling of the reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug", a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under both fasting and non-fasting conditions.

The single-dose post-prandial bioequivalence study should use a three-way crossover design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

Note: The standard breakfast should be as follows:

- one buttered English muffin
- one fried egg
- one slice of American cheese
- one slice of Canadian bacon
- one serving of hashed brown potatoes
- eight fluid ounces (240 mL) of whole milk
- six fluid ounces (180 mL) of orange juice.

5. Please submit a comparative dissolution study for both the test and reference drug products, performed as part of the same experiment (within 8-10 working days). The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number that was used in the *in vivo* bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter.

Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Handwritten signature of Keith K. Chan, consisting of a stylized 'K' and 'C' above the letters 'S' and 'I'.

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

NAI
"Methods Validation
information" [Signature]
3/4/96 file
2/5/96

BIOAVAILABILITY

NEW CORRESP.

February 22, 1996

NC

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

RECEIVED

FEB 23 1996

GENERIC DRUGS

**REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg
ADDITIONAL COPIES (3) OF ANALYTICAL METHODS & VALIDATION**

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg.**

The following response is to your letter dated *February 21, 1996* in which the following is stated:

However, in the interim, please submit three additional copies of the analytical method and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

RESPONSE:

Three additional copies of the analytical methods and validation reports for the bulk active ingredient and finished product are provided as separately bound review (red) copies. The following information is enclosed:

[Signature]

....continued

REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

Page 2

XVI. ANALYTICAL METHODS

1. **Methods for New Drug Substance**
 - a. **Test Methods, Specifications and Data**
 - b. **Method Validation**

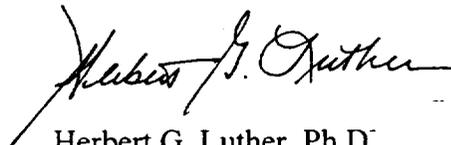
2. **Methods for Finished Drug Product and Stability Testing**
 - a. **Test Methods, Specifications and Data**
 - b. **Method Validation**

The above referenced items are duplicates of Section XVI, Pages 16-00001 to 16-00179 of our original Application. The three review copies contain this cover letter with a complete duplicate copy of Section XVI. The archival copy consists solely of the cover letter, since this information was previously submitted in the original application.

This completes the response to the comment in the Agency's letter dated *February 21, 1996*.

Sincerely,

BARR LABORATORIES, INC.



Herbert G. Luther, Ph.D.
Director Scientific Affairs



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

NAT
"Patent Notice"
[Signature]
4/5/96

March 13, 1996

ORIG NEW CORRES

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

RECEIVED

MAR 14 1996

GENERIC [unclear]

**REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg**

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg**.

At this time, we hereby amend our Application by certifying that Barr Laboratories, Inc., on February 28, 1996, served Eli Lilly & Co. (the patent and NDA holder) with the required Notice in accordance with 21 U.S.C. 355(j)(2)(B)(i) and (ii) with regard to U.S. Patent No. 4,314,081 and U.S. Patent No. 4,626,549.

This Notice met the content requirement as set forth in 21 C.F.R. 314.95(c).

This completes the present Amendment to our Application.

Sincerely,

BARR LABORATORIES, INC.

[Signature: Herbert G. Luther]

Herbert G. Luther, Ph.D.
Director Scientific Affairs

Noted
3-22-96



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

NR
"Patent Notice"
4/5/96

March 14, 1996

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

RECEIVED
MAR 15 1996
GENERIC DRUGS

**REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg
AMENDMENT TO A PENDING APPLICATION**

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg**.

At this time, we hereby amend our Application by providing evidence which verifies that Barr Laboratories, Inc., on February 28, 1996, served Eli Lilly & Co. (the patent and NDA holder) with the required Notice in accordance with 21 U.S.C. 355(j)(2)(B)(i) and (ii) with regard to U.S. Patent No. 4,314,081 and U.S. Patent No. 4,626,549.

Enclosed as Page 1 is a copy of the Return Receipt from Eli Lilly & Co. for the Notice which was delivered to Eli Lilly & Co. on March 4, 1996.

This completes the present Amendment to our Application and Patent Certification commitment as contained in our original Application, Page 1.

Sincerely,

BARR LABORATORIES, INC.

Herbert G. Luther
Herbert G. Luther, Ph.D.
Director Scientific Affairs

This Submission is comprised of **Page 1**.

Admitted

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.C.

1300 I STREET, N.W.
WASHINGTON, DC 20005-3315

202-408-4000
FACSIMILE 202-408-4400

NAI
"Patent infringed!"
JLD 8/12/96
ORIG NEW CORRES

BRUSSELS OFFICE:

AVENUE LOUISE 326, BOX 37
1050 BRUSSELS, BELGIUM
TELEPHONE 011-322-646-0353
FACSIMILE 011-322-646-2135

WRITER'S DIRECT DIAL NUMBER

202/408-4068

April 17, 1996

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1-5, TORANOMON 5-CHOME
MINATO-KU, TOKYO 105, JAPAN
TELEPHONE 011-813-3431-6943
FACSIMILE 011-813-3431-6945

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
7500 Standish Place
Rockville, Md. 20855

Via Federal Express

RECEIVED

APR 18 1996

GENERIC DRUGS

Re: Fluoxetine Hydrochloride Capsules, 20 mg
Abbreviated New Drug Application No. 74-803
Notification of Filing of Legal Action for Patent Infringement

Sir:

We represent Eli Lilly and Company ("Lilly"), owner of U.S. Patent Nos. 4,314, 081 and 4,626,549. We are sending you this letter on behalf of our client under 21 C.F.R. § 314.107(f)(2) to notify you of the following:

(1) On February 28, 1996, Mark E. Waddell of Bryan Cave L.L.P. sent a letter to Lilly by certified mail stating that the sender represented Barr Laboratories, Inc. ("Barr") and was providing information pursuant to section 505(j)(2)(B) of the Food, Drug and Cosmetic Act. The letter included the following information:

- (i) The FDA has received an abbreviated new drug application by Barr containing bioavailability or bioequivalence data or information with respect to fluoxetine hydrochloride 20 mg capsules.
- (ii) The abbreviated new drug application number is 74-803.
- (iii) The established name, as defined in section 502(e)(3) of the Food, Drug and Cosmetic Act, of the proposed drug product is fluoxetine hydrochloride capsules, 20 mg.
- (iv) The active ingredient, strength, and dosage form of the proposed drug product is fluoxetine hydrochloride, 20 mg capsules for oral administration.

Food & Drug Administration
April 17, 1996
Page 2

- (v) The patent number and expiration date, as known to Barr, of each patent alleged to be invalid, unenforceable, or not infringed is as follows:

U.S. Patent No. 4,314,081, which expires February 2, 2001, and
U.S. Patent No. 4,626,549, which expires December 2, 2003.

- (2) Lilly received the letter on or about March 4, 1996.

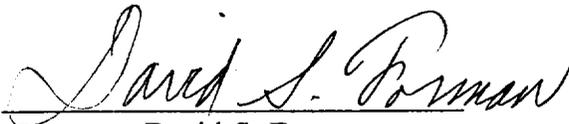
Certification

We hereby certify that on April 10, 1996, Lilly filed an action for patent infringement against Barr in the United States District Court for the Southern District of Indiana (Case Number IP96-0491 C). Lilly alleges, among other things, that under 35 U.S.C. § 271(e)(2)(A), Barr's submission to the FDA of an abbreviated new drug application to obtain approval for the commercial manufacture, use, or sale of fluoxetine hydrochloride before the expiration of United States Patent Nos. 4,314,081 and 4,626,549 was an act that infringes claim 5 of United States Patent No. 4,314,081 and claim 7 of United States Patent No. 4,626,549.

We therefore respectfully request that the approval of Barr's abbreviated new drug application shall not be made effective until at least the expiration of the thirty-month period as provided by 21 U.S.C. § 355(j)(4)(B)(iii), subject to an appropriate ruling by the court.

Yours sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By 
David S. Forman

SDR/dem

cc: Mark E. Waddell, Esq.
Jan M. Carroll, Esq.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

Handwritten signature and date: 6/2/97

June 6, 1997

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

NEW CORRESP

NC/BIO
y/m/e/B
BIOAVAILABILITY

BIOEQUIVALENCE INFORMATION

REFERENCE: ANDA 74-803
FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg
AMENDMENT TO A PENDING APPLICATION

Reference is made to our pending Abbreviated New Drug Application dated *December 9, 1995* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg.**

The following response is to your letter dated *June 10, 1996* in which the following is stated:

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration.

COMMENT:

1. Regarding the single dose fasting study, please provide the following information which was missing from the submission:
 - a. Stability data regarding the effect of room temperature storage during handling of the samples.

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JUN 09 1997

GENERIC DRUGS

cont...

Handwritten note: *McDermott 6-19-97*

REFERENCE:

ANDA 74-803

Page 2

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

RESPONSE:

Please note that although the original ANDA submission did contain stability data, the report did not include data regarding the effect of room temperature storage during handling of the samples. The requested data were not included in the original submission since, at the time of the study, the Agency did not require this information.

Room temperature stability was not an issue because the following in-process stability controls were included with each analytical run.

1. Standards and controls were done for each analytical run and
2. All project samples, standards, and controls for each run were handled simultaneously and were processed simultaneously.

currently includes room temperature stability as part of their validation procedures and revalidated the assay as of March 1997. Barr is submitting in this application the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" at pages 1 to 2158. data regarding the effect of room temperature storage during handling of the samples for both the "Single Dose Fasting Study" and the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg" are found at pages 1582 to 1583. These stability data show that fluoxetine and norfluoxetine are stable for at least 4 hours in room temperature plasma. The data are included in

Method Validation Report LC105.1 Revision 1 entitled: Analysis of Fluoxetine and Norfluoxetine in Human Plasma (Sodium Heparin) dated March 1997 found in Appendix C to the Final Analytical Report at pages 1556 to 1661 of this submission.

- Table 7A Room Temperature Stability for Fluoxetine see page 1582
- Table 7B Room Temperature Stability for Norfluoxetine see page 1583

- b. The batch/lot size for the test product, the assay potency and content uniformity data for both the test and reference products. In addition, the date of manufacture of the test product should be included.

REFERENCE:

ANDA 74-803

Page 3

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

RESPONSE:

The biobatch size for Barr Laboratories, Inc. test product Fluoxetine Hydrochloride Capsules, 20 mg Batch # 5R88719 used in the bioequivalence study entitled: "Single Dose Fasting Study" (and also in the "Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg"; see response to Comment 4) was capsules (page 12-00003; Exhibit 1). The batch size information is also found on the Master Formula in the original application on pages 11-00015 (unexecuted) and 12-00004 (executed) and are included again for your convenience in Exhibit 1 (pages 11-00015 and 12-00004).

The assay potency and content uniformity data for both the test and reference products were also submitted in original ANDA pages 06-02589 to 06-02592 and are included again for your convenience in Exhibit 2. The assay potencies for Barr Fluoxetine Hydrochloride Capsules, 20 mg, Batch #5R87719 and Dista Prozac®, 20 mg Pulvule Lot # 8AM94A were 99.1% and 100.6%, respectively. The content uniformity data were: $\bar{x} = 99.0\%$ (95.7% to 103.4%) RSD = 2.30% for same Barr, and $\bar{x} = 99.9\%$ (98.3% to 101.5%) RSD = 0.85% for Dista, respectively. The date of manufacture of the test product was the date of mixing 6/28/95 (12-00006; Exhibit 2) while the encapsulation date was 7/6/95 to 7/7/95 (12-00009 to 12-00010; Exhibit 2).

COMMENT:

2. The Physician's Desk Reference (PDR), 49 Ed. (pages 943-947) report the following statements:
 - A dose of 20 mg/day, administered in the morning, is recommended as the initial dose.
 - Studies comparing fluoxetine 20, 30, 40 and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response.

cont...

REFERENCE:

ANDA 74-803

Page 4

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

- 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.

In your study, three capsules of 20 mg fluoxetine were administered to each subject. Please explain the rationale for administering a dosage which is three times higher than the recommended starting dose.

RESPONSE:

Barr Laboratories, Inc. was aware of the recommended dosing for fluoxetine (a dose of 20 mg administered once or twice a day up to a maximum dose of 80 mg/day) included in the PDR (pages 943-947) 49 Ed (at pages 2159 to 2163 of this submission). The determination to dose three capsules of the Fluoxetine Hydrochloride Capsules, 20 mg, a dosage three times higher than the recommended starting dose, was selected after careful evaluation of the following considerations.

During preliminary consideration of the appropriate design and dose selection for the bioequivalence study, FDA input was solicited on 4/18/95 when Barr Laboratories, Inc. submitted a written request for a bioequivalence guidance for Fluoxetine Hydrochloride Capsules.

- **NOTE: BARR PROPOSED TO USE A SINGLE 60 MG DOSE (3 X 20 MG CAPSULES OF FLUOXETINE HYDROCHLORIDE in the 4/18/95 Fax Transmission from Herb Luther, Barr Laboratories, Inc. to Mr. Jason Gross, CSO, Division of Bioequivalence, OGD, FDA. The Fax page was a cover for the 4/18/95 Barr letter requesting FDA comments and recommendations for bioequivalence studies for which FDA has no published guidelines. Dr. Luther's communication was specifically directed to the drug product Fluoxetine Hydrochloride Capsules (Prozac®) (at pages 2164 to 2166).**
- **On 4/28/95 the FDA (at pages 2167 to 2168) responded to the 4/18/95 request for bioequivalence guidance for Fluoxetine Hydrochloride Capsules. The 4/28/96 FDA guidance Reference No. Bio 95-060 included the following points.**

cont...

REFERENCE:

ANDA 74-803

Page 5

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

- Reviewed the potential need for a long washout period, (i.e., a minimum of at least 7 half-lives for the most slowly eliminated analyte (M-1) which would correspond to 9.2 weeks using the sponsor's values.
- Confirmed the dosing regimen to be within federal requirements. After an appropriate interval doses above 20 mg/d may be administered on a once a day or twice a day schedule and should not exceed a maximum dose of 80 mg/day. No IND is required since the proposed dose of 60 mg does not exceed the maximum single total daily dose of 80 mg 21 CFR 320.31 (b)(i).
- Note: The 4/28/95 FDA bioequivalence guidance for Fluoxetine Hydrochloride Capsules failed to mention the need for a limited food effect study to be conducted.
- Barr Laboratories, Inc. reviewed data obtained from a previous study experience with the 60 mg single dose conducted by _____ (at pages 2169 to 2177). No significant deleterious adverse effects or any adverse effects of any general interest were noted (verbal communication).
 - Fluoxetine and Norfluoxetine plasma levels following administration of a single oral dose of fluoxetine Hydrochloride 60 mg, i.e., single dosing with three 20 mg capsules of Prozac® were compared with single dosing of three 20 mg capsules Apo-fluoxetine 20 mg capsules (pages 2169 to 2175).
 - In this study, the limit of detection for fluoxetine was established as below 1.0 ng/mL and the limit for norfluoxetine was established as between 1.0 and 2.0 ng/mL (page 2176). The lower limits of quantification were retrospectively set for fluoxetine and norfluoxetine at 2 and 5 ng/mL, respectively (page 2177).
- The 1995 PDR 49 ed (PDR pages 943 to 947; pages 2159 to 2163 this submission) and the AHFS 95 Drug Information (pages 1483 to 1494; pages 2178 to 2191 this submission) report a 40 mg dose of fluoxetine may provide a C-max of 15-55 ng/mL over a range of 1.5 to 12 hours after oral administration. The _____ data, using a study design of a 60 mg single dose (at page 2169) also transmitted as a personal communication to _____ reported a fluoxetine C-max of 40.96 +/-8.7 ng/mL and a

cont...

REFERENCE:

ANDA 74-803

Page 6

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

norfluoxetine C-max of 22.6 +/- 8.2 ng/mL after the single 60 mg oral dose. The analytical laboratory for the study reported their lower limit of quantitation (LLOQ) would "probably" be 1 ng/mL (6/20/96 letter at pages 2192 to 2193).

- Both the Physicians Desk Reference (pages 2159 to 2163) and the AHFS, (pages 2178 to 2191) indicated that variable blood concentrations could be expected to occur after dosing with fluoxetine. Since the expected LLOQ was 1 ng/mL and the metabolite could very conceivably produce data which might not exceed peak levels of 10 ng/mL, a 40 mg dose was deemed unacceptable and the dose of 60 mg was selected. Barr Laboratories, Inc. and investigators, medical personnel and IRB all agreed to proceed with the 60 mg dose.
- Barr Laboratories also consulted with the selected to dose the bioequivalency study and shared all of the above data with them (6/20/96 letter at pages 2192 to 2193).
- The medical team working with had excellent previous experience working with this product within the full range of doses allowed under labeling. Neither the medical investigators, medical colleagues, clinical investigators, or IRB had any concerns with the 60 mg dose beyond potential drowsiness or dizziness. All usual and customary precautions were taken to monitor for either the drowsiness or dizziness response. (6/20/96 letter at pages 2192 to 2193).

In summary, Barr Laboratories, Inc. and reviewed all of the data contained in the above paragraphs and in the FDA response to the protocol submitted to the FDA and concluded that administration of the single 60 mg dose of fluoxetine, using Fluoxetine Hydrochloride Capsules, 20 mg, fulfilled the FDA scientific and regulatory requirements.

COMMENT:

3. Provide a brief description on the analytical methodology procedure.

cont...

REFERENCE:

ANDA 74-803

Page 7

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

RESPONSE:

The analytical methodology used for Barr's Fluoxetine 20 mg Capsule fasting study is entitled "LC105.1- Analysis of Fluoxetine and Norfluoxetine in Human Plasma." A brief summary of this follows. A 1.0 mL sample volume is required for analysis. The sample is kept frozen at -20°C prior to analysis. At the time of analysis fluoxetine, norfluoxetine and the internal standard protryptiline are extracted from basic, heparinized human plasma using hexane/isoamyl alcohol. The compounds are then acid back-extracted into % phosphoric acid. separation is achieved by reverse phase on a column. Fluorescence detection with an excitation wavelength of 230 nm and an emission wavelength of 305 nm is used to detect fluoxetine and norfluoxetine. This method is validated with a minimum quantifiable level of ng/mL for fluoxetine and ng/mL for norfluoxetine. The upper level is ng/mL for each analyte. A linear weighted (1/concentration squared) least squares regression analysis is used to quantitate unknown samples.

COMMENT:

4. Due to the fact that the labeling of the reference listed drug (RLD) indicates that the drug may be administered with or without food and also "food does not appear to affect the systemic bioavailability of the drug", a food study is required for this product to demonstrate that the generic formulation will behave similarly to the RLD formulation under both fasting and non-fasting conditions.

The single-dose post-prandial bioequivalence study should use a three-way crossover design comparing equal doses of the test and reference products. The study should be conducted in a random, three-treatment (Treatments 1&2: the test and reference products should be dosed immediately after standard breakfast, Treatment 3: the test product should be dosed under fasting conditions), three-period, cross-over design using a minimum of 18 healthy subjects. An adequate wash-out period between periods 1, 2, and 3 dosing should be applied.

cont...

REFERENCE:

ANDA 74-803

Page 8

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

Note: The standard breakfast should be as follows:

one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hashed brown potatoes
eight fluid ounces (240 mL) of whole milk
six fluid ounces (180 mL) of orange juice

RESPONSE:

“A Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg” was conducted by _____ Protocol # _____ (at pages 1 to 2158). The study was a randomized, single dose, three-way crossover design involving 24 healthy male subjects under non-fasting conditions. The standard breakfast as described in Comment 4 above was administered to the test subjects. The study compared Fluoxetine Hydrochloride Capsules, 20 mg by Barr Laboratories, Inc. Lot # 5R87719, Expiration date none available, with Prozac® 20 mg Pulvules® by Dista Products Company, A Division of Eli Lilly Industries, Inc. (A subsidiary of Eli Lilly & Company) Lot # 8AM94A, Exp. date: Oct 1, 1997.

Please note that the same Barr Batch # 5R88719 and the same Dista Lot # 8AM94A, Exp. Date October 1, 1997, were also used to dose volunteer subjects enrolled in both bioequivalence studies, i.e., in the “Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg” (pages 1 to 2158) and in the “Single Dose Fasting Study” (original ANDA pages 06-00006 to 06-00030D, Exhibit 3; pages 2194 to 2195).

The study dates for the “Limited Food Effects Study of Fluoxetine Hydrochloride Capsules, 20 mg” were:

cont...

REFERENCE:

ANDA 74-803

Page 9

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

- Period 1: August 10 through September 08, 1996
Period 2: October 12 through November 10, 1996 and
Period 3: January 04 through February 02, 1997.

An adequate washout period between periods 1 and 2 and 2 and 3 was applied as per the 4/28/95 FDA bioequivalence guidance for Fluoxetine Hydrochloride Capsules. The OGD recommended a minimum washout period of at least seven half lives for the most slowly eliminated analyte (M-1 in this case). This would correspond to 9.2 weeks using the sponsor's values (pages 2167 to 2168). The elapsed times between each dosing period are cited below.

- ◆ Dosing Date Aug. 10, 1996 Period 1 and Dosing Date Oct. 12, 1996 Period 2 = elapsed time of 9 weeks
- ◆ Dosing Date Oct. 12, 1996 Period 2 and Dosing Date Jan 04, 1997 Period 3 = elapsed time of 12 weeks

Thus, an adequate wash out period varying between 9 and 12 weeks existed between periods 1 and 2 and 2 and 3, respectively.

In conclusion, the data included in the present submission indicate that Barr Laboratories, Inc. Fluoxetine Hydrochloride Capsules, 20 mg, behaved similarly to the Dista Products Company Prozac® 20 mg Pulvules under both fasting (at original ANDA pages 06-00038 to 06-00039; Exhibit 4) and non-fasting conditions (at pages 5 and 6 of this submission; also included in Exhibit 4 for your convenience). Food did not appear to effect the systemic bioavailability of the drug and thus Barr Laboratories, Inc. drug may be administered with or without food. This fact is indicated in the labeling of our generic product and agrees with the labeling for the referenced listed drug.

COMMENT:

5. Please submit a comparative dissolution study for both the test and reference drug products, performed as part of the same experiment (within 8-10 working days). The dissolution data should include the number of capsules (not less than 12), type and volume of the medium, the method that has been used, and the date the testing was performed. The dissolution testing should be done on capsules from the same lot number

cont...

REFERENCE:

ANDA 74-803

Page 10

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

that was used in the *in vivo* bioequivalence study. The comparative dissolution profiles (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (% C.V.), and date(s) of analysis.

RESPONSE:

The original ANDA submission contained the Analytical Research and Development In-Vitro Comparative Study for Barr Fluoxetine Hydrochloride Capsules, 20 mg Lot # 5R87719 (Pages 06-02589 to 06-02592, Exhibit 2). This report also includes the dissolution testing done on Dista Prozac® 20 mg Pulvules Lot # 8AM94A.

This report contains the comparative dissolution study for both the test and reference drug products performed as part of the same experiment (conducted on 7/11/95 for the test product and 6/3/95 and 6/27/95 for the reference product (page 06-02590; Exhibit 2). Barr Laboratories, Inc. acknowledges that the time between the comparative dissolution testing of the test and the reference products is more than 8 to 10 days; however, Barr has now instituted a new SOP requiring all dissolution testing to be done within the required 8 to 10 days.

The in-vitro comparative dissolution study indicates that 12 capsules were used from each product, describes the type and volume of the medium employed as 900 mL of 0.1 N HCL, and indicates that the dissolution testing was performed using USP 23 Dissolution Applications II (paddles) following the procedure as described in Barr Method TM-419.

Both testing methods and the updated were included in the original submission. Since the original ANDA submission, Barr has revised the analytical method to at pages 2196 to 2218 in this submission.

The dissolution testing was done on capsules from the same lots that were used in the *in vivo* bioequivalence studies. This fact is documented in our response to Comment # 4.

REFERENCE:

ANDA 74-803

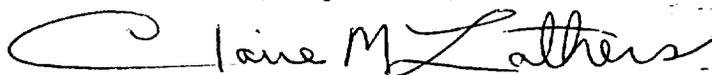
Page 11

FLUOXETINE HYDROCHLORIDE CAPSULES, 20 mg

This completes the present response to the Agency's letter dated June 10, 1996 and a copy is attached as per your instructions.

Sincerely,

BARR LABORATORIES, INC.



Claire M. Lathers, Ph.D., F.C.P.
Chief Scientific Officer

This Submission is comprised of **Pages 1 to 2218 and Exhibits 1 to 4.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 29, 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, Maryland 20855-2773

BIOAVAILABILITY

ORIG AMENDMENT

N/AB

BIOEQUIVALENCY AMENDMENT

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for.

Reference is also made to Barr's bioequivalency data submitted on 6/6/97 and to your letter dated January 8, 1998 in which the following is stated:

COMMENT:

Your dissolution testing of the test product in 900 ml of 0.1N HCL, using USP 23, apparatus II (paddle), at 50 rpm is not acceptable.

Please conduct the dissolution testing in 900 ml of water, using USP 23, apparatus II (paddle), at 50 rpm with valid assay methodology.

The dissolution results should meet the following specifications: Not less than % of the labeled amount of the drug (Fluoxetine) in the dosage form is dissolved in 30 minutes.

Note: The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot numbers of the samples undergoing dissolution testing should be identical to those used in the in-vivo study. The dissolution profile for the test and reference products should include dissolution time points below and above the specification time point (30 minutes).

RECEIVED

APR 30 1998

GENERIC DRUGS

Barr Laboratories, Inc.

RESPONSE:

Barr has conducted the dissolution testing for both test and reference products using water as the dissolution medium. The lot numbers of the samples undergoing dissolution testing are identical to those used in the in-vivo study. The dissolution profile time points were 10, 15, 30 and 45 minutes.

Enclosed please find a copy of the "In-Vitro Comparative Study Report RD 98-033 for Fluoxetine Capsules, USP 20 mg, Lot number 5R87719, Manufactured by Barr Laboratories, Inc. and PROZAC®, 20 mg Lot Number 8AM94A manufactured by DISTA PRODUCTS COMPANY" dated March 2, 1998. Also please find a copy of Barr's finished product test method, TM-419F which has been updated to conform to the dissolution method proposed in the Pharmacopeial Forum, volume 23, number 2, and in response to the Agency's request.

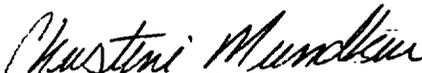
The "In-Vitro Comparative Report" contains dissolution profile, assay and content uniformity for Barr's Fluoxetine Capsules, USP by Barr and DISTA's Prozac. The results are summarized in the form of tables, and demonstrate that the two products compare favorably.

Also please find a copy of a letter from USP stating that the dissolution in Pharmacopeial Forum 23(2) was changed from % to %. The % value published in the Pharmacopeial Previews section of PF 21(4) was in error.

This completes Barr's response to the Agency's letter dated January 8, 1998. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.


Christine Mundkur

Regulatory Counsel and Director of
Regulatory Affairs

/kdb
Enc.

This Submission is comprised of Pages 01 through 38.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

June 15, 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, Maryland 20855-2773

ORIG AMENDMENT

*Labeling review N/AC
drafted 7/16/98
AVS*

MAJOR AMENDMENT

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, 20 MG AND
 SUPPLEMENTAL APPLICATION
 FLUOXETINE CAPSULES, 10 MG**

Reference is made to our pending Abbreviated New Drug Application dated December 9, 1995 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **FLUOXETINE HYDROCHLORIDE CAPSULES, 20 MG**. Please note the name change to Fluoxetine Capsules, USP 20 mg in accordance with the USP 23, Seventh Supplement monograph for this product.

This Major Amendment is being sent in response to your letter dated July 9, 1996 and to Supplement the pending application with the additional strength of Fluoxetine Capsules, USP 10 mg.

Part I: Responses to comment letter dated July 9, 1996

RECEIVED

JUN 16 1998

GENERIC DRUGS

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RESPONSE:

Barr has revised its Related Compounds specifications for Fluoxetine Hydrochloride, USP to replace "Report Results" as follows:

<u>Related Compounds Tests</u>	<u>Limits</u>	
+/- 1-Phenyl-3-methylamino-1-propanol (methaminol) (Barr Impurity I)	NMT	%
1-Phenyl-3-methylamino-propane (methamine) (Barr Impurity II)	NMT	%
p-Triflouromethylphenol (Barr Impurity III)	NMT	%
4-Chlorobenzotriflouride (Barr Impurity IV)	NMT	%
Fluoxetine Related Compound A	NMT	%
Individual Unknown Impurities	NMT	%
Total Known and Unknown Impurities	NMT	%

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Barr intends to continue to use its own validated test method for Barr Impurities I, Impurity II, Impurity III, Impurity IV, and Individual Unknown Impurities. Barr's method offers superior chromatography, yields comparable results to the USP 23, Supplement Seven method, and is capable of quantitating Barr Impurity I, Impurity II, Impurity III and Impurity IV. Barr's method of quantitation via external standardization for each impurity is more reliable than the USP method, which quantitates using area percent normalization. In addition, the USP method does not resolve Barr Impurity IV. However, Barr adopted the USP 23, Seventh Supplement Chromatographic Purity Test Method for Related Compound A since Barr's method does not resolve this compound. To calculate the Total Known and Unknown Impurities, Barr will total the impurities detected using the Barr method with the Related Compound A from the USP method. As supporting documentation for Barr's Related Compounds Tests, enclosed please find the memorandum dated 2/3/98, "Evaluation of Chromatographic purity test procedure from USP 23, Supp. 7 for Fluoxetine Hydrochloride" (Pages 0004 through 0007).

Please note that the specifications for Barr Impurity I (USP Impurity -[2-(methylamino)ethyl]-benzenemethanol) and Barr Impurity II (USP Impurity 1-Phenyl-3-methylamino-propane(methamine)) match the USP 23, Seventh Supplement specifications for these impurities. In addition, the specifications for Individual Unknown Impurities and Total Known and Unknown Impurities are identical to the USP 23, Seventh Supplement specifications.

Barr has petitioned USP to change the Fluoxetine Hydrochloride monograph specification for Total Known and Unknown Impurities from % (see attached letter to Dr. Todd Cecil, Scientist, USP dated June 10, 1998 and supporting documentation on Pages 0008 through 0038). If USP adopts the specification of % for Total Known and Unknown Impurities, Barr will update its method and specification test record accordingly and submit them in the Annual Report.

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Regarding Particle Size, Barr has revised its specifications to the following based on data accrued to date:

<u>Particle Size Test</u>	<u>Limits</u>		
	D (90%)	NMT	µm
	D (50%)	NLT	µm

Enclosed please find Barr's current Acceptance Tests for Raw Materials for Fluoxetine Hydrochloride, USP (RM-318C) and corresponding QC Raw Material Specifications & Test Record (Barr Specification No.: 01-0305, Rev. 3). These have been updated to reflect the changes noted above and to agree with USP 23, Seventh Supplement monograph for Fluoxetine Hydrochloride, USP (see Pages 0039 through 0062). Also enclosed is the method validation report (RD97-137) concluding that Barr Laboratories, Inc. related compounds test method for Fluoxetine Hydrochloride, USP is equivalent to the USP 23, Supplement 7 method for detecting and quantitating Barr Impurities I, II, III and IV (see Pages 0063 through 0096).

Also enclosed on Pages 0097 through 0098 please find a copy of the executed QC Raw Material Specifications & Test Record for Lot H362 of Fluoxetine Hydrochloride used to manufacture Barr's submission batch. This test record was submitted as supplemental pages 08-00017 through 08-00018 in the original application. This lot of material meets the specifications for Related Compounds and Particle Size that are stated above.

COMMENT:

- B. PLEASE REVISE YOUR SPECIFICATIONS FOR FLUOXETINE HYDROCHLORIDE TO INCLUDE TESTS FOR MELTING POINT AND MOISTURE.

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RESPONSE:

Barr commits to testing Fluoxetine Hydrochloride, USP for moisture using Karl Fischer analysis with a specification of NMT %, which is consistent with the 1997 European Pharmacopoeia and USP 23, Seventh Supplement monographs. Barr revised the Acceptance Tests for Raw Materials for Fluoxetine Hydrochloride, USP (RM-318C) and corresponding QC Raw Material Specifications & Test Record (Barr Specification No.: 01-0305, Rev. 3) to include the moisture test and specification (see Pages 0039 through 0062).

The melting point test for Fluoxetine Hydrochloride, USP is currently not contained in USP 23, Seventh Supplement monograph or the 1997 European Pharmacopoeia monograph. Mr. Ashley, Manager of Technical Affairs, Barr Laboratories, Inc. contacted Dr. Cecil, Scientist, USP on November 26, 1996 regarding this matter. In response to questions posed by Mr. Ashley, Dr. Cecil stated that neither the original manufacturer nor FDA had requested USP to add a specification for melting point to the Fluoxetine Hydrochloride monograph. If FDA were to make this request, Mr. Cecil further stated that the test would probably be added to the "Description and Solubility Section", which is a non-binding section for non-required tests and is only used for informational purposes. Therefore, Barr is not adopting the melting point test at this time.

Attached please find a letter to USP from Barr dated January 8, 1997 requesting the USP to not adopt the melting point test for this monograph (see Pages 0099 through 0100) as well as an acknowledgment from USP dated February 11, 1997 documenting that Barr's proposal is under consideration (see Page 0101).

COMMENT:

C. SINCE THE DRUG SUBSTANCE EXISTS AS A RACEMIC MIXTURE, PLEASE REVISE YOUR SPECIFICATIONS TO INCLUDE TESTING FOR OPTICAL ROTATION TO ENSURE THAT A RACEMIC MIXTURE IS USED.

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COMMENT:

- E. REGARDING THE REFERENCE STANDARD FOR FLUOXETINE HYDROCHLORIDE AND RELATED COMPOUNDS:
- II. PLEASE INDICATE THE SOURCE OF REFERENCE STANDARDS FOR FLUOXETINE HYDROCHLORIDE AS WELL AS ALL RELATED COMPOUNDS.

RESPONSE:

the bulk drug substance manufacturer, provided Barr with the following reference standards:

- Fluoxetine Hydrochloride (Manufacturer's Lot 195, Barr Lot H220)
- Impurity (\pm) 1-phenyl-3-methylamine-1-propanol/ -[2-(methylamino)ethyl]-benzenemethanol (Barr Impurity I)
- Impurity 1-phenyl-3-methylamino-propane (Barr Impurity II)
- Impurity p-trifluoromethylphenol/4-Hydroxybenzotrifluoride (Barr Impurity III)
- Impurity 4-Chlorobenzotrifluoride (Barr Impurity IV)

Please note that Barr Impurity IV is now commercially available from Acros Janssen Pharmaceuticals. Barr is currently purchasing Impurity IV from this source.

COMMENT:

- II. PLEASE DESCRIBE ANY IN-HOUSE QUALIFICATION PROCEDURES OR PURIFICATION STEPS USED FOR ALL REFERENCE STANDARDS PRIOR TO USE.

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RESPONSE:

Barr Laboratories, Inc. and Apotex, Inc. are partners in the patent litigation versus Eli Lilly & Co. At the time Barr manufactured the submission batch, Apotex Inc.'s subsidiary, was also developing the liquid Fluoxetine HCl dosage form. Therefore, provided Barr with a Fluoxetine HCl reference standard. The standard was accompanied with "Reference Standard Specification and Certificate of Analysis" records. When Barr manufactured the submission batch there was no USP reference standard. Therefore, certification was accepted. Subsequently, Barr qualified Lot #H220 as its in-house reference standard (see Pages 0103 through 0113) for the supporting report and documentation).

Barr has established standard operating procedures to govern the qualification of all in-house reference standards prior to use. In general, this procedure defines primary, secondary and impurity reference standards. Primary reference standards obtained from standard setting agencies may be used when accompanied by a Certificate of Conformance ("COC") and containing information on storage, expiration, and use. A Certificate of Analysis ("COA") must accompany secondary or in-house reference standards for each lot received. Barr only uses these reference standards for quantitation after full monograph testing has established their equivalence to the current USP/Barr monograph requirements. In addition, the material must have been tested against a primary reference standard as an in-house reference standard, if applicable. For non-USP impurity/related compounds, Barr obtains impurity/related compound primary reference standards from the manufacturer of the bulk chemical. A COA accompanies this material to certify its identity and purity, if available.

COMMENT:

- III. PLEASE SUBMIT SUPPLIER AND IN-HOUSE (IF APPLICABLE) CERTIFICATE OF ANALYSIS FOR YOUR REFERENCE STANDARDS FOR FLUOXETINE HYDROCHLORIDE AS WELL AS ALL RELATED COMPOUNDS.

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RESPONSE:

Attached please find the following Certification of Analyses and additional supporting documentation for the reference standards for Fluoxetine Hydrochloride and Related Compounds used to test the submission batch:

Fluoxetine Hydrochloride Reference Standard:

- Reference Standard Specification and Certification of Analysis ("COA") (Manufacturer's Lot 195) (see Pages 0103 through 0106).
- Final Report dated June 17, 1996 documenting the certification of Fluoxetine Hydrochloride secondary reference standard (Manufacturer's Lot 195) (see Pages 0107 through 0110).
- Barr's subsequent COA for in-house qualification of reference standard, Manufacturer's Lot 195 (see Pages 0111 through 0113).

Related Compounds Reference Standards:

- COAs for Barr Impurities I, III, and IV from (see Pages 0114 through 0116).
- COA for Barr Impurity IV from (see Page 0117).
Please note that Impurity IV is now commercially available from Barr is currently purchasing Impurity IV from this source.
- Correspondences from (distributor for regarding their inability to provide a COA for Barr Impurity II, Lot No. ST 250 (see Pages 0118 through 0120) as well as a COA for Lot No. 6820, a subsequent Lot of Impurity II received from..

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COMMENT:

3. REGARDING MANUFACTURING AND PROCESSING:

- A. PLEASE REVISE YOUR MASTER BATCH RECORD TO INCLUDE THE MANUFACTURER, MODEL, AND MODE OF OPERATION (VERTICAL OR HORIZONTAL) OF THE HIGH SHEAR MIXER.

RESPONSE:

Barr has revised its manufacturing master (master batch record) to include the manufacturer and model of the high shear mixer as follows:

Manufacturer:

Model: Gral 600

The mode of operation of the Gral 600 high shear mixer is vertical. Barr does not routinely include this information in its manufacturing masters.

Attached on Pages 0121 through 0131 is a copy of the updated manufacturing master, master control number 087701A3 (1/26/98) for Fluoxetine Hydrochloride Capsules, USP 20 mg. The following changes were made:

- Added "USP" to product name (active raw material and finished product) to agree with USP 23, Seventh Supplement monographs
- Changed recording of weights to four significant digits to ensure weighing within the capability of Barr's scales
- Updated ingredient names to be consistent with vendors' descriptions
- Updated format

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- Changed system for assigning revision number to make the number more informative, this includes a change to a Master Control Number ("MC#"). The first four numeric digits specify the product code, the next two numeric digits specify the manufacturing revision, the next alpha character signals if a minor change has been made in equipment (i.e., Annual Report submission), and the last numeric digit specifies the site of manufacture. For example,

0873 = Product Code for Fluoxetine Capsules, USP 20 mg
01 = Revision #1
A = Identical Equipment
2 =

- Tightened Accountability Range from %" to %" (step
- Clarified the identification of waste in step by adding "Identify Origin if Applicable"
- Added "Any change to the start-up encapsulation speed must be documented on the encapsulation monitoring record" and added a line to record the encapsulation speed (step
- Added a column to record the encapsulation speed on the encapsulation monitoring record
- Removed spaces throughout to record F.P. thickness, hardness and friability since this information is not applicable for a capsule product

COMMENT:

- B. PLEASE REVISE YOUR MASTER BATCH RECORD TO INCLUDE OSCILLATOR/MESH SETTINGS FOR SCREENING THE GRANULATION.

REFERENCE: ANDA 74-803
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RESPONSE:

The manufacturing master (master batch record), submitted in the original application on Pages 11-00014 through 11-00025, already specifies the oscillator/mesh settings used for screening the granulation. Specifically, steps state "...through an Oscillator fitted with a mesh screen (Equip. No.):..." For your convenience enclosed please find a copy of Page 11-00017 containing steps

COMMENT:

- C. PLEASE REVISE YOUR MASTER BATCH RECORD TO INCLUDE THE RATE OF ENCAPSULATION (NOMINAL OR RANGE IN CAPSULES/HOUR) AS WELL AS ANY LIMITS ON ENVIRONMENTAL CONDITIONS (E.G. TEMPERATURE, RELATIVE HUMIDITY) FOR THE ENCAPSULATION PROCESS.

RESPONSE:

Part of Barr's normal validation process includes validating the full range of the encapsulation speeds. Upon completion of the three full-scale process validation batches, the manufacturing master (master batch record) is updated to include the validated rate of encapsulation. Please note that the enclosed manufacturing master, MC# 087701A3 (Pages 0121 through 0131) has been updated to include a speed column on the encapsulation monitoring record, a place to record the encapsulation speed, and a note specifying that any change to the start-up encapsulation speed must be documented on the encapsulation monitoring record (step 15). Regarding the environmental conditions during the encapsulation process, Barr has a standard operating procedure for the manufacturing areas and manufacturing process concerning the environmental conditions. The procedure states that the temperature limit is 59°F – 86°F and that the humidity be not more than %. The temperature and humidity are monitored in all manufacturing areas.

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COMMENT:

4. REGARDING CONTAINER/CLOSURE SYSTEMS:
 - A. PLEASE SUBMIT USP <671> CONTAINERS-PERMEATION TESTING RESULTS FOR THE PROPOSED CONTAINER/CLOSURE SYSTEM.

RESPONSE:

Enclosed on Pages 0133 through 0134 please find USP 23 <671> water vapor permeation testing results conducted by _____ on behalf of Barr Laboratories, Inc. for the following proposed container/closure system:

100: 60 cc container/ 33 mm metal cap

COMMENT:

- A. WE STRONGLY SUGGEST THAT THE SMALLEST CONTAINER/CLOSURE SYSTEM INCLUDED IN THE APPLICATION BE EQUIPPED WITH A CHILD RESISTANT CLOSURE. PLEASE COMMENT.

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Please note Barr has also updated its Packaging Master for the 100s size using the 60 cc bottle with a 33 mm metal cap as follows (see Page 0147):

- Added "USP" to product name (active raw material and finished product) to agree with USP 23, Seventh Supplement monographs
- Changed system for assigning revision number to make the number more informative, this includes a change to a Master Control Number ("MC#"). The first four numeric digits specify the product code, the next two numeric digits specify the packaging revision, and the last numeric digit specifies the site of packaging. For example,

0873 = Product Code for Fluoxetine Capsules, USP 20 mg
01 = Revision 1
3 =

Barr will correct the Average Weight recording on both Packaging Masters to read "Average Capsule Weight" instead of "Average Tablet Weight" and submit the update in the next Annual Report.

COMMENT:

5. REGARDING LABORATORY CONTROLS:

A. REGARDING EXHIBIT LOT #5R87719:

- I. PLEASE INDICATE THE MAKE, MODEL AND PRINCIPLE OF OPERATION (VERTICAL OR HORIZONTAL) OF THE HIGH SHEAR MIXERS.

REFERENCE:

ANDA 74-803

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RESPONSE:

As stated in the response to Comment 3A, the make, model and principle of operation of the high shear mixer is as follows:

Manufacturer:

Model: Gral 600

Mode of Operation: Vertical

COMMENT:

- II. PLEASE INDICATE NOMINAL ENCAPSULATION SPEED AND ENVIRONMENTAL PARAMETERS.

RESPONSE:

As stated in the response to Comment 3C, the nominal encapsulation speed will be recorded and validated as part of Barr's normal process validation. The environmental parameters for lot #5R87719 were as follows: temperature limit: 59°F – 86°F, humidity: NMT %.

COMMENT:

- B. REGARDING IN-PROCESS CONTROLS:
- I. PLEASE SUBMIT SPECIFICATIONS FOR MONITORING BLEND UNIFORMITY DURING NORMAL PRODUCTION OF DRUG PRODUCT ALONG WITH ANY APPLICABLE JUSTIFICATION OR SUPPORTING DATA.

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RESPONSE:

Barr Laboratories, Inc. commits to perform in-process testing for blend content uniformity. After sufficient data has been collected for the in-process testing (e.g., blend), Barr will submit a prior approval supplement before deleting testing at the blend stage.

The Analytical Specification Test Record used for release and the Acceptance Tests For In-Process and Finished Products have been revised to include blend content uniformity testing and specifications (see Pages 0148 through 0178).

COMMENT:

- II. YOUR MASTER BATCH RECORD INDICATED THAT CAPSULE FILL WEIGHT WILL BE MONITORED BY AGGREGATE FILL WEIGHT AND NOT INDIVIDUAL FILL WEIGHTS, WHICH WILL NOT PROVIDE CONTROL OVER FILL WEIGHT VARIANCE. PLEASE SUBMIT SPECIFICATIONS FOR IN-PROCESS MONITORING OF INDIVIDUAL CAPSULE FILL WEIGHTS, ALONG WITH ANY NECESSARY JUSTIFICATION AND SUPPORTING DATA TO DEMONSTRATE ACCEPTABLE CAPSULE FILL WEIGHT AS WELL AS FILL WEIGHT VARIANCE.

RESPONSE:

Barr routinely monitors the capsule fill weight in two ways; aggregate and individual fill weights. While Barr personnel record the aggregate capsule fill weight on the manufacturing master (encapsulation monitoring record), they also monitor the individual capsule fill weights periodically throughout the encapsulation operation. These weights are recorded on individual weight tapes, which are then attached to the batch record. Enclosed on Pages 0179 through 0211 please find copies of the weight tapes containing the individual capsule fill weights for the submission batch as well as a summary report of all the weight tapes. The guidelines for determining acceptable capsule weights are covered by a standard operating procedure.

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COMMENT:

- C. WE NOTE THAT YOU HAVE INCLUDED COPIES OF YOUR VALIDATION SOP'S AS WELL AS VALIDATION STUDY RESULTS FOR EXHIBIT LOT #5R87719. WHILE THE VALIDATION DATA SUBMITTED MAY BE USEFUL FOR CLARIFICATION PURPOSES, PLEASE NOTE THAT APPROVAL OF THE APPLICATION DOES NOT INCLUDE APPROVAL OF SOP'S OR VALIDATION PROTOCOLS AND REPORTS WHICH ARE THE RESPONSIBILITY OF THE FIELD INVESTIGATOR.

RESPONSE:

Your comment is acknowledged.

COMMENT:

- D. SECTION 1 OF YOUR ACCEPTANCE TESTS FOR IN-PROCESS & FINISHED PRODUCTS (METHOD NO. TM-419B) INCLUDES DESCRIPTION AND REFERENCE TO A 10 MG CAPSULE, WHICH HAS NOT BEEN INCLUDED IN THIS APPLICATION. PLEASE REMOVE ALL REFERENCES TO THE 10 MG CAPSULE FROM THE SPECIFICATIONS AND PROCEDURES IN THIS APPLICATION.

RESPONSE:

At this time Barr is amending it's application for Fluoxetine Capsules, USP 20 mg with the additional 10 mg strength. Therefore, Barr's Acceptance Tests for In-Process & Finished Products will continue to reference both the 10 mg and 20 mg strengths (see Part II for information on the 10 mg strength).

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COMMENT:

- E. YOUR SPECIFICATIONS FOR RELATED COMPOUNDS AND MOISTURE ("REPORT RESULTS") ARE UNACCEPTABLE. PLEASE REVISIONS TO INCLUDE LIMITS BASED ON DATA ACCRUED TO DATE.

RESPONSE:

Barr revised its release and stability specifications for Related Compounds and Moisture to include limits.

Specifically, Barr has set the following Related Compound Specifications based on the release data and 24 months of CRT stability data for the 10 mg and 20 mg strengths accrued to date:

<u>Related Compounds Tests</u>	<u>Limits</u>	
p-Trifluoromethylphenol (Barr Impurity III)	NMT	%
4-Chlorobenzotrifluoride (Barr Impurity IV)	NMT	%
Individual Unknown Impurities (excluding Impurities I and II)	NMT	%
Total Known and Unknown Impurities (excluding Impurities I and II)	NMT	%

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Barr has adopted the USP 23, Supplement Seven method and specifications for related compounds. However, Barr Impurity I and Impurity II will be excluded from the calculations of the Individual Unknown Impurities and Total Known and Unknown Impurities for the finished product since they are process related and are being monitored in the drug substance under tight USP specifications. The Federal Register Notice/Volume 61, No. 54/Tuesday, March 19, 1996 provides the ICH Draft Guidelines on Impurities in New Drug Products and further supports the exclusion of Barr Impurity I and Impurity II. Specifically it states, "The specification for a new drug product should include limits for degradation products expected to occur under recommended storage conditions."

A summary of Barr's stability data through 24 months also supports Barr Impurity I and Impurity II as strictly process related compounds and not degradation products (see attached memorandum, "Justification to Exclude Two Process Related Compounds from the Calculation of Total Related Compounds in Fluoxetine Hydrochloride Capsules, USP 20 mg" dated 2/4/98, Pages 0212 through 0214).

Barr previously set a moisture specification of NMT % (only for stability testing) in its Acceptance Test For In-Process and Finished Products, TM-419C. This test method was submitted to the Division of Bioequivalence in a 6/6/97 response letter to FDA bioequivalence letter dated 6/10/96. Barr has since added a moisture specification of NMT % for release and revised the moisture specification for stability to NMT % based on additional data accrued (see memorandum on Pages 0212 through 0214 providing the rationale for this specification).

Barr has updated its Acceptance Test For In-Process and Finished Products, corresponding QC Analytical Specification Test Record, Marketed Product Stability Specification Sheet, and Stability Protocol accordingly (see Pages 0148 through 0178 and 0215 through 0221).

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COMMENT:

- F. YOUR FINAL PRODUCT SPECIFICATIONS (SPEC. #0877 - REV. 2) FAIL TO INCLUDE MOISTURE AS SHOWN IN THE METHODS (METHOD NO. TM-419B). PLEASE REVISE THE FINAL PRODUCT SPECIFICATIONS TO INCLUDE MOISTURE OR SUBMIT JUSTIFICATION FOR THE DELETION.

RESPONSE:

Barr has revised its finished product specifications to include the moisture specification of NMT %. Enclosed on Pages 0176 through 0178 please find a copy of Barr's QC Analytical Specification Test Record. In conjunction with the change, the statement "for stability testing only" originally placed after the moisture test in the Acceptance Test For In-Process and Finished Products has been removed (see Page 0149).

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COMMENT:

6. REGARDING STABILITY:

YOU HAVE INDICATED THAT A LIGHT YELLOW COLORATION WAS NOTED IN THE GRANULATION WHERE THE GRANULATION WAS IN CONTACT WITH THE HARD GELATIN CAPSULES FOR SEVERAL OF THE SAMPLES TAKEN DURING ACCELERATED STABILITY TESTING AT ONE AND THREE MONTHS. CLOSE REVIEW OF THE INDIVIDUAL CAPSULE DISSOLUTION RESULTS SUBMITTED REVEALED INDIVIDUAL SAMPLES WHICH EXHIBITED DISSOLUTION VALUES AS LOW AS % WHEN THE MAJORITY OF THE CAPSULES EXHIBITED VALUES GREATER THAN %. PLEASE DISCUSS ANY POSSIBLE RELATIONSHIP BETWEEN THE APPARENT LOW VALUES FOR DISSOLUTION AND THE YELLOW COLORATION, AS WELL AS THE POTENTIAL FOR PELLICLE FORMATION. ALL ROOM TEMPERATURE STABILITY DATA ACCRUED TO DATE SHOULD BE SUBMITTED IN SUPPORT OF YOUR DISCUSSION.

RESPONSE:

Barr has conducted an extensive investigation into the possible cause(s) of the "light yellow coloration" found in the capsule contents in both CRT and accelerated stability samples and its possible impact on dissolution. Multiple hypotheses were explored including pellicle formation and the Maillard-reaction. In conclusion, as supported by the 24 month CRT stability data, the "light yellow coloration" of the capsule content has no adverse impact on the potency, impurity level or dissolution rate. In fact, no trends were observed in the CRT data up to 24 months and all stability results (including dissolution) for both the 10 mg and 20 mg strengths easily met specifications after 24 months storage under CRT conditions.

Enclosed please find Barr's Stability Summary Report RD97-224A dated February 20, 1998 and attached memorandum discussing this issue (Pages 0222 through 0251).

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Enclosed in Part II, Section XVII of this Amendment is a copy of Barr's Stability Summary Report through 24 months CRT stability storage for the 10 mg strength.

COMMENT:

B. LABELING DEFICIENCIES

1. GENERAL COMMENTS

WE RECOGNIZE YOUR INTENT TO MARKET THIS PRODUCT BEFORE THE PATENT EXPIRATION DATES OF THE LISTED DRUG. PLEASE NOTE, HOWEVER, THAT AFTER FEBRUARY 28, 1997, THE INFORMATION REGARDING OBSESSIVE COMPULSIVE DISORDER MUST BE INCLUDED IN YOUR LABELING.

RESPONSE:

Your comment is acknowledged. Barr has updated its labeling to include the information regarding obsessive compulsive disorder. A copy of the updated Insert is enclosed on Pages 0257 through 0267 in response to Comment 3.

COMMENT:

2. CONTAINER (100'S)

THE STRENGTH OF THIS PRODUCT IS EXPRESSED IN TERMS OF FLUOXETINE, AND WE SUGGEST CLARIFYING IT AS SUCH BY ADDING AN ASTERISK AFTER THE EXPRESSION OF STRENGTH ON THE MAIN PANEL AS FOLLOWS:

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FLUOXETINE HYDROCHLORIDE CAPSULES

20 mg*

CAUTION: Federal law prohibits
dispensing without prescription.

100 CAPSULES

*Each capsule contains: Fluoxetine Hydrochloride,
equivalent to 20 mg fluoxetine.

RESPONSE:

Barr has updated its container labels to include an asterisk after the expression of strength on the main panel as suggested above. Please find (4) four draft container labels for the 100s package size on Pages 0252 through 0255. Also enclosed on Page 0256 is a side by side comparison of Barr's 20 mg strength new proposed container label versus the old proposed container label submitted with the application.

COMMENT:

3. INSERT

a. General

- i. We recognize your intent to market this product before the patent expiration dates of the listed drug. Please note, however, that after February 28, 1997, the information regarding obsessive compulsive disorders must be included in your labeling.
- ii. Italicize "*in vivo*" and "*in vitro*" where they appear in the insert labeling.

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FLUOXETINE CAPSULES, USP 10 MG**

b. DESCRIPTION

- i. Regarding the use of the phrase “and other ingredients”. We refer you to USP XXIII, General Information, Chapter <1091>, Labeling of Inactive Ingredients, which states that a trade secret may be omitted from the list of inactive ingredients if the list states “and other ingredients”. The chapter further states that an ingredient is considered to be a trade secret only if its presence confers a significant competitive advantage AND its identity cannot be ascertained by the use of modern analytical technology. If you still elect to use the phrase “and other ingredients” please provide supporting data concerning the “trade secret” status of these ingredients, if not, revise your labeling at the time of next printing to include all ingredients in the list of inactive ingredients. Also, include any dye(s) with your listing of inactive ingredients.
- ii. Revise the first sentence in the third paragraph to read “Each capsule, for oral administration, contains...”

c. CLINICAL PHARMACOLOGY (Clinical Trials)

Revise to read, “fluoxetine” rather than “fluoxetine hydrochloride” throughout this subsection.

d. INDICATIONS AND USAGE

- i. Delete the subsection heading, “Depression”.
- ii. Except in the first sentence, revise to read, “fluoxetine” rather than “fluoxetine hydrochloride” throughout this section.

e. CONTRAINDICATIONS

- i. Except in the first sentence, revise to read, “fluoxetine” rather than “fluoxetine hydrochloride” throughout this section.

REFERENCE:

ANDA 74-803

Page 27

FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

- ii. Make the following revision in the penultimate sentence, "...within a minimum of ...".
- iii. Make the following revision in the last sentence, "...doses [see *Accumulation and Slow Elimination* under **CLINICAL PHARMACOLOGY**]) should ...".

f. WARNINGS

In the last sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

g. PRECAUTIONS

- i. Except in the following locations, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":
 - the first sentence of this section.
 - the "Suicide" subsection of the "General" subsection.
 - the first sentence of the "Use in Patients with Concomitant Illness" subsection of the "General" subsection.
 - the "Pregnancy" subsection.
- ii. Revise the "Other Antidepressants" subsection of the "Drug Interactions" subsection as follows:

REFERENCE:

ANDA 74-803

Page 28

FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

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

- iii. Drug Interactions (Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins)

Revise to read "...warfarin...", rather than "Coumadin..."

- iv. Nursing Mothers

Make the following revision in the last sentence, "...were 340 nm/mL..."

- v. Usage in Children

Revise the section heading to read, "Pediatric Use" and make the following revision, "...in pediatric patients have...."

- h. ADVERSE REACTIONS

- i. Except in the following locations, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride":

- the first sentence of the "Commonly Observed" subsection.
- the first sentence of the "Associated with Discontinuation of Treatment" subsection.

REFERENCE:

ANDA 74-803

Page 29

**FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG**

- the penultimate subsection title.
- ii. Incidence of Controlled Clinical Trials
 - A) Revise the first sentence to read, "The table that follows enumerates..."
 - B) Make the following revision in the first sentence of the second paragraph, "...that these figures cannot..."
 - C) Delete the title, "TABLE I".
- iii. Other Events Observed During Premarketing Evaluation of Fluoxetine Hydrochloride
 - A) Make the following revision in the third sentence of the second paragraph, "...already listed in the table, those..."
 - B) Use formatting to increase the prominence of the terms, "frequent", "infrequent", and "rare".
- iv. Postintroduction Reports
 - Revise as follows:

REFERENCE:

ANDA 74-803

Page 30

**FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG**

...the following: aplastic anemia, atrial fibrillation, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccolingual-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 dermatitis, gynecomastia, heart arrist hepatic failure/necrosis, hyperprolactinemia, immune-related hemolytic anemia, kidney failure, misues/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, priapism, pulmonary embolism, QT prolongation, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, baginal bleeding after drug withdrawal, and violent behaviors.

i. **DRUG ABUSE AND DEPENDANCE**

Except in the first sentence, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride" throughout this section.

j. **OVERDOSAGE**

Except in the third paragraph of the "Management of Overdose" subsection, revise to read, "fluoxetine" rather than "fluoxetine hydrochloride".

k. **DOSAGE AND ADMINISTRATION**

i. Delete the subsection heading "Depression". Please note that "Initial Treatment" and "Maintenance/Continuation/ Extended Treatment" should appear with the same prominence as other subsections.

ii. Add the following text as the last two subsections:

REFERENCE: **ANDA 74-803**
FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

Page 31

Switching Patients to a Tricyclic Antidepressant (TCA):

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see *Other Antidepressants* under Drug Interactions of **PRECAUTIONS**).

Switching Patients to or from 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**).

I. HOW SUPPLIED

Clarify that "20 mg" is equivalent to 20 mg fluoxetine and not of fluoxetine hydrochloride.

Please revise your container labels and package insert labeling, as instructed above, and submit final print labeling.

RESPONSE:

Enclosed on Pages 0257 through 0300 please find four (4) draft package brochures, which have been revised according to the Agency's recommendation. Also enclosed is a side by side comparison of Barr's updated proposed labeling versus the old proposed labeling submitted in the original application (see Pages 0301 through 0342). A copy of the reference product's brochure is also attached for informational purposes on Pages 0343 through 0351.

REFERENCE:

ANDA 74-803

Page 32

FLUOXETINE CAPSULES, USP 20 MG
AND SUPPLEMENTAL APPLICATION
FLUOXETINE CAPSULES, USP 10 MG

COMMENT:

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.

RESPONSE:

Barr has provided a side-by-side comparison of their proposed labeling in accordance with 21 CFR 314.94(A) (8) (IV) (see Page 0256 and Pages 0301 through 0342).

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 20 MG
 AND SUPPLEMENTAL APPLICATION
 FLUOXETINE CAPSULES, USP 10 MG**

Page 33

**Part II: Additional strength to pending application: Fluoxetine Capsules, USP
10 mg**

The information on the additional 10 mg strength is provided in duplicate, both as an archival copy, and a review copy. The archival copy of the supplemental application is contained in blue binders and consists of 3 volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 1 volume. The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The information submitted in this application is also in accord with the October 14, 1994 communication from Dr. Janet Woodcock, Director CDER.

An identical copy of this Major Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present response to the Agency's deficiency letter dated *July 9, 1996*. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

/S/
Christine Mundkur
Regulatory Counsel and Director of
Regulatory Affairs

CM/egn
Enclosure

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

August 18, 1998

GENERIC AMENDMENT
N/AB

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

RECEIVED

AUG 19 1998

GENERIC DRUGS

Via Facsimile
Via Federal Express

BIOEQUIVALENCE FACSIMILE AMENDMENT

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg submitted on December 9, 1995.

Reference is also made to the telephone conversation between Karen Bonomi, Regulatory Affairs, Barr Laboratories, Inc. and Lizzie Sanchez, Project Manager, Division of Bioequivalence, OGD/FDA on August 10, 1998. During this conversation, Ms. Sanchez requested information regarding Barr's *In-Vitro* Comparative Dissolution Report No. RD98-034A for Fluoxetine Capsules, USP 10 mg that was submitted in the Major Amendment dated June 15, 1998. Accordingly, Barr is hereby providing the following information:

Barr Laboratories, Inc. originally conducted *in vitro* comparative dissolution testing on Barr's 10 mg submission batch 5R87618 compared to the Dista reference product 8NE08M in June and July 1995 (see Attachment 1). This original comparative dissolution testing for both the 10 mg and 20 mg strengths was conducted in 0.1 N HCl as the medium. In a January 8, 1998 facsimile comment letter, however, the Division of Bioequivalence requested Barr to change the dissolution medium from 0.1 N HCl to water. In addition, the Division requested Barr to reconduct the *in vitro* dissolution comparison simultaneously for both the test and reference products. The comment letter further provided that the lot numbers of the samples undergoing dissolution testing should be identical to those used in the *in vivo* study. In response to this comment letter, Barr submitted a Bioequivalence Amendment on April 29, 1998. In this Amendment, Barr provided the agency with an updated dissolution test method changing the

Barr Laboratories, Inc.

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG
BIOEQUIVALENCE FACSIMILE AMENDMENT

medium to water as well as the revised *in vitro* comparative dissolution testing for the 20 mg strength using water as the medium for both products used in the *in vivo* study, Barr's 20 mg submission batch and the Dista product. Based on the agency's January 8, 1998 comment letter, Barr re-conducted the *in vitro* dissolution comparative study for the 10 mg strength using water as the medium. This dissolution comparative study was tested on the original Barr lot 5R87618 and the Dista reference lot 8NE08M that were originally tested in 1995 in accordance with the spirit of the agency's letter. The dissolution testing on both Barr's 10 mg test product and the reference product using water as the medium was performed on February 23, 1998 and the dissolution profiles were submitted in Section 6 of the June 15, 1998 Major Amendment. Please note that the expiration date of the reference lot 8NE08M manufactured by Dista Products Company was 9/1/96. This date was reported on the first and second pages of the *In Vitro* Comparative Study Report RD98-034A submitted in Section VI, pages 06-00007 and 06-00008. In addition, enclosed as Attachment 1 is a copy of the original dissolution comparative study report dated 11/07/95 demonstrating that the same Barr and Dista lots that were originally tested with 0.1 N HCl medium were also tested with water as the medium.

Barr Laboratories, Inc. is currently a party in a patent litigation with Eli Lilly regarding the Fluoxetine Capsules, USP 10 mg and 20 mg products. This litigation is ongoing, and therefore, Barr has not yet manufactured any validation batches. To manufacture a validation batch of Fluoxetine Capsules, USP would be too premature in the approval process with this ongoing litigation; the batch would expire prior to commercialization. This fact further supports Barr's decision to conduct the comparative dissolution testing using water as the medium on the original test and reference batches.

Lastly, the date of manufacture of the 10 mg submission batch 5R87618 was June 26, 1995.

In conclusion, Barr has provided the following documentation in response the agency's telephone request:

- In-Vitro Comparative Study Report No. RD98-034A dated 3/10/98 (water is medium)
- In-Vitro Comparative Study dated 11/07/95 (0.1N HCl is medium).
- Barr's Acceptance Tests for In-Process and Finished Products TM-419F (2/9/98). Please note that TM-419F was used to conduct the dissolution testing for Report No. RD98-034A and is Barr's current test method.

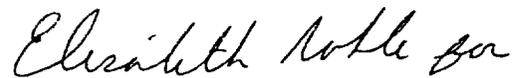
Barr Laboratories, Inc.

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG
 BIOEQUIVALENCE FACSIMILE AMENDMENT**

If you have any questions concerning this Facsimile Amendment, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely

BARR LABORATORIES, INC.



Christine Mundkur,
Regulatory Counsel and Director of
Regulatory Affairs

CM/kdb
Enc.

This submission is comprised of Pages 1 through 40.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

5/25/99 Telephone Amendment to CMC Reviewer JCS

May 21, 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, Maryland 20855-2773

NDA ORIG AMENDMENT

N/FA

TELEPHONE AMENDMENT

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

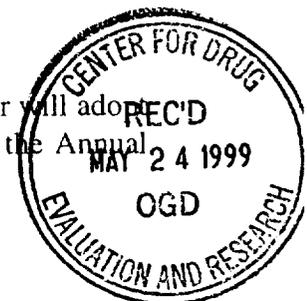
Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's Minor Amendment dated April 12, 1999 and to the May 13, 1999 telephone conversation between Glen Smith, Review Chemist, Div. of Chemistry II, OGD/CDER/FDA and Christine Mundkur, Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc.

Mr. Smith requested that Barr change their proposed specification for Impurity I, drug product, from: NMT % to NMT % to match USP 23/NF 18, Supplement 7. Accordingly, Barr has changed their specification for Impurity I for the drug product to NMT %. Attached please find the following documents:

- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Acceptance Tests for In-Process & Finished Products, TM-419G

When USP adopts the PF Sep./Oct. 98 specification of NMT % for Impurity I, Barr will adopt this specification for both its release and stability testing and submit the changes in the Annual Report in accordance with 21 CFR 314.70 (d).



**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

PAGE 2

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

An identical copy of this Telephone Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Telephone Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and Regulatory
Counsel

CM/egn
Enc.

cc: New Jersey District Filed Office

This Submission is comprised of **Pages 01 through 39.**

9

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

June 7, 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, Maryland 20855-2773

ORIG AMENDMENT

FA

TELEPHONE AMENDMENT

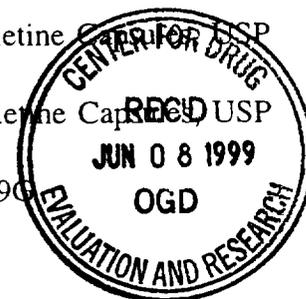
REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's Minor Amendment dated April 12, 1999 and to the May 27, 1999 telephone conversation between Glen Smith, Review Chemist, Div. of Chemistry II, OGD/CDER/FDA and Christine Mundkur, Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc.

Mr. Smith requested that Barr change their proposed specification for Total Known and Unknown Impurities, drug product, to include Barr Impurity I and II. Barr has made this change and, consequently, has changed their specification for Other Individual Unknown Impurities to include Impurity II and change the name to Other Individual Impurities. This latter change was made to account for the known Impurity II in the drug product. Attached please find the following documents:

- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Quality Control Analytical Specifications & Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 10 mg
- Barr's Marketed Product Stability Specification/Test Record, Fluoxetine Capsules, USP 20 mg
- Barr's Acceptance Tests for In-Process & Finished Products, TM-4190



Barr Laboratories, Inc.

When USP adopts the PF Sep./Oct. 98 specifications for Fluoxetine Capsules, USP, Barr will adopt these specifications for both its release and stability testing and submit the changes in the Annual Report in accordance with 21 CFR 314.70 (d).

An identical copy of this Telephone Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Telephone Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.


Christine Mundkur
Vice President, Quality and Regulatory
Counsel

CM/egn
Enc.

cc: New Jersey District Filed Office

This Submission is comprised of **Pages 01 through 39.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 7, 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, Maryland 20855-2773

NOA ORIG AMENDMENT



MINOR AMENDMENT

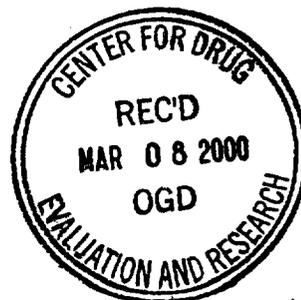
**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's July 23, 1999 correspondence and the Agency's letter dated August 2, 1999 in which the following is stated:

COMMENT:

Review of the data submitted in your correspondence dated July 23, 1999 shows that your drug product fails to meet compendial specifications through the proposed expiry dating when the amounts of Impurity I (\pm) 1-Phenyl-3-methylamino-1-propanol) are included in the determination of Individual and Total Impurities. Please submit stability data demonstrating conformance to compendial requirements in support of the proposed 24 month expiration date.



ALW
3-10-00

Barr Laboratories, Inc.

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

PAGE 2

REFERENCE: **ANDA 74-803**
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

RESPONSE:

Barr manufactured two additional batches; one 10 mg strength and one 20 mg strength and placed each batch into its long-term and accelerated stability program. The stability data demonstrates conformance to compendial requirements in support of the proposed 24 month expiration date.

Please note that Barr changed the packaging and labeling site as follows:

From

To

On February 14, 2000 through February 23, 2000, the Baltimore District inspected the manufacturing and packaging operations at the site and found it to be in compliance with current Good Manufacturing Practices. Enclosed is Barr's Certifications and Assurance of Controlled Manufacturing in Conformance With Good Manufacturing Procedures for the site.

In addition, the procedure for testing in-process blend content uniformity was improved to eliminate possible segregation of blend powder within the sample vials, thereby increasing the accuracy and precision of the test. The approved procedure specifies to test a portion of sample powder (equivalent to one theoretical capsule fill weight). The revised procedure specifies that the entire contents of the sample vial (up to 3.4 times the theoretical capsule fill weight) is rinsed. The working standard concentration range for Fluoxetine Capsules was previously validated in Method Validation Report No. FLU-083195. Therefore, no additional method validation is necessary for this change. Please note that the specification for blend uniformity testing, sample size, and procedures for testing and re-testing have been reviewed and approved by the New York and New Jersey District Offices, Office of Compliance and the U.S. Attorneys Office in accordance with the "Barr Decision" and subsequent Court Order. Based on these prior agreements between Barr and FDA concerning blend content uniformity testing, Barr will adhere to a Stage 2 RSD specification of NMT %.

In accordance with USP 24/NF 19, Supplement 1, Barr also changed the dissolution tolerance from NLT % (Q) to NLT % (Q).

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

PAGE 3

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

In support of this Minor Amendment please find the following:

1. Table of Contents

2. Certification and Assurance of Controlled Manufacturing in Conformance With Good Manufacturing Procedures

3. Finished Product Documentation – 10 mg strength, Batch 308769R01
 - 3.1 Executed Batch Record - Manufacturing
 - 3.2 Executed Batch Record - Packaging
 - 3.3 Testing Specifications and Data
 - 3.4 Copy of Barr’s Acceptance Tests for In-Process and Finished Product, TM-419J, and QC Analytical Specifications & Test Record for the 10 mg strength
 - 3.5 Stability Report

4. Finished Product Documentation – 20 mg strength, Barr Batch 308779R01
 - 4.1 Executed Batch Record – Manufacturing
 - 4.2 Executed Batch Record – Packaging
 - 4.3 Testing Specifications and Data
 - 4.4 Copy of Barr’s Acceptance Tests for In-Process and Finished Product, TM-419J and QC Analytical Specifications & Test Record for the 20 mg strength (see Section 3.4 for a copy of the test method)
 - 4.5 Stability Report

Barr Laboratories, Inc.

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

PAGE 4

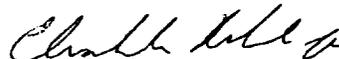
**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

An identical copy of this Minor Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached. Please note that Barr is also submitting, under separate cover, its response dated 3/8/00 to the New Jersey District's July 1, 1999 FDA Record of Inspections Observation (483). This response concerns similar issues raised in the Office of Generic Drug's 8/2/99 comment letter.

This completes Barr's Minor Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 17, 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, Maryland 20855-2773

ANDA ORIG AMENDMENT
[Handwritten signature]

MINOR AMENDMENT

REFERENCE: **ANDA 74-803**
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to Barr's March 7, 2000 Minor Amendment submitted in response to the Agency's letter dated August 2, 1999. As requested by Tim Ames, FDA during a March 15, 2000 telephone conversation with Christine Mundkur, Barr, we are hereby requesting withdrawal of our March 7, 2000 Minor Amendment and are submitting a new Minor Amendment response to the Agency's August 2, 1999 letter which stated:

COMMENT:

Review of the data submitted in your correspondence dated July 23, 1999 shows that your drug product fails to meet compendial specifications through the proposed expiry dating when the amounts of Impurity I (\pm 1-Phenyl-3-methylamino-1-propanol) are included in the determination of Individual and Total Impurities. Please submit stability data demonstrating conformance to compendial requirements in support of the proposed 24 month expiration date.



Barr Laboratories, Inc.

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

REFERENCE: ANDA 74-803

Fluoxetine Capsules, USP 10 mg and 20 mg

RESPONSE:

Barr manufactured two additional batches; one 10 mg strength and one 20 mg strength and placed each batch into its long-term and accelerated stability program. The stability data demonstrates conformance to compendial requirements in support of the proposed 24 month expiration date. Both batches were packaged in their entirety. Enclosed please find the executed batch records and corresponding stability data for these newly manufactured submission batches.

An identical copy of this Minor Amendment has been provided to the New Jersey District Office. A document certification is attached. Please note that Barr also submitting, under separate cover, its response to the New Jersey District's July 1, 1999 FDA Record of Inspections Observation (483). This response concerns similar issues raised in the Office of Generic Drug's 8/2/99 comment letter.

This completes Barr's Minor Amendment. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President Quality and
Regulatory Counsel

This submission is comprised of **Pages 0001 through 0040.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 18, 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, Maryland 20855-2773
Attention: Gary Buehler
Acting Director

VIA FACSIMILE: (301) 443-3839
ORIGINAL VIA FEDERAL EXPRESS

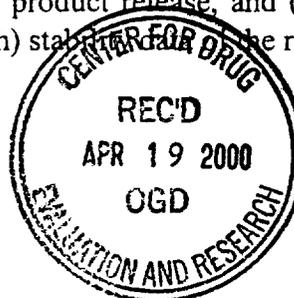
TELEPHONE AMENDMENT

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our pending Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Fluoxetine Capsules, USP 10 mg and 20 mg**.

Reference is also made to the April 2000 phone conversation between Tim Ames, Project Manager, OGD, FDA and Christine Mundkur, Barr Laboratories, Inc. regarding Barr's March 7, 2000 Minor Amendment. Mr. Ames requested that Barr submit 6 month CRT stability data on samples pulled on 2/28/00 as well as additional information on the impurity profiles, particularly the impurity profile for the 10 mg that was just below the total impurities specification at 3 month CRT conditions. Mr. Ames suggested Barr review the 3 and 6 month CRT stability profiles of the recently manufactured 10 mg and 20 mg batches (submitted with the Minor Amendment).

Accordingly, Barr reviewed the drug substance, finished product release, and (T0), accelerated (one, two, and three month) and CRT (three and six month) stability data for the recent batches.



Continued

Handwritten signature and date: GMB 4/19/00

Barr Laboratories, Inc.

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

The data to date shows that the individual known impurities, unknown impurities, and total impurities are well within specification and remain consistent through 6 month CRT. Therefore, Barr's Fluoxetine Capsules, USP Products are expected to meet the impurities specifications through the proposed 24 month expiration dating period.

In support of Barr's conclusions, we are including the following documents:

- Updated Interim Stability Report for Fluoxetine Capsules, USP 10 mg and 20 mg
- Detailed review of impurity profiles
- Representative impurities/degradation product chromatograms from initial release, 3 month CRT and 6 month CRT

If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Regulatory Counsel and
Director of Regulatory Affairs

cc: New Jersey District Field Office

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 30, 2000

NEW CORRESP
NC

Privileged and Confidential
VIA FEDERAL EXPRESS

Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation & Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855



Re: ANDA No. 74 - 803: Barr Laboratories, Inc.
Fluoxetine Capsules, USP 10 mg & 20 mg
Meeting Request - 180 Day Market Exclusivity

To Whom It May Concern:

Barr Laboratories, Inc. ("Barr") hereby submits this correspondence and meeting request to our Abbreviated New Drug Application ("ANDA") (ANDA No. 74 - 803) for Fluoxetine Capsules, USP 10 mg and 20 mg. 21 C.F.R. § 314.102 (a), (e) (1999). Given that Barr is the first paragraph IV filer on Eli Lilly's ("Lilly") '081 and '549 patents, and given the Federal Circuit's recent ruling of invalidity of the '549 patent, Barr is entitled by law to a full 180 days of market exclusivity.

For the reasons fully described in the attached Exclusivity Statement, Barr submits that the agency is prohibited by statute from approving all subsequent fluoxetine capsules ANDAs until Barr's generic exclusivity has expired. Barr's exclusivity should commence upon commercial marketing of the products, which will occur after expiration of the '081 patent and, if awarded, after Lilly's pediatric exclusivity. At the very least, Barr's exclusivity period will not begin until the district court enters judgment pursuant to the Federal Circuit's mandate, and that Barr's exclusivity will not run concurrently with any pediatric exclusivity awarded to Lilly.

Barr Laboratories, Inc.

ANDA No. 74-803: Barr Laboratories, Inc.

Gary Buehler

August 30, 2000

Page 2

Because the agency's application of the statute in this situation will have a profound impact on Barr, the generic industry and American consumers, and because this situation has not previously been before the agency, Barr submits that a meeting with appropriate agency officials is clearly warranted. The purpose of the meeting will be to confirm that Barr's fluoxetine capsules are entitled to a full 180 days of market exclusivity under 21 U.S.C. § 355(j)(5)(B)(iv), regardless of whether Lilly is awarded pediatric exclusivity. Any other application of the statute to Barr's fluoxetine capsules, will render the 180 day exclusivity provision meaningless, vitiating the congressional incentive for future patent challenges.

We will contact your office next week concerning this meeting request. In the meantime, should you have any questions, please contact me at (845) 353 - 8432.

Sincerely,



Christine Mundkur, Esq.

*Vice President, Quality and Regulatory
Counsel*

Barr Laboratories, Inc.

*cc: Cecelia M. Parise
Kimberly Dettelbach
Elizabeth H. Dickinson*



Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 31, 2001

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, Maryland 20855-2773

NEW CORRESP

NC

AMENDMENT

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10MG AND 20 MG

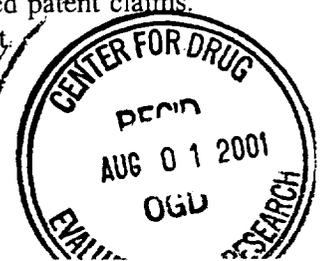
Reference is made to Barr's tentatively approved Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for **Fluoxetine Capsules, USP 10 mg and 20 mg**, dated December 9, 1995. Reference is also made to Barr's May 22, 2001 minor amendment for the 20 mg strength.

Barr is requesting final agency approval of the 20 mg strength of Fluoxetine Capsules, USP. In accordance with the tentative approval letter from the Agency, dated June 14, 2000, Barr is forwarding a copy of the final judgement from the District Court for the Southern District of Indiana, dated July 27, 2001, as well as the Federal Circuit's opinion, dated May 30, 2001, and the mandate that issued therefrom dated July 26, 2001.

Barr is entitled to final approval for its 20 mg fluoxetine capsules when Eli Lilly's pediatric exclusivity expires on August 2, 2002. In December 1995, Barr filed the first ANDA seeking to market 20 mg fluoxetine capsules, a generic version of Eli Lilly's Prozac[®] brand anti-depressant product. Barr's ANDA contained a paragraph IV certification to both patents Lilly listed in the Orange Book in connection with Prozac[®], U.S. Patent Nos. 4,314,081 ("the '081 patent") and 4,626,549 ("the '549 patent").

Barr timely notified Lilly of Barr's paragraph IV certification and, in April, 1996, Lilly initiated a patent infringement action against Barr in the United States District Court for the Southern District of Indiana. In that suit, Lilly asserted that Barr's marketing of fluoxetine hydrochloride for its then-labeled uses would infringe claim 5 of the '081 patent, which claims the fluoxetine hydrochloride compound and claim 7 of the '549 patent, which claims the use of fluoxetine hydrochloride to inhibit the uptake of serotonin.

Lilly asserted only claim 5 of the '081 patent and claim 7 of the '549 patent against Barr and, thus, those two claims were the only patent claims at issue in the *Lilly v. Barr* litigation. On January 25, 1999, the District Court entered judgment in favor of Lilly and against Barr on both of the asserted patent claims. Barr filed a timely appeal of this order to the U.S. Court of Appeals for the Federal Circuit.



Barr Laboratories, Inc.

REFERENCE: **ANDA 74-803**
 FLUOXETINE CAPSULES, USP 10MG AND 20 MG

On May 30, 2001, the Federal Circuit affirmed the District Court's finding that claim 5 of the '081 patent was valid, but reversed the District Court's finding regarding claim 7 of the '549 patent. The panel found that claim 7 of the '549 patent was invalid on double patenting grounds. *Eli Lilly & Co. v. Barr Labs*, 251 F.3d 955, 972 (Fed. Cir. 2001). This opinion replaced an earlier opinion by the same panel, dated August 8, 2000, which had been vacated by the Federal Circuit *en banc*. See *Eli Lilly & Co. v. Barr Labs*, 222 F.3d 973, 988 (Fed. Cir. 2000). On July 26, 2001, the Federal Circuit issued a judgment and mandate (copy attached) directing the District Court to vacate its January 25, 1999 order.

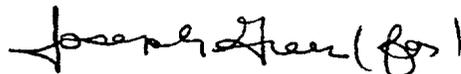
On July 27, 2001, the District Court entered the Federal Circuit's mandate on the District Court docket and, in doing so, the Court "ordered and adjudged that this cause is affirmed-in-part, reversed-in-part and vacated, in accordance with the decision of the Federal Circuit Court of Appeals, entered May 30, 2001." Simply put, the Court vacated its January 25, 1999 order and entered judgment in favor of Barr, and against Eli Lilly because claim 7 of the '549 patent is invalid. A copy of the relevant docket entry is attached. Because Lilly successfully demonstrated that the '081 patent was valid and infringed, Lilly became eligible for a six-month period of pediatric exclusivity following the expiration of the '081 patent. Since the '081 patent expired on February 2, 2001, Lilly's pediatric exclusivity period ends on August 2, 2001. Thus, as a result of Lilly's pediatric exclusivity and the District Court's entry of the Federal Circuit's mandate, Barr is entitled to final approval on August 2, 2001. As the FDA is aware, Barr is entitled to 180 days of exclusivity for its 20 mg fluoxetine capsules, which Barr contends begins on August 2, 2001.

An identical copy of this Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes Barr's amendment requesting final approval for Fluoxetine Capsules, USP 20 mg. If you have any questions concerning this submission, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President of Quality and
Regulatory Affairs

Enclosure

Page 2 of 2

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 24, 2001

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, Maryland 20855-2773

NEW CORRESP
NC

VIA FACSIMILE: 301 443-3847
VIA FedEx

LABELING FACSIMILE

REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our tentatively approved Abbreviated New Drug Application submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluoxetine Capsules, USP 20 mg.

Reference is also made to the telephone conversation between Adolph Vezza, Labeling Review Branch, FDA and Christine Mundkur, Barr Laboratories, Inc. on July 24, 2001 in which Mr. Vezza requested Barr commit to making the labeling changes specified in FDA's June 22, 2001 facsimile at the time of Barr's next printing.

Accordingly, Barr hereby commits to making all of the labeling changes specified in the Agencies' June 22, 2001 letter at the time of their next printing.

This completes the present Labeling Facsimile. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and Regulatory Counsel



Enc.

cc: Adolph Vezza – Labeling Review Branch

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 19, 2001

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, Maryland 20855-2773

ORIG AMENDMENT

N/A F

VIA FACSIMILE: 301 443-3847
VIA FedEx

LABELING AMENDMENT

REFERENCE: AND A 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG

Reference is made to our tentatively approved Abbreviated New Drug Application submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluoxetine Capsules, USP 20 mg.

Reference is also made to the Agency's June 22, 2001 facsimile from the Labeling Review Branch that stated the following:

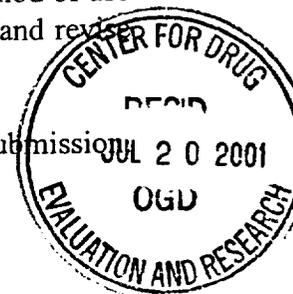
Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. FDA does not authorize certifications with respect to patents that claim a use for the reference listed drug for which the applicant is not seeking approval. The statute required patent certifications, e.g. Paragraph(s) I, II, III, IV, only if the patent claims a use for the reference listed drug for which the applicant is seeking approval (Section 505(j)(2)(A)(vii) of the Act). The statute requires an applicant to make a patent statement when a method of use patent does not claim a use for which the applicant is seeking approval (Section 505(j)(2)(A)(viii)).

We note that you have challenged U.S. Patent 4626549 by filing a Paragraph IV Certification. However, your proposed insert labeling does not contain the method of use covered by the aforementioned patent. Please amend your patent information and revise your insert labeling as appropriate.

We acknowledge that you have requested an opinion on this issue with this submission. Please be informed that it is still under consideration by the Agency.



**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

PAGE 2

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

DRAFT

- b. For additional guidance regarding your patent certification we refer you to the Agency's letter dated March 16, 2001.

Response:

The paragraph IV certification provided in the original ANDA continues to be correct in that Barr proposes to market its product for the treatment of depression and U.S. Patent 4626549 ("549") claims using fluoxetine to block serotonin uptake, which is the undisputed mechanism through which fluoxetine treats depression. However, because Barr never intended to market its product for the treatment of appetite disorders covered by the '549 patent and because the agency suggested in its March 16, 2000 letter that it is reasonable to conclude that bulimia nervosa could be considered an appetite disorder covered by the '549 patent, Barr elected to delete the bulimia nervosa indication from Barr's proposed labeling. Therefore, in order to clarify the original paragraph IV certification to reflect the fact that Barr is not pursuing the bulimia indication, Barr is enclosing the attached section viii statement under section 505 (j)(2)(A)(viii) stating that ANDA 74-803 is not seeking approval for the use of treating bulimia nervosa.

2. INSERT

a. GENERAL COMMENTS

- i. "U.S." rather than "US" throughout the text of the insert.
- ii. "coadministered" and "coadministration" (delete hyphens)

b. DESCRIPTION

First sentence-"...oral administration; it is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, fluoxetine hydrochloride). It is chemically unrelated..."

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

PAGE 3

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

DRAFT

c. **CLINICAL PHARMACOLOGY**

- i. Absorption, Distribution, Metabolism, and Excretion, Metabolism, first sentence-
 "...other unidentified..." (delete comma)
- ii. Clinical Trials

 Depression, second paragraph, first sentence-"...fluoxetine 20 mg..." (delete
 hyphens – two instances)

d. **PRECAUTIONS**

Drug Interactions, Warfarin – "anticoagulant" (delete hyphen)

e. **ADVERSE REACTIONS**

Table 2 – Delete the second row (two by two hyphens)

f. **DOSAGE AND ADMINISTRATION**

Switching Patients to a Tricyclic Antidepressant (TCA)-"...under PRECAUTIONS, Drug Interactions)."

g. **HOW SUPPLIED**

- i. "...of fluoxetine (present as the hydrochloride) are..."
- iii. Add the statement "Sarafem™ is a trademark of Eli Lilly".
- iv. Add the statement "PROTECT FROM LIGHT".
- v. Add "[see USP]" to the end of the storage temperature recommendations.

**OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION**

PAGE 4

**REFERENCE: ANDA 74-803
 FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

DRAFT

Response:

According to the June 22, 2001 phone conversation between Christine Mundkur, Barr Laboratories, and Bob West, FDA, Barr will be making the proposed labeling changes and submitting them post approval in the Annual Report since they are all minor in nature. Specifically, they deal with the following: grammatical changes (deletion of hyphens, commas, and periods); addition of "SarafemTM" wording; deletion of a table row that contains no text; addition of descriptive words; and a change from lower to upper case letters for "PROTECT FROM LIGHT". These are all changes that are typically requested to be submitted in the Annual Report.

This completes the present Labeling Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and Regulatory
Counsel



Enc.

Cc: Cecelia Parise, Special Assistant
Adolph Veza – Labeling Review Branch

This Submission is comprised of **Pages 01 through 04**

labeling review
drafted 6/21/01
A. Vazir

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 22, 2001

Noted NAF.
B. McNeil
6/1/01

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, Maryland 20855-2773



ORIG AMENDMENT

N/AM

Smith (McNeil)
NITL
5/30/01

MINOR AMENDMENT

**REFERENCE: ANDA 74-803
FLUOXETINE CAPSULES, USP 10 MG AND 20 MG**

Reference is made to our tentatively approved Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Capsules, USP 10 mg and 20 mg.

Reference is also made to the Agency's June 14, 2000 tentative approval letter in which the following is stated:

"...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. Your amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved and should include documentation such as a copy of a final order or judgement from the Court of Appeals...or any other relevant information. The amendment should also provide updated information such as final printed labeling, chemistry, manufacturing, and controls data as appropriate."

Barr is expecting to be eligible for final approval on August 2, 2001 with 180 days exclusivity for the 20 mg strength. We believe another generic company will be granted 180 days exclusivity for the 10 mg strength. Accordingly, we are hereby submitting a Minor Amendment for the 20 mg strength identifying changes in the conditions under which the drug product was tentatively approved and providing a status on the case at the court of appeals. We will be submitting a Minor Amendment for the 10 mg strength 60 to 90 days prior to being eligible for final approval.

Reference is also made to a June 1, 2001 telephone conversation between Christine Mundkur, VP Quality and Regulatory Counsel, Barr Laboratories, and Bob West, Acting Deputy Director, OGD/FDA in which Mr. West stated that the following changes would be accepted as a Minor Amendment.

duy
5/31/01

Barr Laboratories, Inc.

I. Site Changes:

- New packaging and alternate analytical testing site of facilities at the application was tentatively approved, it is necessary to file for necessary to file for due to the high volume of the product. Since Barr no longer has packaging site under which the as a packaging site. It is also as an additional analytical testing site to the already approved

II. Test Method and Specification Changes:

III. Manufacturing and Packaging Changes:

Barr Laboratories, Inc.

IV. Labeling Changes:

- Updated labeling in accordance with FDA's March 16, 2001 correspondence and Eli Lilly's last approved labeling, including a "protect from light" statement. Please note that references to the 10 mg strength were removed. In the March 16, 2001 correspondence directed to Barr's fluoxetine capsule products, FDA stated that generic manufacturers, like Barr, may omit from their fluoxetine product labels an indication for bulimia nervosa. Barr decided to remove references to the bulimia nervosa indication (see Section IV for a detailed explanation concerning the bulimia nervosa indication). In so doing, we followed specific instructions received from Adolph Vezza, Div. of Labeling and Program Support, OGD/FDA received during an April 6, 2001 phone conversation held with Barr personnel (Christine Mundkur, Vice President Quality and Regulatory Counsel, Nancy Westcott, Regulatory Affairs Labeling Specialist, and Elisabeth Noble Gray, Technical Group Leader, Regulatory Affairs).
- Changed product capsule description from barr/877 to barr 20/877 at the request of Barr's Sales and Marketing Department. The above affected documents reflect this change (annual reportable change).

Barr commits to place the first batch of the 100's Heat Seal CRC in its long-term stability program in support of all of the above changes. Supporting documentation for these changes is provided in the four enumerated sections that follow.

Court of Appeals Information

Eli Lilly filed a petition for a rehearing; the Court of Appeals has not yet ruled on this rehearing request. On August 9, 2000 the United States Court of Appeals, *Eli Lilly and Co. v. Barr Laboratories, Inc.*, 222F. 3d 973 (Fed. Cir. 2000) issued an opinion holding that the '549 patent was invalid but that the '081 patent was valid. The '081 patent expired on February 2, 2001.

An identical copy of this Minor Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes Barr's Minor Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.


Christine Mundkur
Vice President Quality and
Regulatory Counsel

Barr Laboratories, Inc.

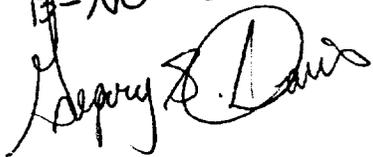
2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 1, 2000

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VIA FEDERAL EXPRESS

NEW CORRESP

Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation & Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

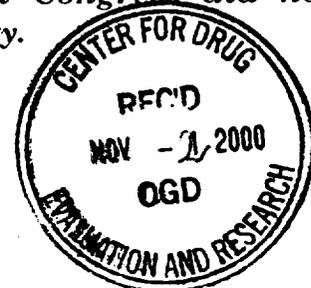
NAT 
13-NOV-2000


Re: ANDA No. 74 - 803: Barr Laboratories, Inc.
Fluoxetine Capsules, USP 10 mg & 20 mg
Supplement to Exclusivity Statement

To Whom It May Concern:

Barr Laboratories, Inc. ("Barr") hereby submits this correspondence to our Abbreviated New Drug Application ("ANDA") (ANDA No. 74 - 803) for Fluoxetine Capsules, USP 10 mg and 20 mg. Barr is supplementing our original Exclusivity Statement dated August 30, 2000. Since submitting its Statement, Barr has had discussions with various individuals from the Office of Generic Drugs and FDA's General Counsel's office. In light of these conversations, Barr submits this supplement to ANDA No. 74 - 803.

For the reasons fully described in the attached Supplement to Exclusivity Statement, Barr submits that pediatric exclusivity and generic exclusivity run consecutively, not concurrently. The plain language of the statute is clear that Congress intended pediatric exclusivity and generic exclusivity to harmoniously co-exist. Additionally, the legislative history of the pediatric exclusivity provision demonstrates that Congress did not intend this extension to interfere with generic exclusivity.



Barr Laboratories, Inc.

ANDA No. 74-803: Barr Laboratories, Inc.
Gary Buehler
November 1, 2000
Page 2

Finally, the Supplement to Exclusivity Statement addresses the Agency's informal inquiry regarding the relevance, if any, of its decision on Citizen Petition No. 99P-1271/PSA 1 and PSA2 (the Cisplatin Petition). As set forth in Barr's Supplement, the Cisplatin Petition is not relevant to the case of fluoxetine hydrochloride.

If you have any questions, please contact me at (845) 353 - 8432.

Sincerely,



Christine Mundkur, Esq.
Vice President, Quality and Regulatory
Counsel
Barr Laboratories, Inc.

cc: Cecelia M. Parise
Kimberly Dettelbach
Elizabeth H. Dickinson



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

December 9, 1995

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Fluoxetine Hydrochloride Capsules, 20 mg.

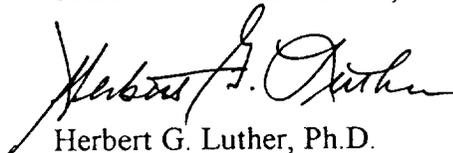
The application is provided both as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 2 volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in orange binders and consists of 2 volumes. The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The information submitted in this application is also in accord with the October 14, 1994 communication from Dr. Janet Woodcock, Director CDER and Mr. Ronald Cheesmore (ORA). As a result of this policy, detailed facilities descriptions and equipment listings as well as specific SOPs are not contained in this application. They are, however, kept current and are available for review and inspection by FDA District Field Investigators.

Included in this application, and in accordance with the Generic Drug Enforcement Act of 1992, a Debarment Certification Statement with a List of Convictions Statement is provided for this application. In addition, in accordance with the FDA's Final Rule (Federal Register, Vol. 58, No. 172, September 8, 1993), a "Field Copy" of this application has been forwarded to the New Jersey District Office.

Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.



Herbert G. Luther, Ph.D.
Director Scientific Affairs

RECEIVED

DEC 11 1995

GENERIC DRUGS

*Standish Place
11/2/96*