DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-046

Forest Laboratories Inc.
Attention: Amy Rubin
Director, Drug Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 073115

Dear Ms. Rubin:

Please refer to your New Drug Application dated October 30, and received November 2, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrobromide) 10 mg/5 ml oral solution.

We acknowledge receipt of your submission dated October 29, 1999. This submission constituted a complete response to our September 2, 1999 approvable letter.

We also acknowledge receipt of your additional communications dated October 1, October 12, October 29, and December 13, 1999. The 2 month primary User Fee goal date for this application is January 1, 2000.

This new drug application provides for a new oral solution formulation of citalopram hydrobromide.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling below. Accordingly, the application is approved effective as of the date of this letter.

LABELING

Below are the revisions to the Celexa labeling to incorporate this new formulation and other safety related revisions. We note your agreement to this labeling in a telephone conversation dated December 14, 1999, between Mr. Paul David, of this Agency, and Ms. Tracey Varney of Forest. Your final labeling for Celexa solution should be identical to your currently approved labeling for Celexa tablets except for revisions to the following sections of labeling (double underline font denotes additions):

DESCRIPTION

Celexa (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated (±)-1-(3-

dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr with the following structural formula:

[Structural formula here]

The molecular formula is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405.35.

Citalopram HBr occurs as a fine white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.

Celexa (citalopram hydrobromide) is available as tablets or as an oral solution.

Celexa tablets are film coated, oval, scored tablet containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base.

The tablets also contain the following inactive ingredients: Copolyvidone, Corn Starch, Crosscarmellose Sodium, Glycerin, Lactose Monohydrate, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Microcrystalline Cellulose, Polyethylene Glycol, and Titanium Dioxide. Iron Oxides are used as coloring agents in the pink (20 mg) tablets.

Celexa oral solution also contains citalopram HBr equivalent to 2 mg/ml citalopram base. It also contains the following inactive ingredients: Sorbitol, Purified water, Propylene Glycol, Methylparaben, Natural Peppermint Flavor, and Propylparaben.

CLINICAL PHARMACOLOGY-Pharmacokinetics

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent.

PRECAUTIONS-Drug Interactions

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

ADVERSE REACTIONS
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 selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The table below, displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Celexa (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Decreased Libido	3.8% (males only)	≤ 1% (males only)
Impotence	2.8% (males only)	≤1% (males only)

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram 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.

HOW SUPPLIED

Tablets:

20 mg
Bottle of 30 NDC # 0456-4020-30
Bottle of 100 NDC # 0456-4020-01
Bottle of 500 NDC # 0456-4020-05
10 x 10 Unit Dose NDC # 0456-4020-63

Pink, oval, scored film coated.
Imprint on scored side with AF@ on the left side and AP@ on the right side.
Imprint on the non-scored side with A20 mg@.

40 mg
Bottle of 30 NDC # 0456-4040-30
Bottle of 100NDC # 0456-4040-01
Bottle of 500NDC # 0456-4040-05

10 x 10 Unit DoseNDC # 0456-4040-63

White, oval, scored film coated.
Imprint on scored side with AF@ on the left side and AP@ on the right side.
Imprint on the non-scored side with A40 mg@.

Oral Solution:

10 mg/5 ml, peppermint flavor – (120 ml) NDC 0456-4130-04

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

1. Expiration Date

   The Agency is approving an expiry date of 18 months at this time.

2. Methods Validation

   Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you are in the process of fulfilling your pediatric study requirement at this time.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-046." Approval of this submission by FDA is not required before the labeling is used.

Additionally, please submit one market package of the drug product when it is available.

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

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

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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

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

Sincerely yours,

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